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Cognitive Disorders

Edited by Humberto Foyaca Sibat

COGNITIVE DISORDERS

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Notice

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Meet the editor

Professor Humberto Foyaca Sibat graduated as a medical doctor in Havana University in 1971. He became a specialist in neurology in 1975 and a second-degree specialist in 1984. He is married and has three daughters and one son. Professor Foyaca Sibat has been an associate professor of Walter Sisulu University for more than 20 years. He also has a master's and a PhD degree in the field of science, and he is a full professor and a full research investigator of the Cuban Academy of Sciences. Professor Foyaca Sibat is a member of 15 medical societies from all over the world. He has presented more than 380 papers in different scientific events, and has published more than 75 manuscripts in peer-reviewed journals. He is the chief editor of The Internet Journal of Neurology, currently the largest electronic journal of neurology worldwide. He has received and delivered many short training courses and organized many national and international conferences. Prof. Foyaca Sibat has edited five books and published nine chapters for InTech, which have been downloaded many times.

Contents

Preface

This book contains a group of selected peer-reviewed chapters that were revised by the members of the IJN editorial board and the chief editor of this project at least twice. An important number of constructive recommendations and necessary modifications were implemented on the chapters before they were finally accepted for publication.

Apart from the introductory chapter on cognitive disorders and their historical background, some authors have dedicated many pages to discuss tau proteins and tauopathies, and an overview of tau proteins as a biological fluid biomarker and tauopathies in different degenerative diseases and even in cancer is presented.

As we will see in this book, dementia is a pathological, neurodegenerative process leading to a progressive decline in cognitive and daily functional abilities. It has many causes, several clinical manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes.

The current situation of patients with dementia at the correction setting is discussed, and important proposals for improving their situation are made.

Many novel aspects on dementia, including relevant information on Alzheimer's disease (AD), frontotemporal dementia, idiopathic normal pressure hydrocephalus, Wernicke–Korsakoff's syndrome, vascular dementia, Lewy body dementia, and Parkinson's dementia, among others, are mentioned.

This book aims to present in synthesized form the role played by diabetes mellitus in cognitive functions.

This project reports results from a systematic search of PubMed, looking for articles published about the different clinical and etiological presentations of dementia.

The effective restorative home support services for patients with cognitive disorders are another important issue highlighted in this book. Finally, we discuss the role of the hypothalamus in AD.

In summary, updated aspects of cognitive dysfunction are sourced from eight chapters from some of the world's top central nervous system researchers and neurologists to provide a timely review of the state of the art in cognitive disorders and dementia, covering historical aspects, genetics, pathogenesis, clinical aspects, and imagenology, among others. Contributors from different countries have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the topics with many explanatory figures to enhance legibility and make the book useful. Countless hours have been spent writing these chapters, and precious free time to be dedicated to our families, relatives, and friends

has been sacrificed, but in the end, we all are very proud of this book. We are looking forward with confidence and pride to the vital role that this book will play for a new vision and mission.

Every effort has been made to check all novel information given in this book, but it is important for our readership to scrutinize the latest information considering that it is a dynamic process of learning. We all attempted to bring in valuable updated information for all issues mentioned in this book. Every effort has been made in the preparation and editing of this book to ensure that the information given is correct, but it is possible that errors have been overlooked. Finally, we would like to highlight that we reviewed all controversial matters and our medical criteria and scientists' opinions have been expressed with modesty, honesty, and respect, but the reader is advised to refer to other published information to check accuracy.

Acknowledgments

First of all, I would like to thank InTech Open Access Publisher that unconditionally supported me in editing this book. Many people helped support the writing of this project. Second, I'd like to thank all the technical reviewers. These folks make sure the examples work, look for technical errors, and make many recommendations on writing quality. Obviously, it's not possible to write a quality medical book without quality scientific reviewers.

From my first editorial job until now, I am extremely grateful for the enthusiasm, skill, and professional support of Intech managers: Natalia Reinic and Dragana Manestar. I also received great support from Ana Pantar every time I needed her help. Currently, I am very grateful to Martina Usljebrka. Her enthusiastic and professional support was decisive for the creation of this book. Martina has meticulously coordinated the whole project with unfailing good mood and patience. She also reviewed my work without unnecessary delay, which allowed me to complete all tasks on time.

In spite of some previous frustration, I agreed to edit this particular book because I identified it as another way of approaching cognitive disorders and dementia covering novel aspects of this problem without ignoring their foundation. Therefore, apart from the classic issues that cannot be missing from any book about dementia, I introduce updated information about dementia and other cognitive disorders. Nevertheless, publication of this book could not have been possible but for the ungrudging efforts put in by a number of people working in the field of cognition and many individuals from many countries and ethnic, religious, and socioeconomic groups that coincidentally are influenced by cognitive disorders.

My family has graciously tolerated the precious time I spent on this project. Fortunately, my mom, my dad, my brother Francisco, and my first daughter Zayra Susana from heaven continue to inspire me. My sisters Mayra Alejandra, Lilia Teresa, and Lorna Irene supported me all the time. My second daughter Lorna Maria (33 years old) and my little one Fatima Susana Adolfina (8 years old) encouraged me all the time to continue moving forward with persistence and tenacity. My son Thabo Humberto Jorge (10 years old) pushed me to play games with him that helped me to relax and to find new ideas and motivations. My whole family contributed to this project in one way or another, and all of them deserve my deep gratitude. My wife Lourdes de Fatima was the strongest supporter of this project, and without her collaboration, it would have never happened. I also want to thank the families, relatives, and friends of all the collaborators for their patience and tolerance of the lost evenings, nights, weekends, and holidays. My special thanks go to Walter Sisulu University (WSU).

The new university was named in honor of an icon of the South African liberation struggle and close comrade of Nelson Mandela, the late Walter Max Ulyate Sisulu. Many thanks go to Dr. E.N. Cishe, the Acting Director Research Development of WSU; Professor A.J. Mbokazi, the Dean of the Faculty of Health Sciences (WSU); Prof. Thozama Dubula, the Head of the Department of Medicine and Therapeutics; Dr. M. Mdledle, the Acting Governor General Director of the Clinical Governance of Nelson Mandela Central Hospital; and Mrs. N.P. Makwedini, the Chief Executive Officer of Nelson Mandela Central Hospital for the best understanding and support. Finally, I extend my deepest sense of appreciation for the support received from Dr. Roberto Morales Ojeda, the Minister of Public Health of Cuba, and Dr. Jorge Delgado Bustillo, the Deputy Director of the Cuban National Unit for International Cooperation in Health.

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Chapter 1

Introductory Chapter: Cognitive Disorders and Its Historical Background

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Lourdes de Fátima Ibañez Valdés

Additional information is available at the end of the chapter

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1. Introduction

Dementia is a neurodegenerative disorder characterized by a progressive decline in multiple cognitive domains leading to deterioration of daily living activities, including social and professional functioning. The aging population has been increasing gradually, and in 1990, 26 countries with more than 2 million elderly citizens aged 65 years and older were identified. It is expected that by 2013 another 34 nations will be added in the list. On the other hand, calculations made in 2000 about the number of elderly peoples (over 65 years old) in the world reached the 420 million (7%), and they estimated around 1 billion by 2030 (12%), mainly in developing countries [1].

Without doubt, the most common form of dementia in elderly people is Alzheimer disease (AD), but it can occur even in patients with 40 years of age.

AD is a progressive disorder of multifactorial origin, well defined clinically with a number of biomarkers also well documented. According to the World Alzheimer Report from 2015, AD will increase exponentially as population ages being one of the biggest problems of our society in this century [2]. Currently, 46.8 million people live with dementia all over the world, and this number will be duplicated every 20 years. Today, the calculated incidence of dementia is 9.9 million new patients, one new one every 3.2 s.

The Monzino 80+ population-based study made in 2015 found that one quarter of 80+-year-old person had dementia even in advanced stages which increased prevalence in extreme ages such as: 15.7% in persons aged 70–84 years to 52 and 65.9% in peoples aged 95–99 and in beyond 100 years, accordingly [3].

Another author reports that 24.3 million patients have dementia at the present moment, and the incidence is 4.6 new cases yearly. They said the number of patients will be duplicated every 20 years to more than 81 million (71%) by 2040 most of them in developing nations [4]. Other author highlighted that the number of patients living with dementia (PLWD) will be a triple by 2050 [5].

We also agree with Vito Moretti [6] who wrote about "Update on Dementia" that the whole society should be involved in the mental health promotion to reduce risk of dementia and in new priorities for research purposes to identify new approaches to this problem and eradicate stigma and discrimination.

The delivery of therapeutic agents specifically designed to enhance memory and cognition in AD patients is increasing gradually. The limited efficacy of the drugs currently available is well known, and the introduction of these medications has shed an entirely new light on the field. Therefore, we believe that this is the best time to look at the past to understand the present and perhaps gain insight into the future [7].

2. Ancient times

Neurological injuries, such as traumatic hemiparesis and cervical dislocation with paraplegia, were described in the well-known Edwin Smith surgical papyrus. Similarly, recognizable in the Ebers papyrus is a description of migraine, but the history of dementia is probably as old as mankind, at least since lifespan reached the age of 60 years of age. After several searches of previous record in the medical literatures in order to summarize the opinions for dementia in ancient China, the earliest description of dementia in the Yellow emperor's internal classic it is found in a book written 2000 years ago. The term of dementia was first delivered by Hua Tuo (AD 140–208) in the book, Hua Tou Shen Yi Mi Zhuan [8].

In the above-mentioned book, the author mentioned that the insufficiency of flowing energy (Qi) is one of the causes of dementia among other such as the stagnation of phlegm; and the stasis of the blood which confirm that dementia disorders were investigated by traditional Chinese medicine in ancient times [8].

An inscription from the tomb of the vizier Westphal, dated c. 2455 BCE, seems to describe stroke, and Herodotus describes epilepsy in Hellenistic Egypt [9].

In the past, everyone presenting an incapacity for reasoning properly including psychosis, neurosyphilis, and other mental disorder was labelled as dementia. Elderly patients presenting similar clinical manifestations, were considered secondary to hardening of the brain arteries.

Dementia has been described to in medical texts since ancient times. One of the earliest known references to dementia is delivered to the 7th century BC Greek philosopher Pythagoras, who included in that concept "senium" peoples aged oldest than 63 years old (a period of mental and physical decay), and after age of 80th being where *"the scene of mortal existence closes after a great length of time that very fortunately, few of the human species arrive at, where the mind is reduced to the imbecility of the first epoch of infancy"* [10].

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The Greek statesman and poet Solon established that if a male people's loss his capacity for judgment due to old age then terms of man's will might be invalidated, this happened in 550 BC and the Chinese authors considered the medical term of dementia related to "foolish old person" [11].

Two ancient Greeks Aristotle and Plato (**Figures 1** and **2**) wrote about mental decay in elderly persons and they considered that process as an inevitable one affecting all old peoples without possibility of its prevention. They also said that these kinds of person were not suitable to carry out high responsibilities or any position because this disorder affects their judgment, imagination, reasoning and memory [12].

A more advanced statement about dementia was established by Cicero who defined it as a process not inevitable related with the aging that "*affect only those old men who were weak-willed*." Cicero also said that dementia could not happen in those persons who remained mentally active and with the capacity to learn new things. Unfortunately, the Aristotle's medical writing prevailed for several centuries above the most modern Cicero's views on aging, and other physicians such as Galen and Celsus simply highlighted the Aristotle's belief [13]. Nevertheless, other authors from Greece and Rome delivered other ideas more similar to our modern concept of dementia including many cognitive and behavioral symptoms of dementia [14].

May et al. [15] delivered the results of electronic searches of Zhong Hua Yi Dian ("Encyclopaedia of Traditional Chinese Medicine"), a CD of 1000 premodern (before 1950) medical books, for single herbs, and other natural products used for dementia, memory disorders, and memory improvement.

They found 127 different books containing 731 citations about products for treatment of memory disorders. A total of 110 natural products for the management of memory problems were identified including yuan zhi (Polygala tenuifolia), fu shen (Poria cocos), and chang pu (Acorus spp.) All the above-mentioned products have been cited many times in the literature over the past 180 years.

Figure 1. Roman copy in marble of a Greek bronze bust of Aristotle by Lysippos, c. 330 BC. The alabaster mantle is modern. Born 384 BC in Northen Greece. Died 322 BC in Euboea Greece (Source: https://en.wikipedia.org/wiki/Aristotle).

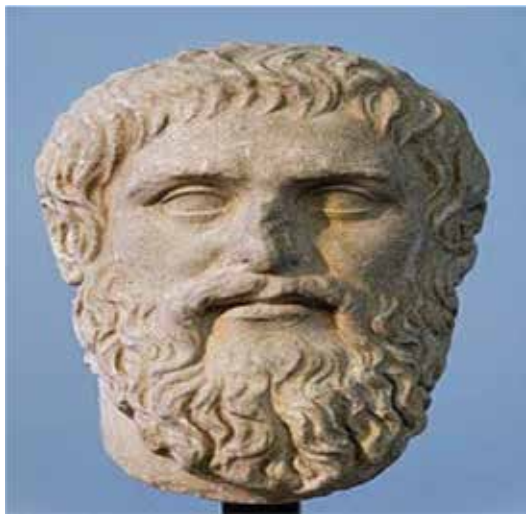

Figure 2. Plato: Roman copy of a portrait bust by Silanion for the Academia Athens. Born 428/427 or 424/423 BC in Athens, Greece. Died 348/347 BC (age) c. 80. Athens (source: https://en.wikipedia.org/wiki/Plato).

Dementia was defined in the ancient period (under Ayurveda) as well. The ancient period dates back to the mid-second millennium Before Christ (B.C.) during the creation of the Ayurvedic Indian system of Medicine, which detailed descriptions of neurological disorders called Vata Vyadhi. Knowledge about dementia was increasing gradually through the early twentieth century witnessed the birth of modern Indian medicine with the onset of formal physician training at the nation's first allopathic medical colleges located in Madras (1835), Calcutta (1835) and Mumbai (1848) [16].

Neurology, in the modern sense, did not exist in ancient times, where medicine was a group of belief, magical, natural, and religious elements. There were different practitioners for each form of therapy. However, Egyptian doctors made careful observations of illness and injuries, including problems of the nervous system. Egyptians had words for the skull, brain, vertebrae, spinal fluid and meninges, though they do not say if they assigned any function to them. They also described unconsciousness, quadriparesis, hemiparesis and dementia [17].

Even in contemporary societies, extended life expectancy results in elderly leaders, suffering from various diseases connected with gerontology and without exception, their peoples and the whole nation suffer the consequence. From 87 Byzantine emperors, 7 of them reached older age and showed symptoms of dementia, as well as other manifestations of elderly peoples.

Many Byzantine doctors considered dementia secondary to multiple causes mainly some kind of pathogenic humor and cerebro-vascular disorder.

Loss of mental skills is considered dangerous and remains a problem from antiquity to the modern day. Fortunately, Byzantium handled all these cases with diplomacy [18].

The reference to "imbecility" was described for the first time in Greece around sixth century BC and the Japanese term "Mow-roku" (age and devitalized) in eleventh century. In 1960, this

term was replaced by "Chee-hou" (absent-mind imbecile), and finally in 2014, it was changed by "Nonchee-show" for humanistic reasons [19].

In Constantinople, there was one special hospital to admit those patients with dementia or insanity excepting the emperors who were above the law and whose health problems could not be divulgated publicly. During 1700 years, information about dementia on Western medical literature was poorly recorded.

In the thirteenth-century, Roger Bacon wrote about dementia who considered advanced ages as celestial punishment for original sin. He also delivered the same Aristotelian's criteria saying that dementia is a natural consequence of long lifespan but established that the brain was the center of memory and not the heart [20]. Years later, poets, novelists, and other playwriter's mentioned the loss of mental function secondary to old age, and it should be highlighted Shakespeare and his allusion to dementia in his play Hamlet and King Lear [21, 22].

At that time, elderly people presenting dementia was called as senile dementia or senility, and it was considered as a normal consequence of the advance age and not a brain disorder, but years later, the same cause of the same problem was identified as cerebral atherosclerosis and or ischemic stroke in the cerebral vascular territory.

Before the end of nineteenth century, the concept of dementia is wider than twentieth century and later and under the umbrella of that definition, it was included several mental disorders and any type of psychosocial disability, including conditions that could be reversed [23].

The history of vascular dementia is related to patients presenting cognitive decline post apoplexy reported by Thomas Willis in 1672. In almost all eighteenth and at the beginning of nineteenth century, the pathological process of "brain congestion" was the most common diagnosis performed by the medical doctors when several conditions ranging from stroke to anxiety and to dementia due to effects of untreated hypertension were diagnosed.

The modern history of vascular dementia is written by Otto Binswanger and Allois Alzheimer (**Figure 3**). In 1894, they had a merit to distinguish vascular dementia from dementia paralytica caused by tertiary syphilis [24].

In 1907, a 50-year-old lady presenting a cognitive decline and some associate microscopy abnormalities in the brain was reported by Allois Alzheimer who considered it as a rare disorder of the middle age. Alzheimer's findings were originally published in the form of a conference abstract where the author described a delusional woman (Auguste D) who had slowly lost her cognitive function and died at 55 years of age [25].

In recognition of the job done by Allois Alzheimer (1864–1915), Emil Kraepelin introduced the term of Alzheimer's disease in 1910 and also differentiated the presenile form of dementia (reported by Alzheimer) from the commonest senile variant [26].

During the first half of the twentieth century, the vascular etiology for almost all cognitive disorders was prevalent until 1960s where the link between neurodegenerative diseases and age-related cognitive decline was documented. Ten years later, the vascular etiology of dementia is considered less common than was before though and AD the commonest cause of almost

Figure 3. Emil Kraepelin in his later years. Born in 1856 and died in 1976 (aged 70). (Source: https://en.wikipedia.org/wiki/Emil_Kraepelin).

all mental impairment in elderly peoples. Currently, it is well known that vascular dementia and AD can be associated.

Around 2010, many countries have 10–14% of people over 65 and in Germany and Japan, this percentage was even higher (>20%). As we mentioned earlier, life spasm over 80 years before twentieth century was extremely uncommon. Therefore, all disease related advanced age were rare as well.

Before World War II, elderly persons constituted an average of 3–5% of the population. Syphilitic dementia widespread all over the word until it was almost complete eradicated (when penicillin is discovered) after the war. We know that it allows increasing the life span expectancy in developed countries remarkably. Between 1913 and 1920, the medical term dementia praecox had been used to suggest the development of senile-type dementia at a younger age and this terminology also referred to patients with schizophrenia (including paranoia and decreased cognitive capacity) which could be expected to affect any elderly person [27].

In 1920, the uses of *dementia* for what is now understood as schizophrenia and senile dementia helped limit the word's meaning to "permanent, irreversible mental deterioration." This began the change to the more recognizable use of the term today.

Prior to India's independence from Britain in 1947, only 25 medical schools existed in the entire country where concepts about dementia were taught. In 1951, physicians across the field of neurology and neurosurgery united to create the Neurological Society of India (NSI).

Four decades later in 1991, neurologists branched out to establish a separate organization called the Indian Academy of Neurology (IAN) where a lot of research on dementia was done. With the transition to modern medicine that occurred more recently through formal training at medical schools beginning in the 1930s, some criteria about different presentations on dementia changed. The future of neurology in India continues growing rapidly and currently, there are 1100 practicing neurologists attending patients with cognitive decline and dementia and more than 150 post-graduate trainees who join the ranks every year [16].

In 1970s, dementia was delineated from normal aging, and the present concept of dementia was established in Japan [19].

In 1970s, the concept of vascular dementia (VaD) is finally separated and internationally accepted from the purely neurodegenerative form of AD. Many efforts have been released in order to distinguish these entities from the clinical, neuropsychological and pathological point of view for find out a homogenous group of patients who share a common specific underlying mechanism of cognitive decline [28]. The link between senile dementia and Alzheimer's disease was published by Katzmann in 1976 [29]. He described the prevalence and malignancy of AD as a major killer in peoples older than 65 years based on identical pathological findings in both processes. He established non-pathological difference between senile dementia (older than 65) and AD occurring before 65 years old, and the treatment for both entities should be the same. He also considered "senile dementia" as part of aging and not a proper disease. Katzmann documented that AD is a common disease and the fourth or fifth leading cause of death. Thanks to Katzman's criteria, dementia was not considered a part of the normal healthy aging process anymore but the debate between "senile dementia of the Alzheimer's type (over 65 years old) and Alzheimer's disease in younger peoples with the same pathology continue. It was agreed that the age limit was not certain, and the term AD should be reserved for those patients presenting the classical clinical manifestation and the brain pathology described regardless of the age of the patient.

Based on the evidence that many supercentenarians (more than 110 years old) have not dementia, these authors concluded that there was no age at which all persons develop AD, although the incidence of AD increases with age. Nevertheless, dementia is more frequent at the ages of 80 and 84 but peoples reaching the oldest stages have lower chance of developing it and women are more affected than men probably because women have longer lifespan than men [24].

Finally, psychiatry conditions like schizophrenia were removed from the organic brain syndrome group in 1952 and it was not considered as a cause of dementia anymore. On the other hand, the rational cause of senile dementia such as: hardening of the arteries became a main etiology for vascular dementias (VD) when presenting small strokes and now it is named: multi-infarct dementia.

In the 1960s, the seminal neuropathological and clinical studies of the New Castle school in England inaugurated the modern era of vascular dementia [24]. The general concern about AD increased gradually after 1994 when the US president Ronald Reagan disclosure he had been diagnosed with AD.

The term dementia with Lewis Body and the clinical criteria were first introduced and proposed by Mc Keith and colleagues in 1996 during the First International Workshop of the Consortium on Dementia with Lewy Bodies [30].

In the twenty-first century, many types of dementia have been identified being AD and VaD, the commonest one. Fortunately, from the last century, cognitive disorders such as idiopathic normal pressure hydrocephalus have specific treatment, and patients can reach a complete recovery.

Currently, apart for the advance role on the therapeutic field in almost all types of dementias, we highlighted the tremendous progress got in the field of diagnosis mainly in the field of pathological examination and metabolic activity in nuclear medical imaging tests such as single photon emission computed tomography and Positron Emission Tomography scans of the brain.

3. Brief comment about our chapters

In the second chapter of this project, we delivered our personal experience on the most common cognitive disorders and discuss the novel information available in the medical literature on some types of dementia. We described Alzheimer Disease as a progressive non-reversible neurodegenerative disorder, characterized by cognitive decline including learning capacity, emotional and behavioral alterations, motor skills impairment, including dysfunction of the autonomic nervous system and desynchronization of circadian rhythms. It has been predicted that a novel therapeutic agent that delays disease onset and progression by just 1 year would result in 9 million fewer cases by 2050 [31].

Vascular dementia (VaD) can be caused by disturbance of the blood supply to the brain leading to deprivation of the necessary such as nutrients including glucose, amino acids and oxygen to the neurons and its supporting cells. This particular type of dementia is strongly related with multifocal strokes, hypertension and diabetes mellitus type II and it is characterized by mental slowness; impaired initiative, planning, and executive function impairment; personality changes; and gait disorders. Arteriosclerotic brain disease presents as multiple focal areas of hypoperfusion randomly distributed in the cortex, also compromising subcortical structures. This particular pattern is never been observed in A.D. A familial form of VaD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is associated with vascular migraine headache and a subcortical ischemic lesion. CADASIL is caused by a mutation in the NOTCH3 gene on chromosome 19 being the most common genetic form of VaD. The disease is autosomal dominant. Dementia with Lewis Body is a type of dementia associated with abnormal protein deposits (α-synuclein) called Lewy bodies in the central nervous system (CNS), and these abnormal depositions affect the normal activities of the brain leading to clinical features of fluctuating consciousness, behavioral disorders, visual hallucinations, and parkinsonism. The metabolic defects described in this disease are very close to those found in AD, but there is also hypoperfusion in the occipital lobes. Parkinson dementia is characterized by bradykinesia, tremor at rest, gait disturbance, postural problems, rigidity, dysarthria, dysfunction of the judgment,

reasoning, memory, depression, anxiety, insomnia, and cognitive decline due to loss of midbrain dopaminergic neurons in the pars compacta of the substantia nigra and consequent loss of dopamine input to the caudate nucleus and putamen (striatum), and is more prevalent in men. Idiopathic Parkinson disease with dementia can show hypoperfusion patterns similar to those observed in AD, but basal ganglia hypoperfusion is far more frequent, as is frontal precentral hypoperfusion [32].

Dementia is also part of the clinical manifestation of some types of Parkinsonism such corticobasal degeneration in which bilateral and symmetrical hypoperfusion of the frontal, parietal lobe and basal ganglia are present. There is symmetrical severe basal ganglia hypoperfusion also affecting the mesial regions of the frontal lobes in supranuclear palsy. The hallmark finding in multiple system atrophy is cerebellar hypoperfusion, besides symmetric basal ganglia hypoperfusion [33].

Mixed Dementia: the association of AD and vascular dementia is the commonest cause of mixed dementia. Idiopathic normal pressure hydrocephalus is characterized by late onset, surgically treated progressive neurodegenerative disease caused by inadequate cerebrospinal fluid (CSF) dynamics and ventriculomegaly while other types including low pressure hydrocephalus are usually secondary to head injury, subarachnoid hemorrhage, infections, and other problems that cause an accumulation of the cerebrospinal fluids (CSF) in the ventricular system of the brain mainly associated to its impaired drainage. Wernicke encephalopathy and Korsakoff syndrome (Wernicke-Korsakoff syndrome) and Alcohol related dementia are preventable, life-threatening neuropsychiatric syndromes resulting from thiamine deficiency mainly in patients with chronic alcoholism, anorexia nervosa or patients that have undergone bariatric surgery for obesity, chronic hepatic disease, immunodeficiency syndromes, nutritional deficiencies of any cause, metastatic carcinomas, hyperthyroidism, prolonged parenteral nutrition, hyperemesis gravidarum, long-term dialysis and diuretic therapy among other causes and clinically, patients' complaints about short-term memory, confusional states, and neuropsychiatry manifestations, HIV-associated neurocognitive disorders (HAND). Many of the complications secondary to HIV-1 infection (including all opportunistic infections) have decreased dramatically excepting HAND which is quite common CNS disorder caused by HIV infection. Huntington disease: in our series of patients presenting Huntington's disease (HD), an important number of them do not have extrapyramidal signs of chorea. Frontotemporal dementia: patients with the different diseases in this group present severe bilateral hypoperfusion in the frontal lobes, predominantly in the mesial structures [34].

We comment about Creutzfeldt Jacob Disease as an extremely uncommon degenerative disorder due to a slow virus (prion) infection that affects the brain and it is also known as mad cow disease. The diagnosis of CJD is usually made when patient older than 60-year-old died and the spongiform changes in the brain post-mortem examination are confirmed. We also discussed about the available update information on the commonest cognitive screening test used to evaluate cognition, and finally we documented our conclusion from previous investigations done.

In the chapter titled "Identification of cognitive impairment markers (Neurospecific proteins, Magnetic Resonance Image) in patients with Diabetes Mellitus type 1," the authors studied

the effects of metabolic disorders on the development of cognitive disorders in patients presenting the abovementioned disorder. They concluded that chronic hyperglycemia and glucose variability are risk factors for the development of cognitive dysfunction, which confirm the need for more severe compensation of the disease. They also highlighted: "For type 1 diabetic patients with unsatisfactory compensation of carbohydrate metabolism the neurophysiological tests looking for cognitive decline should be done."

In the chapter: Dementia Friendly Assistive Brotherhood Communities, authors from Bournemouth University in United Kingdom highlighted the usability of an assistive software application developed for 8 patients living with dementia (PWLD) and 40 volunteers at 5 different cities of Pakistan.

Overall, the PWLD showed great interest in all the functionalities of the assistive brotherhood community application and were keen to adopt it permanently in their daily life activities. The PWLD specifically appreciated the increased socialization opportunities through the use of assistive brotherhood community application. The implementation of assistive brotherhood community application in the lives of the PWD will increase their confidence, self-esteem, and independence.

Another important chapter on Re-framing and Re-thinking Dementia in the Correctional Setting is written by two authors from University of Adelaide and University of South Australia. They raise the concern about the aging population in the Australian correctional setting. They highlighted the increasingly complex healthcare needs in the prisoner population who present with poorer physical, social, and mental health than the general population, and they also concluded that healthcare services within the correctional environment needs to match that in the general community and this requires the development of policies to support staff to put processes in place that will improve health outcomes for prisoners.

One chapter written by two Korean colleagues from Korea Institute of Science and Technology cover the most relevant aspects of Tau in Tauopathies that leads to Cognitive Disorders and in Cancer. They refer Tau as a copious microtubule-associated protein mainly expressed in neurons; it is also expressed in non-neuronal cell. Tauopathies are neurodegenerative diseases occurring mostly within the neuronal and glial cells of the central nervous system with a conspicuous tau pathology. Tau might have significant functions in non-neuronal cells. In this chapter, authors describe the associations between tauopathies and cancer.

Nowadays, some drugs used for the treatment of cancer are also used for the treatment of different neurological disorders like Parkinson's disease and AD. They said that Nilotinib is an FDA-approved protein tyrosine kinase inhibitor (TKI)—used for the treatment of chronic myeloid leukemia but it also targets AD and produces neuroinflammation and misfolded proteins that ultimately reduce cognitive damage. In Parkinson's disease, nilotinib triggers autophagy to remove hyperphosphorylated tau from the brain before they accumulate as plaques.

The hypothalamus plays a central role in autonomic functions, including the generation and control of the circadian rhythms, the thermoregulation, the homeostasis of proteins, the maintenance of energy supply and the feeding behavior. Five authors from Aristotelian University,

Department of Neurology, Laboratory of Neuropathology and Electron Microscopy in Greece afforded this topic (The hypothalamus) and the AD and made a Golgi and electron microscopic study.

They found that the pathological alterations of hypothalamic nuclei in AD would induce the autonomic instability, which would be particularly prominent at the advanced stages of the disease, aggravating the clinical condition of the patients exceedingly, a fact which is also observed in experimental models of AD as well as in the behavioral variant of frontotemporal dementia.

Finally, they concluded that a serious autonomic dysfunction in advanced stages of AD compose the tragic epilogue of the disorder which is related with the involvement of the hypothalamus during the continuous pathological process of the disease.

Other authors from New Zealand made a study about "Effective Restoration Home Support for Older Peoples Living with Dementia and their Caregivers." One of the most relevant aspects of this investigation was the identification of 10 key factors supporting the adequate restorative home support services for those patients. Its grouped in three primary headings that are congruent with the information published in the medical literature, and they have international implications which include policy and practice that keep the needs and well-being of the dementia diagnosed person and their caregiver central to all decision-making and keeping track of their progression. They also agreed that local solution will influence future decision-making, and this is one of the most important aspects that this chapter highlighted.

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Chapter 2

Cognitive Impairment in Patients with Diabetes Mellitus

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Additional information is available at the end of the chapter

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Abstract

Diabetes mellitus (DM) is a risk factor for the development of cognitive impairment, when unsatisfactory glycemic control is associated with glioma biomarkers and changes in neuronal integrity. Given some limitations in the performance of neuropsychological testing, it is important to indicate specific markers of brain damage.

Keywords: diabetes mellitus, cognitive disorders, neurospecific proteins, magnetic resonance imagining

1. Introduction

One of the most significant in the social aspect of the categories in the population was and still is patients with diabetes mellitus (DM). According to the estimates of the International Diabetes Federation, there are 415 million people with diabetes in the world in 2015, and by 2040, it is projected to grow to 642 million people. In the last decade, it has been proven that diabetes mellitus causes disturbances in the functioning of regulatory systems and the psychological and emotional state has both direct and indirect effects on the development of

complications from the central nervous system, manifested by morphological and functional disorders. The reflection of brain neuroplasticity is the dynamics of cognitive impairment.

According to the latest revision of the international guidelines for the diagnosis of mental disorders, cognitive disorders include a decrease in one or more higher cerebral functions, in comparison with the premorbid level, that provide the processes of perception, preservation, transformation, and transmission of information. The presence of cognitive impairments has an extremely negative effect on the quality of life of the patient and their immediate family and complicates the treatment of concomitant diseases and the conduct of rehabilitation activities. Therefore, timely diagnostics and the earliest possible initiation of therapy for existing cognitive disorders are very important.

Figure 1 shows that the effect of dysglycemia in the debut of type 1 diabetes mellitus, especially in childhood, leads to a statistically more significant pronounced cognitive impairment, as well as structural changes in the brain over time [1].

To date, it is urgent to search for a quick, simple, and well-tried method for diagnosing cognitive impairment, taking into account the minimum costs. One of the promising methods that can be considered is the identification of neurospecific proteins, which are signals of brain damage [2–4]. To diagnose central nervous system diseases, magnetic resonance methods of brain examination are used as additional techniques for detecting morphological changes [5, 6].

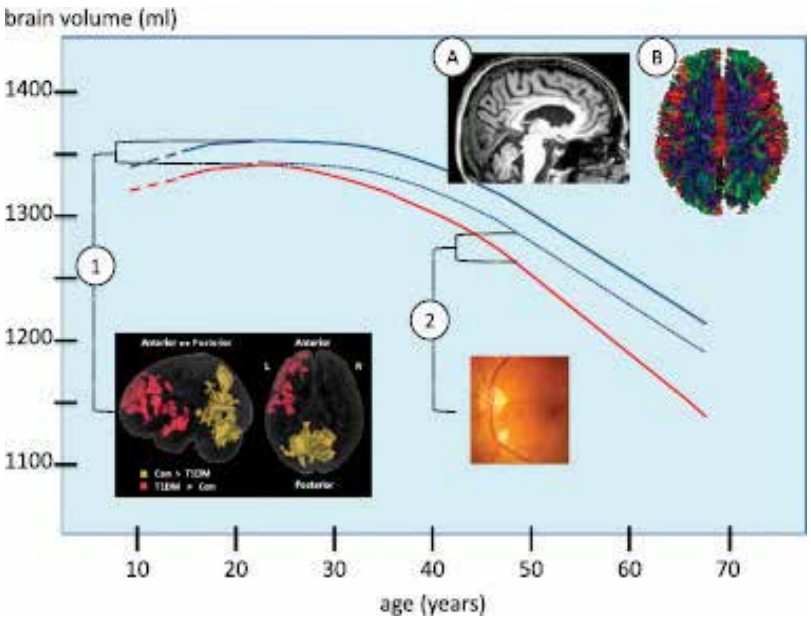

Figure 1. The trajectory of disorders from the brain's magnetic resonance imaging data in patients with type 1 diabetes mellitus is associated with loss of brain volume (blue line, evolution of brain volumes with age in the general population, and red line, estimated trajectories for type 1 diabetes mellitus (A), and brain atrophy is a loss of neuron communication (B)) [1].

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2. Pilot study: identification of cognitive impairment markers (neurospecific proteins, magnetic resonance tomography) in patients with type 1 diabetes mellitus

The study of cognitive dysfunction in patients with type 1 DM was carried out at the clinical bases of the Departments of Endocrinology and Diabetology, Neurology and Neurosurgery of the Siberian State Medical University, and the plan and the study were in full compliance with the principles of Good Clinical Practice (GCP) and Helsinki Declaration (including amendments).

The study included 116 patients with type 1 diabetes mellitus at the age of 22.4 ± 4.6 years, 58 men and 58 women, and the duration of the disease was 6.6 ± 3.9 years. The control group consisted of 29 healthy people, aged 22.4 ± 4.8 years, 14 men and 15 women, without acute and chronic diseases. Inclusion criteria are patients with type 1 diabetes mellitus at the age of 16–30 and signed informed consent of the patient to participate in the study.

Exclusion criteria are hypoglycemic and ketoacidotic coma for 1 year prior to study; presence of hematological, oncological, and serious infectious diseases; condition after severe cranioce-rebral injuries and surgeries; participation in other clinical trials in the last 30 days; and now refusal to sign an informed consent of the patient to participate in the study.

To detect violations of carbohydrate metabolism, glucose was determined by the glucose oxidase method on the biochemical analyzer "Hitachi 912" (Hoffmann-La Roche Ltd./Roche Diagnostics GmbH, Germany). HbA1c content was analyxed in capillary blood - by liquid chromatography method on DS5 Glycomat analyzer (Drew Scientific, the Netherlands).

With the biochemical methods of research, the content of neurospecific proteins in plasma was determined. To analyze the quantitative content of the S100 protein (S100A1B + S100BB), a kit was used (FujirebioS100 EIA, BioC himMak, Russia). GFAP was determined by enzyme immunoassay using a standard protocol using a reagent kit from the manufacturer (BioVendor Laboratory Medicine, Inc., Germany). The myelin basic protein (MBP) level was studied using the "DSL-10-58,200" kit (BioChimMak, Russia). The complex of mandatory diagnostic methods included magnetic resonance imaging of the brain on the Harmony 1.0 T apparatus (Siemens, Germany) by MDCS-Tomsk Ltd., which was carried out according to the standard procedure in the axial, sagittal, and coronal projections using T2 (TR (time of repetition) 4932 ms, TE (Echotime) 90 ms) and T1 (TR 280 ms, TE 6.1 ms) and using programs with free water signal suppression fluid-attenuated inversion recovery (FLAIR; TR 8000 ms, TE 105 ms, TI (time in version) 2200 ms). Evaluation of gliosis foci of brain substance was carried out according to the size and quantity in the frontal (subcortical, paraventricular), temporal (white matter, hippo-campal area), parietal (subcortical, paraventricular), and occipital (subcortical, paraventricular) areas. Taking into account the classification of F. Fazekas, in the modification of NN Yakhno, a quantitative gradation of focal changes in the white matter was carried out [7]. The severity of leukoareosis was assessed in scores proposed by Liu et al. [8]. For the quantitative evaluation of the expansion of perivascular spaces, the estimated scale of MacLullich [9] was used.

Screening for mild and moderate cognitive impairment was performed using the MoCA test, which assesses various cognitive functions: visual–spatial perception (the test of drawing a clock and a cube); executive functions (task of creating an alternating path and testing the ability to abstract thinking); attention, concentration, and operational memory (serial subtraction by 7 and playback of the digital series in forward and reverse order); and speech (naming animals, repetition of two syntactically complex sentences) and the specificity of the method is 90% [10]. Statistical processing of the obtained data was carried out using the application software package R Systems International.

Characteristics of the carbohydrate metabolism parameters showed a difference in the parameters between the main group and the control group. The average level of HbA1c in patients with type 1 diabetes mellitus was 8.8 ± 1.8%, and the average level of fasting glycemia was 11.5 ± 5.0 mmol/l. This indicated an unsatisfactory metabolic control. In addition, differences in the parameters of carbohydrate metabolism were revealed taking into account gender characteristics, so women had better values of fasting and HbA1c glycemia than men.

In the control group, healthy volunteers complained of asthenic syndrome (37.9%), manifestations of which were fatigue (13.3%), dizziness (6.7%), and headache (16.9%). Patients with type 1 diabetes mellitus also had these complaints but in a more pronounced form. The next in frequency recorded cephalic syndrome, occurring in 25.9% of patients. Among the localizations, the most frequent areas were occipital (60%) and temporal (2.6%) areas, with the same frequency; headache was diffuse and was found in the frontal region. The most common cause of headache was overexertion due to stress. In addition, complaints were found from the peripheral nervous system on paresthesia (37.9%), pain (22.4%), numbness (12.1%), and convulsions in the lower extremities (6.9%). Often, patients with type 1 diabetes mellitus complained of memory loss. This was manifested by the difficulty in concentrating, remembering new information, and solving short-term problems. The objective status of patients was characterized by autonomic symptoms, manifested as anxiety. Neurological symptoms of the examined patients were mainly represented by disorders of the autonomic nervous system, namely, distal and diffuse hyperhidrosis (in 43.1% of patients) and persistent red spilled dermographism (in 22.4% of patients) in the face, neck, and décolleté area. The manifestations of lesions of the peripheral nervous system were in the form of diabetic polyneuropathy. Sensory disorders were noted from the lower extremities in 62% of cases and the upper ones in 27.5%. A clinical study of random movements in the limbs with an evaluation of the tone revealed a hypotonia of the upper limbs in 51.7% and lower in 34.5% of cases.

2.1. An analysis of the neuropsychological status in patients with type 1 diabetes mellitus

This study based on the results of a screening MoCA test showed that type 1 diabetes mellitus may manifest cognitive dysfunction in 72.4% of cases. Thus, one-third of patients with type 1 diabetes mellitus had cognitive dysfunction compared to the control group (**Table 1**).

When assessing the individual tasks of the MoCA test, a statistically significant decrease in the parameter of the short-term memory was registered. The exercise included memorizing

Parameters	Type 1 DM (n = 98)	Control group (n = 29)
Alternating Trail Making	3.0 ± 0.4	3.0 ± 0.1
Alternating path (drawing)	3.0 ± 0.8	3.0 ± 0.1
Cube (drawing)	3.0* ± 1.3	5.0 ± 0.2
Clock (drawing)	2.0* ± 0.6	2.0 ± 0.1
Naming	1.0 ± 0.9	1.0 ± 0.1
Memory	2.0* ± 0.8	3.0 ± 0.1
Number series	2.0 ± 0.4	1.8 ± 0.4
Concentration	1.0 ± 0.8	0.8 ± 0.3
Serial subtraction by 7	2.0 ± 0.4	2.0 ± 0.1
Repeat suggestions	6.0 ± 0.2	6.0 ± 0.1
Fluency of speech	25.0* ± 0.8	30* ± 0.4
Abstraction	3.0 ± 0.4	3.0 ± 0.1
Orientation	3.0 ± 0.8	3.0 ± 0.1
Sum of points	3.0* ± 1.3	5.0 ± 0.2

Note: The significance of differences between the control group and patients with type 1 diabetes mellitus at the parameters of MoCA test: *$p < 0.001$, m is the median, and SD is the standard deviation.

Table 1. Characteristics of the MoCA test parameters in patients with type 1 diabetes mellitus and control group.

five words and repeating them after subsequent tasks in about 5 minutes. Patients with type 1 diabetes mellitus had difficulty in reproducing words, were confused, and invented new words. At the same time, this task was performed unsatisfactorily by both men and women. The attention function was evaluated using two tasks. The first task is a numerical series, that is, a repetition of the numbers mentioned. With this task men were worse than women. The second task is the serial subtraction by 7, which was given equally hard.

2.2. Analysis of parameters of neurospecific proteins in patients with type 1 diabetes mellitus

As a result of the analysis, a significant increase in all studied proteins was revealed in patients with type 1 diabetes mellitus, S100, MBP, and GFAP, compared to the control group ($p < 0.001$) (**Table 2**).

The levels of neurospecific proteins, depending on the duration of the disease, had fluctuations. So, the S100 protein was higher in patients with a short duration of the disease (1–4 years) and the smallest with duration of the disease for more than 15 years. While MBP had an equally stable level in patients with different durations of type 1 diabetes mellitus. The fluctuations in the level of GFAP were also insignificant and tended to decrease with increasing duration of the disease. According to our study, in women, the level of GFAP was significantly lower than in men ($U = 643.0$, $z = -2.4$, $p < 0.05$).

Neuro-specific proteins	Type 1 DM (n = 98)	Control group (n = 29)
	0.13 ± 0.05*	**0.10 ± 0.036**
Myelin basic protein (MBP) (ng/ml)	0.12 ± 0.04*	0.08 ± 0.033
Glial fibrillary acidic protein (GFAP) (ng/ml)	125.65 ± 66.97*	62.85 ± 19.66
S100 (ng/ml)	0.13 ± 0.05*	0.10 ± 0.036

Note: The significance of differences between the control group and patients with type 1 diabetes mellitus at the level: *$p < 0.01$.

Table 2. Characteristic levels of neurospecific proteins in patients with type 1 diabetes mellitus and the control group.

2.3. Characteristics of magnetic resonance imaging of the brain in patients with type 1 diabetes mellitus and in control group

Analysis of magnetic resonance imaging of the brain revealed indirect signs of atrophy of the gray matter of the frontal and partly parietal lobes. Thus, in patients with type 1 diabetes mellitus, arachnoid changes (93.1%) and expansion of the convective liquor spaces (72.4%) were significantly more frequent. In the control group, changes in thearachnoid changes were detected in 67% (**Table 3**). **Figure 2** in the coronal projection (mode T2) shows the expansion of the convective fluidic spaces.

MRI of the brain showed the presence of gliosis sites in 15.5% of cases and lesions of leukoareosis in 18.3% of cases in patients with type 1 diabetes mellitus, whereas in the control group no changes were revealed (**Table 3**). In **Figure 3**, in the axial projection (FLAIR mode) in the white matter of the frontal and parietal lobes, small foci of a dystrophic character are defined.

In **Figure 4**, coronal lesions are identified in the coronal projection. According to the classification proposed by Lui, the severity of leukoareosis is two points.

Perivascular spaces of Virchow-Robin are a morphological and functional structure of the central nervous system; therefore, various versions of their dilatation can be an indirect reflection of changes in the brain substance and indicate atrophy. In the study, expansion of Virchow-Robin spaces occurred in 80.6% of cases in patients with type 1 diabetes mellitus, which was significantly higher than in the control group, 6.7%, respectively (**Table 3**).

These changes are shown in **Figure 5**, where in the coronal projection in the thalamus region, nonuniformly expanded Virchow-Robin spaces are determined from both sides. Given the classification of MacLullich, they are estimated at 2 points.

Thus, according to MRI, the morphological changes in the brain in patients with type 1 diabetes mellitus are represented by arachnoid changes in the liquor cystic, the expansion of the convective spaces, and the Virchow-Robin spaces of the brain.

2.4. Interrelations of clinical-metabolic, neuropsychological features and markers of cognitive impairment in patients with type 1 diabetes mellitus

When evaluating the results, a negative correlation was found between the fasting glycemia and HbA1c levels with the test parameters responsible for memory and attention (task for

Indicators	Type 1 DM (n = 98)	Control group (n = 29)	$\chi 2$
Arachnoidal changes in the cerebrospinal fluid	108 (93.1%)	2 (6.7%)	$\chi 2$; p
Expansion of convective fluidic spaces	71 (72.4%)	0 (0%)	$\chi^2 = 63.84$; $p = 0.01$
Expansion of Virchow-Robin spaces	79 (80.6%)	2 (6.7%)	$\chi^2 = 43.4$; $p = 0.01$
Gliosis	15 (15.3%)	0 (0%)	$\chi^2 = 4.32$; $p = 0.01$
Leukoareosis	18 (18.3%)	0 (0%)	$\chi^2 = 5.19$; $p = 0.02$

Note: The significance of the differences between the control group and patients with type 1 diabetes mellitus at the level: $^{*}p < 0.001$.

Table 3. Characterization of the magnetic resonance pattern of the brain of patients with type 1 diabetes mellitus in comparison with the control group.

number series and serial subtraction). That is, the higher the levels of carbohydrate metabolism, the worse the memory and attention are (**Table 4**). On the part of other indicators of the MoCA, the connection was not found.

In assignments for attention, a negative correlation was found only with the protein S100 ($r = -0.3$, $p = 0.02$, $r = -0.3$, $p = 0.004$). We revealed relationship between the decrease in memory functions and the increase in the level was the decrease in memory functions with a simultaneous increase in the level of the studied neurospecific proteins, that is, the presence of a negative correlation with the S100 ($r = -0.4$, $p = 0.001$), GFAP ($r = -0.4$, $p = 0.02$), and MBP ($r = -0.5$, $p = 0.001$) proteins.

To assess the significance for the diagnosis of proteins, sensitivity and specificity were assessed. It was shown that they are highly specific and have a moderate sensitivity (**Table 5**).

Thus, in patients with type 1 diabetes mellitus and identified cognitive dysfunction, an increase in the content of all neurospecific proteins against hyperglycemia is characteristic. Based on the assessment of specificity and sensitivity, a high level of diagnostic significance of neurospecific proteins is shown, which makes it possible to use them in general medical practice.

When evaluating the effect of carbohydrate metabolism parameters on the change in the results of magnetic resonance imaging of the brain in patients with type 1 diabetes mellitus, positive correlation relationships were recorded. Thus, moderate strengths between the expansion of the cerebrospinal fluid and the level of HbA1c ($r = 0.6$, $p = 0.001$) and fasting glycemia ($r = 0.5$, $p = 0.001$) were revealed. In addition, connections have also been found with extensions of the Virchow-Robin spaces ($r = 0.6$, $p = 0.001$, $r = 0.5$, $p = 0.001$) and convective spaces ($r = 0.5$, $p = 0.004$, $r = 0.3$, $p = 0.003$) with the indices of carbohydrate metabolism. Analysis of the effect of cognitive dysfunction on the results of magnetic resonance imaging of the brain showed the presence of a bond. A correlation was found between memory loss in patients with type 1 diabetes mellitus and the expansion of arachnoid ($r = -0.3$, $p = 0.02$) and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$). A link was also found between the decrease in attention and atrophy of gray matter in the brain in patients with type 1 diabetes mellitus. Patients with an expansion of arachnoid ($r = -0.3$, $p = 0.007$), convective spaces

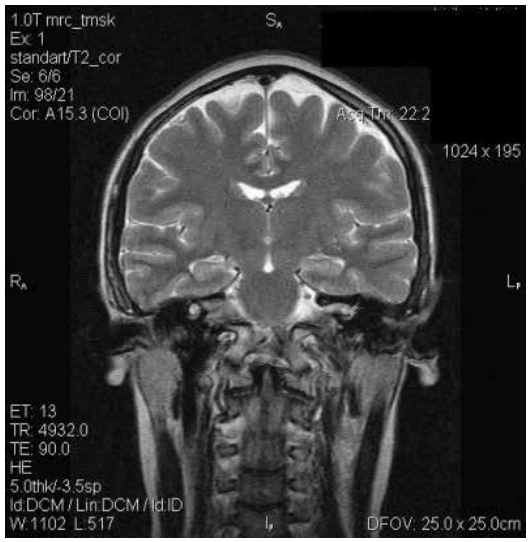

Figure 2. A snapshot of the brain in the coronal projection in T2 mode is determined by the expansion of the convective fluidic spaces (photo by Matveeva, 2015).

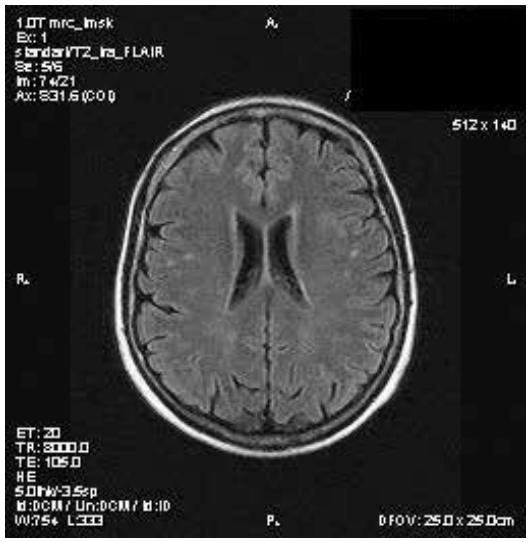

Figure 3. A snapshot of the brain in the axial projection in the FLAIR mode in the white matter of the frontal and parietal lobes is determined by small foci of increased signal on T2 and FLAIR, without signs of perifocal edema, of a dystrophic nature (photo by Matveeva, 2015).

(r = −0.3, p = 0.007), and Virchow -Robin spaces were worse performing the tasks for attention ("numerical series" and "serial subtraction" by 7) (r = −0.3, p = 0.007). To assess the significance of changes reflected in magnetic resonance imaging of the brain in patients with type 1 diabetes

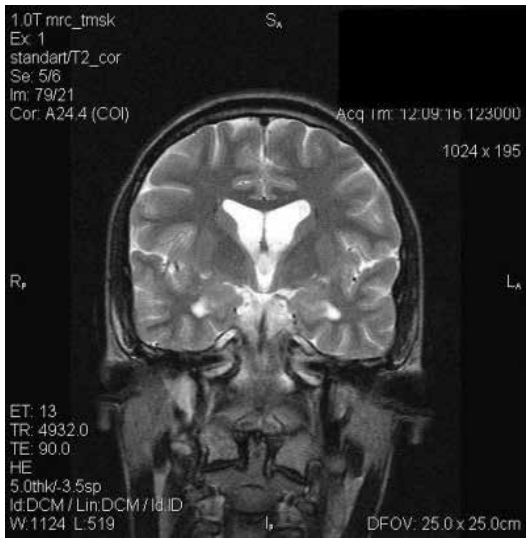

Figure 4. A snapshot of the brain in the coronal projection in T2 mode in the white matter of the frontal and parietal lobes,; the focus of the leukoareosis is determined by the severity of two points [8] (photo by Matveeva, 2015).

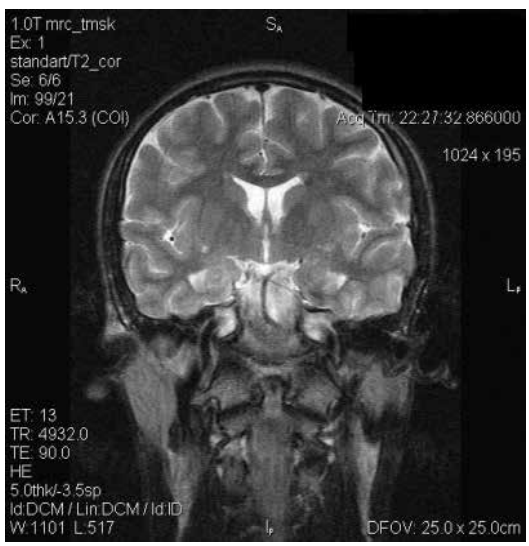

Figure 5. A snapshot of the brain in the coronal projection in the T2 mode in the thalamus region on both sides of unevenly expanded Virchow-Robin spaces is determined (two points according to MacLullich (2003)) (photo by Matveeva, 2015).

mellitus, sensitivity and specificity were assessed. Morphological signs of gray matter atrophy of the brain, namely, arachnoid changes in the liquor cystic nature, widening of the convective spaces, and Virchow-Robin spaces, are highly sensitive, but are not specific (**Table 6**).

	S100	MBP	GFAP
HbA1c	r = −0.69; p = 0.01	r = −0.30; p = 0.01	r = −0.35; p = 0.04
Fast glucose	r = −0.45; p = 0.02	r = −0.36; p = 0.01	r = −0.31; p = 0.01

Note: The significance of the correlation: *p < 0.05.

Table 4. Interrelation of the parameters of the MoCA test with HbA1c and fasting glycemia.

Thus, the obtained data showed the relationship of gray matter atrophy of the brain magnetic resonance imaging in patients with type 1 diabetes mellitus with chronic hyperglycemia and cognitive impairment. In addition, nonspecificity of the revealed changes was revealed in patients with type 1 diabetes mellitus in comparison with the control group.

2.5. Comparison of the results and literature data

As methods for finding markers of cognitive impairments, neurophysiological and biochemical methods with certain limitations are described in the literature. We conducted a comprehensive study that included as a neuropsychological technique a screening MoCA test, an evaluation of neurospecific proteins, and a magnetic resonance imaging data in patients with type 1 diabetes mellitus. In our study, screening for cognitive dysfunction with the MoCA test showed a decrease in only memory function and attention in patients with type 1 diabetes mellitus, while other functions were not impaired. Analysis of the relationship of cognitive dysfunction with sex, age, and duration of the disease did not reveal these. The results confirm the meta-analysis conducted in 2007 by Brands and Bissels, where it was shown that there were moderate cognitive impairments that did not manifest themselves in daily life, but influenced the professional sphere, where high concentration, attention, and memory are required [1]. The question of the metabolic component as the cause of the development of cognitive dysfunction for a long time was debatable. The data obtained in this study on cognitive dysfunction allowed a mathematical analysis of the effect of carbohydrate metabolism on it and the effect of hyperglycemia on the development of cognitive dysfunction in patients with type 1 diabetes mellitus. In patients with type 1 diabetes mellitus, Russian scientists also noted a decrease in memory function, which worsened with chronic hyperglycemia [11]. In the endocrine community, a large-scale study on the control and complications of diabetes (DCCT/EDIC) is considered authoritative [12], which confirmed the absence of the effect of hypoglycemia on the development of cognitive dysfunction. The analysis of additional markers of cognitive dysfunction was carried out with the help of biochemical methods, which made it possible to evaluate neurospecific proteins. In patients with type 1 diabetes mellitus, S100, GFAP, and MBP proteins were elevated, which may indicate microscopic brain damage. One of the proteins studied was S100; as a result, it was found that patients with unsatisfactory control of carbohydrate metabolism had higher levels of S100 protein. So, a positive correlation of S100 protein with the HbA1c level and fasting glycemia was found, which can prove the role of chronic hyperglycemia in the dysmetabolic processes of the brain. A study of this protein in patients with type 1 diabetes mellitus was also conducted by Strachan (2000) [13], but significant changes in groups with

NSP	Value	Sensitivity (%)	Specificity (%)
MBP ng/ml	0.1025	45.7	81
GFAP ng/ml	0.106	41.3	76.2
S100 ng/ml	65.15	58.7	95.2

Table 5. Characteristics of specificity and sensitivity of neurospecific proteins as markers of cognitive dysfunction.

type 1 diabetes have not been found [13]. Comparison of MBP with HbA1c and fasting glucose showed a positive correlation. Most likely, fluctuations in glycemia caused damage to the oligodendrocytes of the brain with the release of more MBP. In the literature, such data were not found. A third, but no less important, protein was the GFAP marker for astrocyte damage. In our study, a positive correlation was found between the parameters of carbohydrate metabolism and the level of GFAP, which indicates the effect of hyperglycemia on the mechanisms of apoptosis of astrocytes. The results obtained are confirmed by the studies of F.E. Saravia and coauthors; they showed the effect of hyperglycemia on higher amounts of GFAP during the manifestation of type 1 diabetes mellitus, when uncompensated hyperglycemia is observed, that is, hyperglycemia has the greatest impact on brain damage [14].

As an additional method for evaluating cognitive dysfunction, magnetic resonance imaging of the brain was proposed; this was performed according to a standard procedure, that is, as screening without additional functional options. As a result of the study, signs of cerebral atrophy were found, namely, arachnoid changes in the liquor cystic and expansion of the convective fluidic spaces, which correlates with the data of the special literature [15]. The data obtained during the study confirm the presence of indirect signs of cerebral atrophy in patients with type 1 diabetes mellitus of a nonspecific type. In addition, the literature addresses the duration of type 1 diabetes mellitus and the possible weighting of morphological changes. In our study, the association with age and duration of the disease was not revealed. However, Trofimova et al. found that the degree of severity of structural changes in the brain substance is associated with the progression of type 1 diabetes mellitus and with an increase in the age of the patients [16]. In the study, an evaluation of the influence of glycemia on the morphological structure of the brain showed the relationship of hyperglycemia with the expansion of fluidic spaces, convective spaces, and Virchow-Robin spaces. In the literature, cases of atrophy of the gray matter of the brain, which was detected predominantly in the frontal lobes and central areas of the parietal lobes [17], is described, both in acute cases of ketoacidosis and prolonged increase in HbA1c. In addition to the relationship with the parameters of carbohydrate metabolism, the analysis revealed the relationship of cognitive impairments to brain atrophy, which was also noted in the publications of Hoogma [18]. In our study, there was a correlation of memory loss in patients with type 1 diabetes mellitus with an expansion of arachnoid and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$). Also, a connection was found between poor performances of tasks for attention (numerical series and serial subtraction by 7) by patients with the expansion of arachnoid, convective spaces, and Virchow-Robin spaces ($r = -0.3$, $p = 0.007$).

Indicators	Sensitivity (%)	Specificity (%)
Arachnoidal changes in the cerebrospinal fluid	92	37
Expansion of convective fluidic spaces	73	26
Expansion of Virchow-Robin spaces	78	34
Gliosis	11	17
Leukoareosis	21	43

Table 6. Characteristics of specificity and sensitivity of signs of magnetic resonance imaging.

3. Pilot study: the role of glycemia variability in development of cognitive disorders in patients with type 1 diabetes mellitus

Design: observational, transverse, and one-stage study. Clinical characteristics of patients is as follows: 30 patients with type 1 diabetes mellitus at the age of 27 (22–31) years and duration of the disease 17 (5–23) years; among them 14 men and 16 women were examined. Patients were divided into two groups: the first group (main)—with the presence of cognitive impairment, and the second group (control)—with normal cognitive functions.

For the diagnosis of fluctuations in the glucose level, continuous monitoring of glycemia was conducted using the iPro2 device (Medtronic, USA) and the CareLink iPro™ software, as well as the Medtronic MiniLink and MMT-700 transmitter, and the Medtronic Diabetes CareLink USB device. Fixation of data on the level of glycemia was carried out at a 5-minute interval for 72 hours using a system of constant monitoring of glycemia. We used the EasyGV calculator (version 9.0), proposed by Hill (2011) [26] (**Figure 6**).

The following glucose variability values were assessed: mean glycemic mean (MEAN), standard deviation (SD), mean amplitude of glycemic fluctuation (MAGE), long-term glycemic index (CONGA), glycemia lability index (LI), hypoglycemia risk index (LBGI), an index of risk of hyperglycemia (HBGI), and average hourly rate of change in glycemia (MAG).

The study found that patients with type 1 diabetes mellitus among the main group of cognitive disorders prevailed violation constructive praxis, memory, and attention. The average score in this group was 23.8 ± 0.66, while in the control group, it was 26.4 ± 0.13 points, respectively ($t = 3.6$, $p = 0.001$) (**Table 7**). In the study of HbA1c in plasma, the mean level in the main group was 10.5 ± 1.3%, and in the control group 6.7 ± 0.23% ($t = -2.5$, $p = 0.015$).

The analysis of the GV indicators is presented in **Table 8**. There is a significant difference in MEAN, SD, CONGA, Gindex, LBGI, HBGI, MAGE, Mvalue, and MAG.

Correlation analysis shows that cognitive functions are generally affected by the level of HbA1c ($\chi 2 = -0.450$, $p = 0.014$), as well as the MEAN variability parameters ($\chi 2 = -0.584$, $p = 0.001$), SD ($\chi 2 = 0.022$, $p = 0.022$), CONGA ($\chi 2 = -0.853$, $p = 0.001$), Gindex ($\chi 2 = -0.504$, $p = 0.005$), LBGI ($\chi 2 = -0.451$, $p = 0.014$), HBGI ($\chi 2 = -0.053$, $p = 0.003$), MAGE ($\chi 2 = -0.480$, $p = 0.008$), Mvalue ($\chi 2 = -0.593$, $p = 0.001$), and MAG ($\chi 2 = -0.573$, $p = 0.001$).

Figure 6. Example of a glycemic profile according to iPro data.

On the constructive praxis in the job, the alternating path is most affected by the CONGA parameter ($\chi2 = -0.502$, $p = 0.006$) and MAGE ($\chi2 = -0.555$, $p = 0.002$), and the clock is MEAN ($\chi2 = -0.379$, $p = 0.043$), LI ($\chi2 = -0.471$, $p = 0.010$), Gindex ($\chi2 = -0.497$, $p = 0.006$), LBGI ($\chi2 = -0.477$, $p = 0.009$), HBGI ($\chi2 = -0.384$, $p = 0.040$), MAGE ($\chi2 = -0.386$, $p = 0.038$), Mvalue ($\chi2 = -0.446$, $p = 0.002$), and MAG ($\chi2 = -0.505$, $p = 0.005$). To reduce memory, the MEAN indicator is most important ($\chi2 = -0.455$, $p = 0.013$). Violation of the task of repeating the phrase depends on the level of HbA1c ($\chi2 = -0.390$, $p = 0.036$), LI ($\chi2 = -0.463$, $p = 0.011$), LBGI ($\chi2 = -0.604$, $p = 0.001$), MAGE $\chi2 = -0.422$, $p = 0.031$), Mvalue ($\chi2 = -0.483$, $p = 0.008$), and MAG ($\chi2 = -0.501$, $p = 0.002$). The assignment of MoCA test (repeating speech) depends on the level of HbA1c.

The study showed a decrease in cognitive functions in (constructive praxis, repetition, and memory) in patients with type 1 diabetes mellitus. The currently available markers for the control of glycemia-HbA1c do not always reflect an excursion of hyperglycemia and hypoglycemia [19].

Parameters	The main group	The control group
Alternating path (drawing)	0.26 ± 0.11*	0.92 ± 0.07
Cube (drawing)	1.00 ± 0.00	1.00 ± 0.00
Clock (drawing)	2.60 ± 0.13*	2.14 ± 0.09
Naming	3.00 ± 0.00	3.00 ± 0.00
Memory	2.80 ± 0.32*	3.64 ± 0.24
Number series	1.80 ± 0.10	1.92 ± 0.71
Concentration	1.13 ± 0.13	1.14 ± 0.14
Serial subtraction by 7	2.66 ± 0.18	2.92 ± 0.07
Repeat suggestions	1.46 ± 0.13*	1.07 ± 0.07
Fluency of speech	0.66 ± 0.12	0.92 ± 0.07
Abstraction	1.53 ± 0.19	1.50 ± 0.13
Orientation	0.26 ± 0.11*	0.92 ± 0.07
Sum of points	1.00 ± 0.00	1.00 ± 0.00

Note: *$p \leq 0.05$.

Table 7. Characteristics of parameters of the Montreal scale of cognitive functions in the main and control groups.

Parameters	The main group	The control group	Significance
MEAN	9.17 (8.36–10.00)	7.25 (6.77–7.87)	U = 29, p = 0.001
SD	4.54 (3.86–5.79)	2.95 (2.61–3.47)	U = 26, p = 0.001
CONGA	6.66(5.77–7.81)	4.32 (4.15–4.51)	t = −4.9, p = 0.001
LI	22.35 (20.76–92.99)	27.17(22.84–55.68)	U = 98.5, p = 0.776
Gindex	56.41 (52.00–79.69)	45.50 (36.85–50.76)	U = 43, p = 0.007
LBGI	11.16 (8.24–17.26)	6.77 (4.44–7.53)	U = 53.5, p = 0.023
HBGI	13.19 (11.01–21.25)	8.00 (6.91–10.45)	U = 43, p = 0.006
MAGE	4.86 ± 0.23	2.44 ± 0.13	U = 34, p = 0.002
Mvalue	28.38 (20.46–26.90)	14.43 (11.92–17.04)	U = 124.5, p = 0.001
MAG	59.60 (53.54–88.43)	34.60 (30.83–42.17)	t = −8.5, p = 0.001

Note: Mann-Whitney U test, Student's t-test.

Table 8. Characteristics of VG indicators by groups.

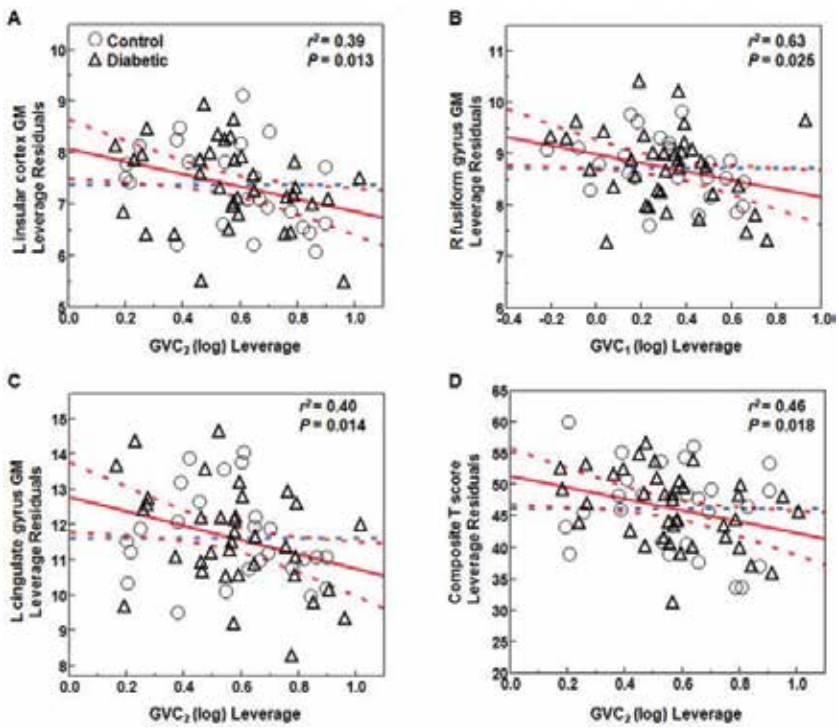

Figure 7. Examples of models with the smallest squares indicating a negative relationship between a multi-scale SH, the volumes of regions of the brain, as well as cognitive functions: (A) the ratio between GVC2 and volume of GM in the left island cortex, (B) the ratio between GVC1 and GM volume in the right spindle-shaped gyrus, (C) the ratio between GVC2 and GM volume in the left cingulate gyrus, and (D) the ratio between GVC2 and total cognitive performance (composite T) (SD, triangles; control, circles).

Patients with similar levels of HbA1c and average glucose values may have a significantly different daily variability in glycemia. In his study, Rizzo et al. showed that MAGE was associated with impaired cognitive functioning, regardless of the level of HbA1c among patients with diabetes ($R = 0.83$, $p < 0.001$) [20]. Although the mechanisms by which the variability of glycemia affects cognitive function are not clear, they can also be associated with oxidative stress. In this context, daily glucose fluctuations, such as peaks and falls, affect the development of oxidative stress more than chronic hyperglycemia. The work of Abbatecola et al. also demonstrated that an increase in postprandial glucose variability is associated with attention impairment [21] (**Figure 7**).

Thus, the present study demonstrated a link between high HbA1c, glycemic variability, and cognitive function in patients with type 1 diabetes mellitus. Since dysglycemia is a risk factor for both mild to moderate cognitive impairment and dementia, the present data provide opportunities for interventional studies to stabilize glycemia, not only by reducing HbA1c but also leveling out acute glucose fluctuations.

4. Pilot study: magnetic resonance spectrometry as a method of estimation of brain metabolism in type 1 diabetes mellitus

The proton magnetic resonance multilocular spectroscopy of the brain was carried out on a MAGNETOM Symphony 1.5 T (Siemens) device with the relaxation time TE = 135, and the voxel volume was 1.5 cm3; the main spectra of choline (Cho), creatine/phosphocreatine (Cr, Cr2), and N-acetylaspartate (NAA) were analyzed [22]. With the help of the regional approach, the data of metabolites Cho (choline), creatine), Cr2 (phosphocreatine), NAA (N-acetylaspartate), localized in the hippocampal region on the left and right.

The study revealed that the average age of patients with type 1 diabetes mellitus was 26 ± 4.8 years, and the control group was 30 ± 6.4 years. When comparing patients with type 1 diabetes mellitus (30 people) and control group (18 people) in metabolites Cho (choline), Cr (creatine), Cr2 (phosphocreatine), NAA and (N-acetylaspartate), distributed by the method of linear grouping and regional approach, no statistically significant differences were found.

When comparing the values obtained for the Cho metabolite, a statistically significant difference in the Cho12 index was found: in patients with type 1 diabetes mellitus, 0.82 (0.75–0.84), compared with a higher value in the control group, 0.87 (0.81–2.02).

When comparing the tables for the Cr metabolite, statistically significant differences in the indices were found: Cr5, Cr10, Cr25, Cr26, Cr28, Cr31, and Cr36.

In the study of the metabolite NAA, no significant differences in voxels were found. The study revealed changes in the ratio of metabolites Cho, Cr, Cr2, and NAA.

Thus, the main differences in patients with type 1 diabetes mellitus and in the control group were found by the metabolites Cr and Cr2. At the same time, these parameters are energy metabolism markers in their function and promote glycolysis [23, 24]. In addition, it was reported that in the voxel assessment there are significant differences in Cr and Cr2 in the

hippocampus region. This is due to the presence of a concentration gradient of these metabolites between the anterior and posterior parts of the hippocampus in the main group.

5. Conclusion

The central nervous system is one of the key targets for diabetes mellitus, and the disruption of which is manifested by cognitive impairment [25]. More recently, it has been shown that in patients with diabetes not only the risk of developing dementia is increased but also the likelihood of progression from a mild cognitive disorder to Alzheimer's disease [21]. Chronic hyperglycemia and also glucose variability are risk factors for the development of cognitive dysfunction, which confirms the need for more severe compensation of the disease. A complex diagnosis of cognitive impairment by studying the neuropsychological status of patients is suggested. The markers of cognitive dysfunction-neurospecific proteins and structural changes in the magnetic resonance imaging of the brain are studied. The test markers were associated with unsatisfactory metabolic control. In addition, the effect of cognitive impairment on QoL of patients with type 1 diabetes mellitus has been shown, especially in cases of impaired memory and attention functions. In addition, modern metabolism of the brain was studied with the help of the modern MRS method in type 1 diabetes mellitus, and changes in the parameters of Cr and Cr2 in the hippocampal region responsible for cognitive changes were detected. That confirms the fact of functional changes in the brain in diabetes and in the early stages of the disease and can be corrected with the help of rehabilitation measures in the form of cognitive training and/or therapeutic physical training.

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Chapter 3

Tauopathy

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Additional information is available at the end of the chapter

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Abstract

Tauopathy is a category of neurodegenerative diseases that are caused or associated with pathological tau protein. Some of the diseases are relatively common, which include Alzheimer's disease (AD) and various Parkinsonism (PD). Tau protein is a type of microtubule-associated protein (MAP), encoded by the gene MAPT (microtubule-associated protein tau). Normally, tau binds to microtubule, supporting the assembling and structure of cytoskeletons. However, in tauopathy, normal tau protein undergoes abnormal posttranslational modifications and detaches from microtubule; furthermore, they may aggregate forming paired helical filaments (PHF) or straight filaments (SF). Abundant PHF could be observed under microscope as fibrillary tangles. In this chapter, we will introduce the pathogenesis process of tauopathy with regard to the posttranslational modifications of the protein, the animal models, and the developing treatments against tauopathy from a clinical prospective.

Keywords: tau, phosphorylation, truncation, kinases, Alzheimer's diseases, clinical trials

1. Introduction

Tauopathy is used to summarize all the diseases that the pathogenesis processes are related to tau protein. Tau is one of the most common proteins involved in neurodegenerative diseases. In many tauopathy cases, tau protein seeds and forms intracellular fibrillary tangles on itself, one of the pathological hallmarks of Alzheimer diseases [1]. The tangles formations are believed mostly due to altered posttranslational modifications of tau protein, which detaches from microtubules and binds each other forming aggregates. In several parkinsonism-associated movement disorders, including frontotemporal dementia with parkinsonism-17 (FTDP-17), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), mutations in tau have been identified, and those altered tau are prone to tangles formation [2]. The common

involvement of tau protein in a range of neurological disorders makes it one of the most studied proteins. However, despite it has been studied for approximately 30 years since tau is coined as the major component of fibrillary tangles, concrete evidence that detail tauopathy in molecular and cellular levels is still limited [3], and most of the pathological data are obtained from studies using postmortem brain. Therefore, how tau protein and its dynamic changes affect the pathogenesis of various neurodegenerative diseases is still a mystery. Many outstanding questions are being stressed, including which posttranslational modifications are critical for it to gain toxicity, does other neurodegenerative diseases involved proteins interact with tau protein, which brain regions or cell types are most susceptive to the toxicity of tau and how the aggregates cause cellular dysfunction, and which forms of tau during the tangle formation process are toxic. In this process, some widely accepted concepts are being challenged. For example, traditionally, it is believed that hyperphosphorylation of tau induces it to detach from microtubule and increases its toxicity, but recent findings suggest some phosphorylations are protective instead [4, 5]. These findings will be emphasized in the following sections. Apparently, more efforts are needed before we can reach a definitive answer for these questions. Some exciting technological advances promise further exploration of some exist questions and more unexplored fields involving tau protein.

2. Tau biology and pathology

Tau pathology, namely fibrillary tangles, was observed way before the protein was identified. In fact, it was Alois Alzheimer who first described the heavy burdens of this never reported feature in his demented patient back to 1906 [6]. Seventy years later, tau protein was isolated as a factor that is critical for the re-polymerization of some depolymerized tubulins to form microtubules in vitro [7]. After another 10 years, a series studies confirmed that the tangles observed in AD brain are composed of tau [3, 8–10]. Since then, tau received significant attention in AD research. Nevertheless, as researchers soon realized tau pathology in a panel of neurological dysfunction, solving the underlying mechanism of tauopathy has been regarded as a unique field of neurobiology.

2.1. Tau biology

2.1.1. Tau's interaction with microtubule

The expression of tau protein varies in different tissues, but the brain has the most abundant level. In brains, tau is predominately expressed in neurons but can also be detected in glial cells, especially in oligodendrocytes [11]. In neurons, tau proteins are mainly localized in axons, but they are not excluded from dendrites [12]. Functional analyses in vitro demonstrated that tau plays critical roles in both microtubules assembly and maintaining the structural stabilization [7, 13]. But not until recently, researchers are starting to understand the interactions between tau and microtubule in real-time by adopting different newly developed techniques. By fusing a Halo-tag, a dehalogenase modified to bind certain fluorescent ligand; tau could be labeled and monitored in live imaging [14]. With tubulins being labeled

with photoactivatable green fluorescent protein (PAGFP), the interactions between tau and tubulins are viewed under total internal reflection fluorescence microscope (TIRF). With such high resolution and relatively short time frame, the live imaging revealed that tau moves on microtubule quickly without direction. In authors' words, it could "hops on and off" to another microtubule in milliseconds and moves along a microtubule with little dwindle time [14, 15]. In another study, under transmission electron microscope (TEM), it was found that tau could promote the microtubule assemble by laterally crosslinking protofilaments [13]. Moreover, tau showed a preference to bind GDP-tubulin over GTP-tubulin, but the reason behind it is not understood [13].

2.1.2. Tau structures and functions

Tau is encoded by the gene MAPT (microtubule-associated protein tau), which is located on chromosome 17q21. *MAPT* has 15 exons, and the alternative splicing of the mRNA resulted in six different isoforms. The longest one among these has 441 amino acids, which is often referred as full-length tau. In late 1980s, the basic protein structure of tau was defined [16, 17], and it was realized that the C-terminus of tau protein contains repeated domains responsible for the binding of microtubules [17]. The basic structure and functions of each functional region of it are summarized as follow:

On the N terminal side (1–150), it has two N-terminal domains. Each has 29 amino acids, one from 45 to 74 and another from 75 to 103. The physiological functions of N terminal domain are largely unknown, and speculations on that including it could play roles in signal transduction as tau could co-immunoprecipitated with phospholipase C gamma through the binding sites within N terminus [18].

The N terminal side is followed by two proline-rich domains, one from 151 to 198 followed by another from 199 to 243. Studies showed that this region interacts with src kinase family members, such as fyn serving for signal transductions [19, 20]. Furthermore, it was shown that tau could interact with beta and gamma actins, which are the subtypes of actins commonly seen in neurons [21]. A panel of different truncated and or mutated tau was generated to test the interactions of it with actins, and it was found that the proline-rich regions were responsible for this interaction [21].

The proline-rich region is followed by microtubule binding region (244–370), which is composed of four repeated domains and each one of them contains 18 highly conserved amino acids. The microtubule binding region directly binds to tubulin, which plays the most critical role in microtubule interaction [22]. Because the N terminal side does not bind to microtubule and was thought to interact with other proteins, the N terminal side plus the first proline-rich domain is often referred as projection domain of tau. The rest residues, including the second proline-rich domain and microtubule binding domains as well as the C terminal tail, are often referred as microtubule assembly domain [23].

Because the full-length tau has all these N terminal regions (2 N) and C terminal repeats (4R), it is also referred as "2N4R" tau. The rest of other tau isoforms found in brain are the combinations of either lacks one (the second N terminal domain; 1 N) or two N terminal

domains (0 N) or does not contain the second microtubule-binding domain (3R). Therefore, isoforms "1N4R", "0N4R", "2N3R", "1N3R," and "0N3R" are simply denoting the major functional domains of tau [22, 23]. The dominate forms found in human brain are 2N4R and 2N3R. Under physiological conditions, the ratio of isoforms with 4R and 3R is around 1 [24]. While in pathological conditions, the expression of tau isoforms could favor one form, especially 2N4R for most tauopathies. Researchers have long noticed the ratio alterations in disease conditions, but the exact meaning and the reason behind this change are still unknown [25].

Under physiological condition, tau exists in an unfolded state, and 80% of the proteins interact with microtubule in neurons [22, 26]. When tau is not interacting with other proteins, it may curl on its own, and this random curled state is believed important for preventing interactions with other tau proteins by masking the possible interacting sites [27, 28]. The protein itself is bipolar; the N-terminal side is highly negatively charged in normal physiology, while the proline-rich domain and C-terminal end are positively charged, allowing it to interact with the negatively charged C-terminal of tubulins [22, 29]. Various posttranslational modifications could alter its charge. Paired helical filaments (PHFs) are relatively acidic compared to normal full-length tau, which is believed due to the phosphorylation of the amino acid residues [30, 31]. Tau is also very hydrophilic, containing only a small portion of hydrophobic residues [27]. Both the net charge changes and a possible shift from being hydrophilic to hydrophobic are speculated of contributing to its aggregation behavior under pathological conditions [28, 31]. Also, normal tau proteins only exhibit transient secondary structures [27]. Phosphorylation of certain residues may prompt tau to form secondary structures, which is revealed by pseudophosphorylation of all the residues that could be recognized by phospho-tau specific antibodies AT8, AT100, and PHF1 and are shown by the structural changes in nuclear magnetic resonance spectroscopy [32]. But how normal tau proteins are transformed to form aggregates remains a mystery.

Given that tau may exist in various forms and structures, one shall be mindful not to overstate the possible role of tau based on data derived from truncated/engineered tau, which may only have the N terminal side or the C terminal side [18, 33–35]. Nevertheless, we have gained more understanding of tau and its function from previous works, but better manipulations are needed before we can be comfortable about applying those bench-side results to tauopathies treatment.

2.2. Tau pathology

Tauopathies feature a variety of pathological brain defects, such as neurites dystrophy, cell loss of certain brain regions, and brain shrinkage. The patients show associated symptoms like the decline of cognitive function, memory loss, and defects of the visual system. In the postmortem brains of most affected patients, tau aggregations are commonly found.

2.2.1. Formation of fibrillar tangles

The fibrillar tangle is the hallmark of tauopathy. The formation process of this aberrant salient could generally be categorized into several stages described as follow:

Step 1. Conformational change of tau: Certain sites phosphorylation and other posttranslational modifications or genetic mutation of MAPT rendering tau bind to tubulins with reduced affinity and detaches from microtubules no longer support the microtubule assemble, increasing the free tau protein pool [22, 36].

Step 2. Oligomer formation: The detached tau proteins form globular oligomers, which are composed of 40 monomers in vitro in the presence of heparin [37]. The mainstream opinion speculates that the detached/modified tau proteins, especially the hyperphosphorylated types, are prone to interact with each other. The phosphorylation on the residues of C-terminal and proline-rich domains neutralizes the charges of the region and reduces the net charge of the protein by which it may contribute to losing the natively unfolded property and prohibit the intramolecular interactions of tau protein [22, 38, 39]. On the other hand, it was reported that the two cysteine residues on tau, cysteine-291 and cysteine-322, play a pivotal role in the tau dimerization [40] because oxidation of the residues may lead to the disulfide bond formation between tau monomers, which potentially seeds for the oligomerization process. This theory is supported by the frequent observation of oxidative stress in tauopathies [41]. Moreover, a recent study showed a compound which could effectively inhibit heparin-induced tau oligomerization was through its interaction with the cysteine residues [37]. However, tau can also form cysteine-independent oligomers [40]. Another recent study adopted tau fragment (aa. 297–391), which is the core of PHF, to study the role of cysteine in the polymerization of tau in the absence of heparin [42]. The results showed that replacement of the cysteine residue or in the presence of reducing agents, the polymerization process was accelerated rather than decelerated [42].

It is noteworthy that most of these studies used anionic agents like heparin to induce the oligomerization of different recombinant tau isoforms or fragments to test the intrinsic properties and the effects of the modifications in vitro. But to what extent could this artificially induced tau oligomerization reflects the real pathological process is questionable. A recent study showed that heparin-induced recombinant tau tangles have little seeding ability in the wild-type mouse. In contrast, tau tangles isolated from patients have a strong seeding ability, and the pathology could spread quickly to different brain regions, shedding lights on the difference between in vitro generated tau tangles and in situ harvested tau tangles [43].

Step 3. PHF formation: Tau oligomers may further develop into more complex structures like PHF or straight filaments (SF) [44]. It has been shown that in different tauopathies, the ratio of PHF/SF and their sizes may vary [45, 46]. For example, in Alzheimer's disease, PHF is more commonly observed than SF [45]. On the other hand, in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and pick's disease (PiD), SF is predominately found [46]. In certain cell types beyond neurons, tau inclusions may exhibit different morphologies and have been given different names to describe their shapes [47]. With the help of Cryo-Electron Microscopy (Cryo-EM), we are now able to identify the structures with high resolutions [48]. It becomes clear that the cores of the filaments are composed of eight β-sheets which requires some hydrophobic interactions between individual peptides; the difference between PHF and SF is due to the lateral interactions between the sheets. However, disulfide bonds formed in the structures remain to be determined [48]. The β-sheets formed in tau oligomers and PHF could be detected with thioflavin T or S staining [28].

2.2.2. Uniqueness of different tauopathies

As mentioned above, tau inclusions are found in different types of cells in different tauopathies. In Alzheimer's disease (AD), tau inclusions are found in neurons as neurofibrillary tangles (NFT). While in many other tauopathies, the inclusions are found both in neurons and glia cells. Also, the compositions of the inclusions are different. In many tauopathies, the inclusions are mainly composed by 4R tau, while in PiD, 3R tau is the dominant form in the inclusions. In AD, the ratio of 3R/4R is close to 1 albeit the expression favors 2N4R [46]. How the different tau tangles are constructed and what the chemical and physical factors attributing the assembled pattern are still an enigma. Moreover, the locations where the aggregates are first found are also different, following different transmission pathways [46]. Together these indicate that although tau aggregate is the hallmark for all tauopathies, the properties of the inclusions are different and the factors that trigger various pathological changes may also be different [43, 46].

2.2.3. Tau degradation

Normally, the lifetime of tau is short. It was tested in cultured cells that the lifetime of tau is within 24 hours [49, 50]. It is presumed that tau proteolysis is mainly controlled by proteasomes degradation and in vitro studies also support this notion [51]. Since many endogenous proteolytic enzymes can cleave tau proteins, it is likely there is some coordination which may exist among them and also with the proteasomes [51]. Nevertheless, in tau pathology, the turnover time for tau significantly increased. It has been reported that tau phosphorylation inhibits the protein degradation [52], which could explain its pathogenic link. Recently, studies showed autophagy is involved in the digestion of tau, especially for those bulky inclusions that are probably hard to be digested by the proteasome [53]. It was found hyperphosphorylated tau co-localized with LC3 positive vesicles, a critical autophagy adaptor protein, in postmortem brains of different tauopathies [54]. More importantly, many evidence directly shows that both proteasome and autophagy systems are impaired in tauopathies, likely resulting from the assault of tau aggregation [55, 56].

For proteasome-mediated degradation of tau, different studies have shown that proteasome activities are decreased in tauopathies. Both in a tauopathy animal model or AD brains, isolated tau of sarkosyl-insoluble fraction was co-immunoprecipitated with proteasome subunits [57, 58]. Furthermore, incubating proteasome with fibrillar tau or tau oligomers decreased the activities of the proteasome, whereas when it was incubated with monomer tau, the activities were not affected, demonstrating that pathological tau might cause proteasome dysfunction [57]. It was observed that the ubiquitinated protein levels are increased in a tauopathy model, and PHF tau was also ubiquitinated in both animal models and AD brains [57, 59, 60]. While these results demonstrate a nice correlation between proteasome function and tau degradation, whether the turnover of normal or pathological tau depends on proteasome or not is still unclear [61].

For autophagy, it was observed that the dystrophic neuritis of postmortem AD brains contains huge amounts of autophagic-like vacuoles, which are presumably to be autophagosome

or autolysosomes. These observations imply a significant upregulation of autophagy activities preceded by certain stimuli like cytoskeletal dysregulation or oxidative stress, likely causing the neurons to initiate apoptosis and contribute to neurites dystrophy [55, 56, 62]. Dense lysosome proteases staining results in AD brains also indicate defective degradation of major intracellular protein aggregates. Moreover, in the familial AD, presenilin 1 mutation is one of the most common mutations causing the disease. Traditionally, it is believed the pathogenic mechanism is that the expression of presenilin 1 mutations results in the generation of Amyloid-beta, as this molecule constitutes the active domain of γ-Secretase. However, presenilin 1 also plays a critical role in autophagy that functions as an ER chaperon transporting enzyme subunit critical for lysosome protease activation. Deletion of presenilin 1 could abolish autophagy [56]. All these results support the notion that tau aggregation may cause upregulation of autophagy activity.

3. Pathogenesis of tauopathy

There are two forms of tauopathy, familial and sporadic. Familial tauopathy is linked with genetic mutations of tau, and sporadic tauopathy is often associated with altered posttranslational modifications. Since the pathogenesis of the two forms is different, so they are discussed separately in the sections below.

3.1. Genetic mutations of tau

3.1.1. Tau mutations in neurodegenerative disorders

Genetic mutations of tau can cause familial tauopathies, which are commonly found in frontal temporal dementia (FTD), including a range of clinical conditions like Pick's disease, corticobasal dementia, and progressive supranuclear palsy [63, 64]. Mutations of tau were first discovered in the late 1990s in inherited FTD families [65], and it was the first known monogenic mutations that could cause FTD [63, 64]. Epidemiological surveys showed MAPT mutations are responsible for 5–20% FTD cases [63]. Since MAPT is localized to chromosome 17 and the subject showed FTD with parkinsonism syndrome, it was named frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) to refer tau mutations-associated FTD [66]. More than a hundred tau mutations have been identified, and not all of them are pathogenic. A detailed mutations list and their associated impacts can be found online at Alzforum.org [67]. Tau mutations are rarely found in Alzheimer's disease (AD) and normally are not considered as a major genetic risk factor for the disease's familial form. But certain mutations could contribute to the pathogenesis of AD, and some found that mutations' pathogenicity has not been integrated yet [67, 68].

3.1.2. Tauopathy animal models

Pathogenic tau mutations typically result in either RNA splicing variation causing the ratio change of 3R/4R or a structure change, which will further affect its binding affinity with

microtubule and other proteins or promote its self-assembly [66, 67, 69]. The mutation sites cover the whole protein and could also be in the introns affecting the RNA splicing [67]. Some much more common mutations have been selected in generating transgenic models for studying tauopathies [70]. To date, 28 tauopathy mouse models have been reported according to Alzhforum.org and many of which are overexpressing models [67]. Other tauopathy animal models in *Drosophila*, zebrafish, and *C. elegans* also help the field to untangle the molecular and cellular complexity of this clinical condition [71–74].

Transgenic expression of normal human tau in mouse models with either 3R or 4R forms were unable to induce significant pathological changes [75]. While with strong pan-neuronal promoters could induce more pathological features, this approach also raises a concern of overwhelmed tau expression, which may lead to possible artificial effects by causing heavy burdens on protein degradation systems, which obviously deviated from the progressive pathogenesis that is responsible for the sporadic tauopathy [75–77]. Notably, a recent study created transgenic mice expressing an N-terminal truncated tau under the control of human tau promoter so to mimic the normal expression level and by which recapitulated some major pathological features of tauopathies [76]. The authors claimed that a similarly truncated tau could be found in postmortem progressive supranuclear palsy brains, which makes this finding quite interesting.

In comparison, expressing disease-linked mutant tau can induce more pronounced pathological effects, and some of the models are widely used in basic or pre-clinical research settings if not in combined with other tauopathy-related protein expression [67, 70, 75, 77]. The most commonly adopted tau mutations in transgenic animal models are P301L, P301S, R406W, and V337 M [59, 77]. All these mutants were found in FTD patients, and their expression showed reduced binding affinity to the microtubule. Importantly, all of them could efficiently induce tau filaments formations in mouse models, although the composition of the filaments may be different for different tau mutations [66, 70]. Among them, three mouse models stand out in terms of their wide usage in basic research, as well as in the pre-clinical tests of drug development. These are P301L, PS19, and rTg4510 (r for regulatable), all of which were developed in the mid-2000s [78–80]. P301L mice overexpress 2N4R tau with P301L mutation under the pan-neuronal driver Thy1 [78]. PS19 mice overexpress 1N4R tau with P301S mutation driven by mouse prion protein promoter [79], and rTg4510 adopts the tet-off system to overexpress 0N4R tau bearing P301L mutation only in the absence of tetracycline that controlled by Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) promoter [80]. In general, rTg4510 and PS19 mice show more massive pathology burdens in comparison with to P301L. Although overt tau aggregations were observed in all three types of mice and showed cognitive defects, only rTg4510 and PS19 were reported to induce significant neuronal loss [79, 80]. PS19 mice showed severe hippocampus shrinkage at the age of 9 months, while rTg4510 mice showed gross forebrain atrophy at the age of 10 months [79, 80]. It is noteworthy that human tau expression levels were several times higher than the endogenous mouse tau levels for all three models [78–80].

These data collectively show that while significant tau aggregates can be induced by expressing mutant tau, the models are different from sporadic tauopathy, especially in terms of studying

the pathogenesis and treatment methods for tauopathy with a mouse. Another major concern is related to the modulation of endogenous enzymes at the time of human tau expression, which is an issue difficult to control. Some key features related to general pathogenesis process were missed from the transgenic mice models, including robust tau propagation and significant cell apoptosis [48, 81]. In one study, by injecting insoluble tau to mouse hippocampus, it was found that the seeding and propagation ability of the synthesized insoluble tau are much weaker than the insoluble fraction of isolated tau from the AD in vivo [48]. Together, it shows there is still a long way to go before using these animal models to find a strategy for detour tauopathy.

Recent advances in human stem cell research may provide a solution for tauopathy and related research. By grafting human stem cell-derived neuron to express amyloid-beta in mouse brain, a study revealed that the human neurons are more susceptible to the toxicity of amyloid-beta than mouse neurons [81]. This observation proved the discrepancy of cells from the two organisms. Therefore, if the quality of the grafted cells and the surrounding microenvironment represent the physiological conditions in the human brain, shall we also expect human neurons are more susceptible to the toxicity of tau?

3.2. Posttranslational modifications of tau

Most patients who suffer from tauopathies carry wild-type MAPT. Therefore, posttranslational modifications of tau are believed to be the key of tau pathogenesis and have been the major area of tauopathy research for years. Understanding the posttranslational modifications of tau not only helps us to pin down the pathogenic mechanism but also offers a viable path for drug screen by targeting certain enzymes that modifying tau. As mentioned in the above sections, altered posttranslational modifications of tau could render the protein to lose its native unfolded structure and by which to promote aggregate formation. In this process, the modifications also changed the interactions between tau and other proteins in addition to tubulins. So far, 10 types of tau posttranslational modifications have been documented [82], among which phosphorylation and truncation are most found, representing the majority of the modifications, while other modifications (ubiquitylation, oxidation, glycosylation, glycation, nitration, acetylation, and sumoylation) are either not often discussed in this setting or just recently founded. In total, over 100 sites on a tau protein have been proposed that could be modified if not considering the truncation [83].

3.2.1. Phosphorylation

In one of the pioneer studies aimed to prove that neurofibrillary tangles are made of tau, the researchers found treating the tissue section with phosphatase could dramatically increase the antibody labeling of tau on the tangles [9], and the researchers coined the staining as "atypical phosphorylated" tau. Since then, the "hyperphosphorylated" tau under pathological conditions received a great deal of attention. Many protein kinases have been proposed to play roles in tau phosphorylation, and some of them have been confirmed by in vivo studies [9, 84]. Recent developments have proposed to try out some kinase inhibitors as potential tauopathy therapeutics [85]. For a 2N4R tau protein, it consists of 45 serine residues, 35 threonine

residues, 12 histidine residues, and 5 tyrosine residues. Current postulated phosphorylation sites have essentially covered most of the available sites, and indeed many of these residues are found being phosphorylated under physiological conditions. Therefore, the widespread, and likely dynamic, tau phosphorylation appears to serve for certain uncovered functions. Nevertheless, it also indicates that the differences in general phosphorylation and changes of phosphorylation state in certain residues may play a critical role in tauopathies [83, 84]. Moreover, hyperphosphorylated tau could also be detected in other pathological conditions aside from tauopathy. It was found that phosphorylated tau proteins are co-aggregated with alpha-synuclein in Parkinson disease and Lewy bodies dementia [86]. In some reports, phosphorylated tau aggregation can be found in Huntington disease and amyotrophic lateral sclerosis brains [87, 88]. In traumatic brain injury patients, the levels of phosphorylated tau, but not total tau, are significantly increased [89]. Recently, it is also suspected that tau phosphorylation may play a role in type 2 diabetes, rendering the patients incline to have cognitive defects [90]. These data collectively indicate hyperphosphorylation of tau has a strong correlation with a variety of brain pathologies, not just tauopathies.

However, the scenario of pathogenesis in tau hyperphosphorylation is more than merely the activation of some kinases or down-regulation of some phosphatase. As a matter of fact, different kinases are interacting, regulating, and even competing with each other for acting or interfering on same sites [91, 92], it is conceivable that the dynamics of transferring/removing phosphate groups on tau protein could be complex. Besides, kinases have multiple substrates, and some of them have important roles in normal cell functions [91]. The activities change of a kinase could lead to a domino effect toward the change of cellular activities. Last but not least, not all phosphorylations are toxic as some of them are required for normal tau functions, and certain sites phosphorylation may even serve as a protective effect in tauopathies [4, 5]. Therefore, a systemic dissection of disease-prone tau phosphorylations and their regulation is a pre-requisite before aiming such complex regulation for a therapeutic exploration.

To study the phosphorylations, many antibodies recognizing specific phosphorylated residues on tau have been generated, and a list can be found on Alzforum.org [93]. For analyzing the effect of phosphorylation, recombinant MAPT constructs bearing site-specific mutations to mimic potential phosphorylation status of tau are regularly utilized in tauopathy research, which provides some insights regarding the genotoxic and structural impacts upon modifications [94]. However, even with the recombinant tau with or without pseudo-phosphorylations, it is hard to generate significant polymerization in vitro postulated due to a lack of "nucleation" process, although pseudo-phosphorylated tau may be prone to aggregate [95].

3.2.1.1. GSK3β

It is well acknowledged that glycogen synthase kinase 3 beta (GSK3β) plays a pivotal role in tau hyperphosphorylation [96, 97]. An early study showed that recombinant tau and microtubule-associated GSK3β that were harvested from bacterial lysates could be co-eluted in immunochromatography with anti-GSK3β and co-immunoprecipitated [98]. A subsequent study found active GSK3β co-localized with tau inclusions in tauopathy brain tissues, and the amount of active GSK3β was significantly increased in the patients [99]. Moreover, in vitro

study found active GSK3β could efficiently facilitate tau tangles formation after tau are initially polymerized in the presence of arachidonic acid [100]. It should be noticed that effects of GSK3β in tau-mediated toxicity are unsettled; a report found that overexpression of GSK3β in tauopathy models may not necessarily lead to shortened lifespan or accelerate pathological burden in the animal model [101]. In contrast, results from some studies hinted that activation of GSK3β is critical for exacerbating tauopathy [102, 103]. These observations should be interpreted carefully as the tau models used or compared are not in the same background.

GSK3β is a constitutively active protein that can autophosphorylate its tyrosine residues like Tyr 216 to increase the enzyme stability [104]. The activity of GSK3β is mainly regulated by insulin and Wnt signaling pathways [105]. When insulin pathway is activated, protein kinase B/Akt will be activated, which in turns phosphorylate serine 9 on GSK3β and causes its inactivation. In the case of activated Wnt signaling pathway, the inhibition of GSK3β activity would alleviate the degradation of β-catenin, whose nuclear translocation is responsible for the downstream genes activation of the pathway, but the precise mechanism regarding tauopathy modulation is still unknown [106, 107]. Nevertheless, a report showed both pathways are being downregulated in AD [96].

It was postulated that the phosphorylation by GSK3β requires the priming of adjacent proline residue as GSK3β is a member of proline-directed kinase family [84]. So far, more than 40 sites in tau, either serine or threonine, have been reported could be phosphorylated by GSK3β, and some of them are exclusively found in pathological conditions [84]. Among these sites, in vitro study first identified tau could be phosphorylated by GSK3β at the sites S202, S396, and S404 [108]. Since then, different studies reported many different phosphorylation sites with the availability of the corresponded phospho- site-specific antibodies. Some in vitro/in vivo studies later confirmed that frequent phosphorylation sites include S262, S396, and S404 [101, 109]. The phosphorylation of some residues may play important roles in affecting the binding affinity between tau and tubulins or regulating synaptic plasticity [4, 110, 111]. However, it is still unknown which residues are most frequently phosphorylated by GSK3β under different pathological states in contrast to normal condition, and if there is any protective effect by GSK3β phosphorylation against tau from forming the aggregates. Probing these questions is a major challenge but will help our understanding of the role of GSK3β in tau-associated disease conditions.

3.2.1.2. Other kinases

Besides GSK3β, other kinases such as p38, cyclin-dependent kinase 5 (CDK5), c-Jun N-terminal kinase (JNK), extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), casein kinase (CK), protein kinase A (PKA), and Ca2+ /calmodulin-dependent protein kinase II (CAMKII) have been reported to involve in directing tau phosphorylation [4, 84, 112–114]. Although the possible phosphorylation sites mediated by these kinases, especially in tauopathy conditions, may be less than GSK3β, it is fair to say that their roles in modulating tau toxicity are less well studied, thus whether the modulations by these kinases are less critical than GSK3β in tauopathy remain to be addressed. Indeed, a recent study found P38γ overexpression could ameliorate excitotoxicity

induced by amyloid-beta in a tau-dependent manner. Further experiments showed that the effect was mediated by the phosphorylation of tau S205 through the action of P38γ, and the phosphorylation of this residue could abolish the interaction between tau and Fyn and PSD95, which otherwise could form a complex interacting with NMDA receptor to induce excitotoxicity [4]. This result strongly suggests different kinases may have different roles in tauopathy, and not every up-regulated tau phosphorylations under pathological conditions are for enhancing the toxicity. Given such complex modifications, more studies shall emphasize the difference of activity among these kinases under physiological and pathological conditions, as another recent study showed that ERK1/2 does not phosphorylate tau under physiological condition [115]. Furthermore, since the pathology development in tauopathy usually takes years, whether there is any sequential activation of the kinases appears to be another intriguing issue. Indeed, a recent study examining tau-staining in the postmortem AD brains of different stages showed that N-terminal side of tau is preferentially phosphorylated at early stages [116].

3.2.2. Truncation

Proteases including calpain and caspases are involved in tauopathy pathogenesis [117, 118]. They are activated in tauopathies, either directly cleave tau or indirectly cleaving its associated kinases, affecting the structure/function of tau [118–121]. While less commonly reported, other proteases are suspected to play roles in tauopathy-related protein truncations [122].

Two truncated tau proteins have caught attention in tauopathy, as they are abundant in the postmortem AD brains [123]. In fact, truncated tau could also found in other tauopathies beyond AD. Importantly, researchers used live multiphoton imaging combined with thioflavin S administration and a dye for activated caspases and observed that the tangle formation was preceded by caspases activation in a classic P301L tauopathy mice (tg4510) [124], indicating a close tight between tau cleavage and toxicity. Currently, two truncation sites, E391 and D421, have been characterized and both are on the C-terminus. We also learned that the truncation on D421 is mediated by caspases, mainly by Caspase-3. D421-truncated tau is associated with lysosome in AD brain, indicating that the truncated tau may be favored to be degraded through autophagy or maybe impairing the autophagy system [124]. However, it is still unclear what kind of proteases are responsible for the cleavage at E391, albeit the site was the first-identified cleavage site in tau, and its C-terminal cleavage product appears in PHF core [118, 123, 125–128]. While various reports have suggested that caspase and calpain are capable of cleaving tau and both present as an early event in pathogenesis and could aggravate tau toxicity [124, 129, 130], an important issue should be solved in studying tau truncation that is whether the aberrant increase of tau truncation is a consequence of tau aggregation or actually the cause that induces tau aggregate formation [124].

3.2.2.1. Calpains

Calpains are cytosolic calcium-dependent cysteine proteases. In an analysis of a postmortem brain lysates, calpain 1 was found to activate at early stages of AD, close to the stage when GSK-3β and CDK5 were activated [130]. The human genome has two identified calpain family members, calpain 1 and calpain 2. Calpain 1 is mainly expressed by neurons and thus received

most attention by researchers concerning neurodegeneration, and calpain 2, on the other hand, is mostly expressed by glial cells. Studies have shown that calpain 1 can cleave p35 to generate p25, which could further induce prolonged activation of CDK5 [120]. Calpain can also cleave GSK3β to generate a C-terminal truncated form, which makes its inhibitory site less likely to be phosphorylated and thus produces a dominant-active GSK3β [121, 131]. Also, calpain can directly process tau and generate small fragments. However, the physiological or pathological impacts of those cleaved calpain products in regarding tauopathy are unclear, and the calpain-mediated tau cleavage site(s) remains elusive [120, 127, 132].

3.2.2.2. Caspases

Among the caspases, executive caspases, especially caspase-3, play a critical role in the direct processing of tau at the site D421. As mentioned above, D421-truncated tau can be found in AD brains, and this cleaved form is suspected to facilitate tau aggregate formation and thus enhancing the toxicity [124, 129, 133, 134]. Phosphorylation at S422 could prevent the truncation, which could be mediated by JNK and TTBK-1 [114, 135, 136]. Nevertheless, JNK and TTBK-1 could also phosphorylate tau at the sites other than S422, which complexes the protective scenario [114, 136]. Caspase 3 can also regulate the phosphorylation of tau through cleaving and activates protein kinase B and thereby activates GSK3β [119].

Besides caspase-3, other caspases may involve in tauopathy as well. A recent study showed that caspase-2 could cleave tau at the site D314. This truncated tau could not participate in tau aggregation but is existing in the brains of P301L mice by a significant amount. Pseudophoshorylation of this site prevented caspase-2 cleavage and consequently caused memory and cognitive defects of the mice [137].

3.2.3. Acetylation

Tau lysine residues could be acetylated by certain endogenous acetyltransferase, and such modulations were first demonstrated by p300 and Creb-binding protein (CBP) [138, 139]. Importantly, the insoluble tau protein fraction isolated from postmortem brains of the AD patients could be recognized by an anti-acetylated tau antibody [138]. Since then, tau acetylation studies start to emerge, and up to date, four tau acetylation sites, K174, K274, K280, and K281, have been confirmed in pathological conditions [140]. Acetylation of K280 and K281 reduced tau binding affinity to microtubules in vivo and facilitated tau aggregation in vitro [140, 141]. Moreover, acetylation of K280 exacerbated tau toxicity in a *Drosophila* model, and acetylation of K174 worsened neurodegeneration and behavior defects in PS19 mice [142, 143]. An overall tau acetylation effect is likely to aggravate tau toxicity. A study showed the administration of salsalate, a drug that could inhibit p300, ameliorated the tau pathology and memory defects in PS19 mice [143]. Interestingly, a recent study reported acetylation of K321 could impede S324 phosphorylation, a frequent modification in postmortem AD brains. This observation leads to an intriguing prospect that some switches from acetylation to phosphorylation might affect disease progression [144]. Altogether, these studies bring up questions including to what extent tau acetylation could affect tau toxicity and whether there are interactions between tau acetylation and other posttranslational modifications.

3.2.4. Other posttranslational modifications

So far, our understanding of other tau modifications is still limited [82]. Take glycosylation as an example, glycosylation of tau was only found under pathological conditions but not physiological conditions [145], indicating that this type of posttranslational modification has a significant impact toward cell function. However, probed glycosylation sites of tau are limited, and some of the proposed sites might overlap with the known phosphorylation sites, suggesting a potential competition between glycosyltransferase and phosphorylation kinases [145]. The role of glycosylation in tauopathy is unknown [82]. A recent study using *Drosophila* showed that different gene locus of glycosyltransferases might have a different impact on tauopathy [146].

4. Tauopathy treatment

To date, no drug targeting tauopathies has entered the market [147]. Over the past two decades, a dozen representative drugs have been pursued in the clinical trials [148], and these drugs represented the major therapeutic approaches in tauopathy treatment, including tau aggregation inhibitors, tau phosphorylation-related kinase inhibitors, microtubule stabilizers, and immunotherapy against tau. However, since these strategies have yet to show significant benefit, new approaches are being probed, among which a scheme to enhancing protein homeostasis is an intriguing approach [147, 149]. Other alternative approaches including using traditional Chinese medicine are also being pursued [150].

4.1. Treatment approaches target features of tauopathy

Five treatment approaches mentioned above have been scrutinized in clinical trials, and only microtubule stabilization and immunotherapy against tau are still active tau aggregation inhibitors, and phosphorylation kinase inhibitors, including GSK3β inhibitors and CDK5 inhibitors, were once favored, but they showed little efficacy in clinical trials [151].

4.1.1. Tau aggregation inhibitors

The direct inhibition of tau aggregation was the major therapeutic strategy being developed and had entered the clinical trials [151]. The development of tau aggregation inhibitor was initiated in the mid-1990s. The first platform to screen the drugs was reported in 1996 with the discovery of phenothiazine, a relatively potent tau aggregation inhibitor in vitro [152]. In this platform, recombinant PHF core tau fragment was incubated in wells, by reciprocal treating the wells with recombinant full-length tau, the protease-resistant tau aggregation could form [152]. By incubating the wells with compounds, the goal was to identify inhibitors that could effectively disrupt tau aggregation through the high-throughput assay, and phenothiazine showed a strong potency [152]. Unfortunately, phenothiazine was found no efficacy in clinical trials, and it was blamed for its poor absorption and was difficult to be transported into the brain [153]. Years later, a renewed platform was designed [153]. In this platform, fibroblasts

overexpressing a cocktail of different tau isoforms were incubated in wells. This setting could yield tau aggregations inside the cells, and compounds were tested to compare the labeled tau immunofluorescence as the readout [153]. Although this platform was a lower throughput, it overcame the shortages of the first platform in which cytotoxicity was unknown [153, 154]. With this platform, TRx0237 was later selected to be the lead candidate and went into clinical trials [151]. Unfortunately, the drug did not work in phase 3 as it failed to slow cognitive decline in AD patients [155].

Biochemically, the inhibitors could be categorized into two types, covalently and no-covalently tau aggregation inhibitors [156]. However, although they are called "tau" inhibitors, these chemicals are most likely inhibitors to other protein aggregations, and their selectivity is highly questionable [151]. Therefore, a highly selective with high-affinity tau inhibitor is still waiting to be discovered [151, 156].

4.1.2. Tau immunotherapy

The aim of immunotherapy is to clear pathological tau through the immune system [157]. It could be achieved either by applying antibodies that could recognize pathological tau or by vaccination to elicit activation of antigen presenting cells and subsequently the B cells and T cells to clear up pathological tau [157, 158]. Ten years have passed since the publication of the first study on tau immunotherapy [159]. In the study, the researchers showed that inoculation of a tau peptide aa R379-L408, which covers two critical phosphorylation sites S396 and S404 that being phosphorylated in P301L tau mice, could successfully elicit endogenous immune system to generate antibodies against tau, and the animal showed ameliorated symptoms of tauopathy-related behavior and decreased tau aggregation [160]. Multiple different antibodies or vaccines aiming at different tau epitopes have been developed since then, and some have entered the early phases of clinical trials [157].

4.2. Novel treatment approaches

Molecular chaperones play important roles in protein homeostasis. It was reported that inhibiting heat shock protein 90 (Hsp90) could inhibit tau toxicity in tauopathy model [160]. The mechanism behind could involve Hsp90 stabilize p35, the activator of CDK5, GSK3β, and tau, inhibiting their degradation [160, 161]. On the other hand, Hsp70 could facilitate protein ubiquitination and degradation by the proteasome [162]. Overexpression of Hsp70 in cells could decrease tau aggregation in vitro [163]. Recently, it is also suggested that targeting co-chaperones of Hsp90 could offer another approach to ameliorate tauopathy [164].

Several traditional Chinese medicines have been suggested that might be useful for treating tauopathies [150, 165]. Huannao Yicong Decotion was shown to improve learning and memory in rat AD model. Immunolabeling showed the expression levels of GSK3β, CDK5, and TTBK1 in CA1 region of the hippocampus are downregulated in the drug treatment groups [150]. Interestingly, it was also suggested that some traditional Chinese medicines, including Huperzine A and Tianma, could induce upregulation of ubiquitin ligases, indicating that they might facilitate protein degradation through ubiquitin-proteasome pathway [166].

5. Conclusion

In this chapter, we discussed major basic aspects of tauopathy, from tau normal functions to pathology formation process and from tau genetic mutations to posttranslational modifications. Finally, we discussed currently proposed tauopathy treatment methods. With the findings showing tau proteins are involved in many brain pathology conditions beyond tauopathy and more evidences showing the roles of tau in Alzheimer's disease are critical, it is expected to receive more basic research attentions in the future [167, 168]. Better animal models tailored for different tauopathy are of pursuit, which will benefit both basic research and clinical drug developments.

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Chapter 4

Tau Protein as a Biological Fluid Biomarker in Neurodegenerative Dementias

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Additional information is available at the end of the chapter

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Abstract

Tau is a microtubule-associated protein, whose main function is the modulation of the stability of axonal microtubules. In physiological conditions tau is abundant in neurons while its expression in glial populations is low and restricted to astrocytes and oligodendrocytes. The aggregation of tau in neurofibrillary or gliofibrillary tangles is the main hallmark of tauopathies, a complex group of human neurodegenerative conditions where tau hyper-phosphorylation causes its increased insolubility and aggregation leading to tangle formation and microtubule destabilization. Tau can be detected in biological fluids in physiological and pathological conditions. In several neurodegenerative dementias, either associated or not to a primary tauopathy, tau levels are altered in a disease-specific pattern, which can be used as a biomarker for disease diagnosis and prognosis. The study of tau levels in biological fluids has been mainly performed in the cerebrospinal fluid (CSF), although the recent development of ultrasensitive techniques allows the robust quantification of tau in blood-based biofluids such as serum and plasma. The presence of elevated total-tau in the CSF is assumed to reflect the degree of axonal damage in the brain tissue. Consequently, highest total-tau CSF levels are found in sporadic Creutzfeldt-Jakob disease, which is characterized by massive neuronal damage and a rapid progressive course. Elevated total-tau is also detected in Alzheimer's disease and dementia with Lewy bodies, while in other dementia conditions such as vascular dementia, frontotemporal dementia and corticobasal degeneration are unchanged, inconclusive or not determined. Additionally, total-tau rises temporarily due to cerebral infarction. In contrast, elevated phospho-tau levels seem to be restricted to Alzheimer's disease pathology, most likely mirroring the presence of the hyper-phosphorylated form in the brain tissue, although phospho-tau levels are mainly unaffected in tauopathies. Additionally, isoforms and different structural and truncated tau forms have also been reported to be altered in neurodegenerative dementias. In this complex scenario the diagnostic accuracy of diverse tau forms as disease-specific biomarkers needs to be established. In this chapter, we summarize the current knowledge on the alterations of diverse tau forms

in biological fluids of neurodegenerative dementias and its relevance in the differential diagnostic context. Additionally, we explore how tau alterations in the brain tissue may explain the etiology of its regulated levels in CSF and blood.

Keywords: total tau, phospho-tau, neurodegenerative diseases, cerebrospinal fluid, serum, plasma

1. Introduction

Tau is a microtubule-associated protein produced through alternative splicing of the MAPT (microtubule-associated protein tau) gene. Tau is highly abundant in the axons of nerve cells [1] where it plays a role in the stabilization and dynamics of the microtubules. To a lesser extent tau is also localized in the synaptic compartments [2] where it is suggested to modulate postsynaptic receptor activity by interaction with a broad range of synaptic proteins [3]. Besides its neuronal localization, tau is also expressed in oligodendrocytes, where it stabilizes microtubules during process outgrowth and myelination [4–6] and in astrocytes at trace levels [4], where it does not appear to be a major cytoskeletal protein. Although tau is mainly an intracellular protein, it can also be actively secreted by neurons to the brain interstitial fluid. The mechanisms of tau secretion under physiological conditions are not well understood, but it can be induced by neuronal hyperexcitability [7] and its release through ectosomal and exosomal vesicles [8, 9] or alternative secretory pathways [10] has been proposed. Additionally, under certain pathological conditions associated to neuronal degeneration tau can be released from the neurons to the brain interstitial fluid, usually correlating with the degree of neuro-axonal damage.

Tau released into the interstitial fluid may drain into the cerebrospinal fluid (CSF) within the subarachnoid space as well as into blood. Therefore, alterations of tau levels in biological fluids may mirror the pathological state of the brain in those conditions associated to neuronal degeneration. Additionally, since tau is hyper-phosphorylated in patients suffering from primary tauopathies and Alzheimer's disease (AD), a tauopathy associated with beta-amyloid deposition, increased phospho-tau (p-tau) levels in biological fluids may reflect the undergoing tau pathology in the brain tissue.

Consequently, the quantification of tau levels in biological fluids is extensively studied as a diagnostic and prognostic biomarker in a broad range of neurological conditions either associated or not to a concomitant tauopathy. Additionally, the analysis of different tau forms is also explored in the evaluation of the efficacy of disease-modifying therapies and to better understand the underlying molecular mechanisms associated to neuronal degeneration and tau pathology.

2. Tau pathology and neuro-axonal damage

Tauopathies are a complex and heterogeneous group of neurodegenerative diseases characterized by the presence of hyper-phosphorylated and aggregated tau forms in neuronal and

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glial cells [11, 12]. The spectrum of tauopathies encloses more than 20 sporadic and familial diseases, in which their neuropathological phenotypes can be classified according to the involvement of different cell types (neurons of glial cells), affected brain regions, and the type of tau form/s associated to the pathological protein deposits [12]. In contrast to primary tauopathies where the common pathological hallmark is the presence of disease-related tau forms, AD is a neurodegenerative disease where tau pathology is accompanied by the accumulation of abnormally folded amyloid beta peptides in the tissue in form of extracellular amyloid plaques [13].

Keeping this in mind, the understanding of correlation between different tau forms present in the biological fluids regarding and the pathological changes occurring in the brain tissue is challenging. On one hand, there are neurodegenerative mechanisms not associated to tauopathies (or tauopathies associated to beta-amyloid deposition such as in AD), but leading to acute or chronic neuronal damage drive to a release of tau forms in their non-pathological (basal) state: i.e. basal phosphorylation levels and absence of truncated forms. On the other hand, in the presence of a tauopathy, tau release due to neuro-axonal damage could be accompanied by the release of its pathological forms (hyper-phosphorylated and truncated forms). In this regard, the tau biomarker field has been closely associated to the study of AD pathology since, among the group of tauopathies, AD cases are showing the most robust and clinically relevant alterations on tau levels in biological fluids. However, the precise cellular and molecular mechanisms leading to tau alterations in biological fluids remain elusive. Indeed, the current knowledge about the pathophysiological mechanisms of these diseases does not completely explain the disease-specific changes observed in biological fluids.

3. Cerebrospinal fluid tau

Enzyme-linked immunosorbent assays (ELISA) has been used extensively for the analysis of tau concentrations in the CSF. The most established immunoassays are developed for the quantification of total-tau (t-tau), which detects non-phosphorylated and phosphorylated tau forms, and phospho-tau (p-tau), which detects tau being phosphorylated at specific epitopes. Among them, the quantification of phospho-threonine-181 (p-tau-181) is broadly extended for research and clinical diagnosis purposes, especially in the context of AD-related pathology. Additionally, several studies have also shown the usefulness of assays detecting phospho-serine-199 (p-tau-199) and phospho-threonine-231 (p-tau-231) [14]. Finally, the recent development of a non-phospho-tau assay detecting non-phosphorylated tau at positions Thr-175, Thr-181 or Thr-231 [15], extended the range of available tools for the dissection of the contribution of each specific tau form in the pathology of the spectrum of neurological conditions with altered tau concentrations in the CSF.

3.1. Total tau

The presence of increased total-tau (t-tau) levels in the CSF is reported in several neurodegenerative diseases such as sporadic Creutzfeldt-Jakob disease (sCJD), AD and dementia with Lewy bodies (DLB) [16–18].

The highest t-tau levels are recurrently detected in sCJD, the most common form of human prion disease where deposition of prion protein, gliosis and massive neuronal damage accompanied with spongiform degeneration are common neuropathological hallmarks in the brain tissue [19]. The first report on the presence of high t-tau in the CSF of sCJD cases was in 1997 in a relatively small cohort of cases [20]. Further, several studies validated these observations in large populations [21–24]. A cut-off point of 1300 pg/mL t-tau was established for the discrimination of sCJD from non-CJD cases [21] and although t-tau is not included in the World Health Organization diagnostic criteria for sCJD, its quantification is used in several worldwide diagnostic centers as a supportive tool in the differential diagnosis of prion diseases.

In sCJD, patient's molecular subtype is composed of two different kinds of information: (1) codon 129 genotype in the *PRNP* gene (MM, MV, or VV) and (2) prion protein (PrP) type (1 or 2) and it is a prognostic marker for disease progression and patient survival [19]. The different progression rates for each molecular subtype are associated to their differential neuropathological hallmarks, which in turn reflect the degree of neuronal degeneration. Accordingly, a significant association between CSF t-tau levels and sCJD molecular subtype was reported [25, 26]. Additionally, CSF t-tau levels are inversely associated with disease duration, suggesting a role for CSF t-tau as a prognostic marker for sCJD [27]. While t-tau protein tends to increase in sensitivity from onset to the advanced stage, these changes are only statistically significant in patients with methionine-valine (MV) heterozygosis at codon 129 in the *PRNP* gene [28].

Besides sporadic forms, prion disease can also present a genetic (or hereditary) etiology [29]. Hereditary prion diseases are a heterogeneous group of conditions classified as familial or genetic CJD prion diseases (gCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS-S) and fatal familial insomnia (FFI), all of them associated to mutations in the prion protein gene and with an autosomal inheritance pattern. The most common gCJD types in the European population are those associated to mutations at codon 200 (E200K) and codon 210 (V210I). From a clinical and neuropathological point of view gCJD E200K and gCJD V210I resemble sCJD [30, 31]. Indeed, gCJD cases are often misclassified as sCJD in the absence of family history and genetic testing. In agreement with this, CSF t-tau levels in gCJD patients show levels comparable to those in sCJD [22, 32]. Instead, in GSS-S (associated to several mutations such as P102L, P105L, A117V, F198S) and FFI (associated to D178N mutation accompanied by a cis-129 M), CSF t-tau is usually below the sCJD cut-off point, [22, 32]. These differences are explained by the differential clinico-pathological hallmarks observed in these cases. First, GSS-S and FFI patients usually present a slower disease progression and prolonged disease duration compared to sCJD and gCJD cases [30]. Secondly, the brain regions affected are not overlapping those affected in sCJD. Indeed, FFI cases present a pathology which is usually restricted to the thalamic and olivary nucleus with spongiform changes in the cerebral cortex only in patients with long disease duration [30, 33, 34]. In contrast, neuropathological findings in GSS-S cases are heterogeneous depending on mutation type, but in general a widespread accumulation of PrP positive plaques in the cerebral and cerebellar cortices and the basal ganglia is observed [35, 36]. Although t-tau quantification lacks of clinical significance in the differential diagnosis of FFI and GSS-S, it is worth to mention that their mean CSF t-tau levels are increased compared to controls [22] indicating that, at some extent, t-tau may also reflect brain damage occurring in both conditions.

In AD, CSF t-tau is considered as one of the three core biomarkers together with p-tau and amyloid beta-42. The first studies reporting elevated t-tau concentrations in AD patients compared to controls date from 1995 [37–40]. Since them these results have been replicated in many studies [41, 42] with a predictive value around 90%.

Since t-tau is considered a marker of neurodegeneration, its levels are proposed to be changed latter during the progression of the disease and correlating with clinical symptom severity. This is in contrast to amyloid beta peptides which become abnormal before alterations in neurodegenerative biomarkers and cognitive symptoms are detected [43]. Importantly, as CSF t-tau reflects the intensity of acute neuronal damage and chronic neuronal degeneration elevated t-tau levels in MCI patients has been demonstrated to predict the progression to dementia [44], especially in short-term prognosis [45]. These observations are in agreement with a meta-analysis study that strongly supports the use of CSF t-tau in the identification of MCI-diagnosed subjects at higher risk of evolving to AD [46]. However, higher predictive values are reached when combined with p-tau, amyloid beta-42 and/or imaging biomarkers [45, 47]. Indeed data from longitudinal studies indicate that the combination of CSF t-tau, p-tau and amyloid beta-42 at baseline reach high prognostic values (95% sensitivity and 83% specificity) in the detection of early AD cases with MCI [48].

Besides the well documented elevated t-tau levels in sCJD, AD and DLB, several studies found slightly elevated t-tau levels in the spectrum of frontotemporal dementia (FTD)-related disorders [17] as well as in vascular dementia (VaD) [49, 50], although the reproducibility of these alterations are under discussion [17, 51]. Although meta-analysis studies support the presence of elevated t-tau levels in frontotemporal lobar-degeneration (FTLD) and VaD, these alterations are not as high as those detected in AD and CJD [52]. Importantly, alterations on t-tau levels in VaD and FTLD are dependent on the heterogenic presentation of these conditions. For instance, elevated t-tau is observed in VaD patients without progressive leukoaraiosis, while VaD patients with progressive leukoaraiosis have normal t-tau values [49]. Additionally, studies in VaD cases may have selection bias as co-occurrence of vascular and AD-related pathology is well-known [53]. In regard to FTLD cases, the two major subtypes, FTLD-TDP (FTLD with TAR DNA-binding protein 43 inclusions) and FTLD-tau (FTLD with tau inclusions) did not seem to differ on t-tau levels [54], although it has been recently shown that t-tau harbors a better discrimination rate than TDP-43 proteins in the differentiation of both FTLD subtypes [55]. Overall, in FTLD cases, despite the presence of slightly to moderate increased tau levels compared to controls in several studies, these differences, when observed, do not harbor clinical significance [56]. However, a potential prognostic role of t-tau levels in FTD has been suggested as non-inherited FTD patients with high t-tau levels (≥400 pg/mL), who had shorter survival than those with low levels. Instead, p-tau concentrations were not associated with disease prognosis [57].

In Parkinson's disease dementia (PDD) t-tau levels are also elevated compared controls or to Parkinson's disease patients with normal cognition, but lower than those detected in DLB [58, 59]. Whether elevated levels of t-tau in PDD are related to an underlying tau pathology participating in the development of dementia, similar to AD, or just reflecting increased neuroaxonal damage compared to PD cases is still a matter of debate.

In corticobasal degeneration (CBD), initial reports suggested the presence of elevated t-tau levels [60, 61], but decreased or non-altered levels were later reported in other studies [62, 63]. Similarly, patients with progressive supranuclear palsy (PSP) showed total-tau levels comparable to those detected in controls [61, 63].

Increased CSF t-tau levels in normal pressure hydrocephalus (NPH) patients compared to controls have also been reported [64]. Interestingly, t-tau levels correlated with the severity of dementia, urinary incontinence, and gait disturbance. However, further studies have not been able to replicate the presence of elevated t-tau in NPH patients [65, 66].

In Huntington's disease (HD), a recent study reported elevated levels of CSF t-tau in gene expansion carriers compared with their control subjects. Additionally, t-tau concentrations were associated with phenotypic variability, thus a role for t-tau as a biomarker of disease progression was proposed [67]. However, a diagnostic role for t-tau in HD is excluded as no differences between HD patients compared with pre-manifest gene expansion carriers have been reported [68].

As a marker of neuronal damage, elevated t-tau levels have been reported in acute stroke [69] and head trauma [70]. CSF t-tau levels in acute brain injury present a transitory peak. For instance in traumatic brain injury (TBI), t-tau levels increased shortly after contusion, peaking in the second week post-trauma, slowly decreasing after this period and reaching basal values at 43 days [70]. Instead, in Olympic boxers subjected to repetitive trauma t-tau levels increased after boxing and remained elevated after a rest period of at least 14 days [71]. In acute stroke, t-tau levels are associated to disease severity and long-term outcome [72]. The sizes and localization of the lesion generally affects the profile of CSF t-tau levels after stroke which vary to a great extent, generally reaching maximum levels after 3 weeks to 1 month and returning to normal levels after 3–5 months [69, 73]. Other neurological conditions with transiently elevated t-tau levels include acute Wernicke's disease [74, 75], after chemotherapy treatment for hematologic malignancies [76], and patients with temporary neurologic dysfunction after aortic surgery [77]. Altogether, these studies support the idea of CSF t-tau reflects the degree of brain injury and harbors a prognostic value in transient acute neuronal damage syndromes.

An important confounding factor in the biomarker field is the age of subjects in the study. In this regard, the discriminative power of CSF t-tau is higher in young old (<70 years) than in old (≥70 years) control and AD cases, indicating that CSF t-tau loses its discriminative power along the aging process [78]. Therefore, the age effect should be considered when establishing the diagnostic parameters of t-tau quantification as CSF biomarker. Increased t-tau levels during aging in healthy individuals have been validated in several independent cohorts [79], which in turn were associated to ApoE genotype [80, 81]. Consequently, age-dependent t-tau cut-off values in neurologically and psychiatrically healthy individuals have been established [82].

3.2. P-tau

While t-tau reflects axonal degeneration, p-tau levels reflect the phosphorylation state of tau in the brain tissue. This idea is supported by the absence of alterations in p-tau in neurological diseases presenting neuronal damage but no p-tau pathology in the brain tissue, such as in acute stroke [69].

Contrary to t-tau, elevated CSF p-tau levels seem to be more restricted to AD cases [83]. This is an interesting recurrent observation as aberrant tau phosphorylation also occurs in the brain tissue of tauopathies such as FTD with Parkinsonism linked to chromosome 17 (FTDP-17), Pick disease (PiD), CBD and PSP leading to aggregation into neurofibrillary tangles (NFT) and axonal transport dysfunction [84–86].

Neurofibrillary changes are composed of hyper-phosphorylated tau forms that correlate with disease duration and severity [87]. Indeed, the severity of cognitive impairment correlates better with the burden of neocortical neurofibrillary tangles than with amyloid pathology [87–89]. While meta-analysis studies indicate that CSF p-tau levels are a moderate prognostic marker in AD [90], longitudinal studies show that p-tau-181 levels correlated with the progression of cognitive decline [91]. Additionally, a low p-tau-181/tau ratio has also been reported as a strong predictor of cognitive decline [92]. In contrast, p-tau-231 levels correlate with the rate of hippocampal atrophy in AD cases, which are independent of disease duration and severity [93] as well as with a reduction hippocampal volume detected by magnetic resonance imaging (MRI) [94]. Since rates of hippocampal atrophy are suggested to reflect reduction of neuronal density, these observations suggest that p-tau231 is directly associated to extensive neuronal damage but not to disease stage. Additionally, p-tau-199 levels have been shown to be useful in the discrimination of AD patients from non-AD-related dementia and non-demented patients in a large-scale multicenter study [95].

A comparative study on p-tau231, p-tau181 and p-tau199 performance showed that the three p-tau forms were significantly elevated in patients with AD compared with FTD, DLB, VaD and control cases [96]. This study also indicated that p-tau231 and p-tau181 assays performed similarly in the discrimination of AD from non-demented controls, whereas the p-tau199 assay showed a weaker discriminatory value. However, the combinations of the three measurements did not add discriminative power compared to single measurements. Although alternative p-tau epitopes have been studied in the context of AD pathogenesis, it is generally considered that p-tau181, 199 and 231 are those more characteristic to AD. Indeed, most studies have focused on p-tau231 and p-tau181 [14], which in turn, are the most standardized assays for p-tau quantification.

For p-tau-181, a cut-off of >60 pg/mL is generally used to define pathological levels due to AD pathogenesis [97].

While other p-tau species have also been measured such as p-tau199, p-tau199 + 202, as well as p-tau396 + 404, importantly, p-tau levels in AD are increased not only compared to controls, but also compared to other tauopathies and neurodegenerative diseases [98]. Measurement of them becomes a useful marker in the differentiation of AD from its most relevant differential diagnoses. Phosphorylation at Thr-231 is helpful in the discrimination of AD from FTD, and its levels are correlated with disease progression, whereas p-tau-181 (the most established p-tau assay [99]) improves the differentiation between AD and DLB [96, 100, 101]. Additionally, p-tau, when used in combination with amyloid beta-42 (p-tau/amyloid beta-42 ratio), shows the best diagnostic performance in the discrimination of AD from FTLD [102]. This meta-analysis study also reports that p-tau alone would be more useful for high Mini-Mental-State-Examination (MMSE scores), while p-tau/amyloid beta-42 would be preferable for low MMSE scores and younger patients.

Several explanations have been postulated for the specific preserve of high CSF p-tau concentrations in AD. First, it could be that primary tauopathies may present different phosphorylation profiles than those observed in AD. While the complete differential phosphorylation signatures in the spectrum of tauopathies is still not completely defined, in AD, tau is hyperphosphorylated at multiple sites (>30 sites). However, presence of tau hyper-phosphorylation at several epitopes such as 181, 199, 231,396 and 404 is a common hallmark in tauopathies [103].

A decrease on CSF t-tau in non-AD tauopathies could compensate the absence of elevated p-tau levels. However, t-tau levels are altered neither in the brain, nor in the brain tissue of non-AD tauopathies. Another aspect to be considered is the differential susceptibilities to clearance between tau forms. While tau turnover is delayed for insoluble forms, it is accelerated for soluble and phosphorylated tau [104]. Therefore, it is tempting to speculate that the combination of some or all these factors may have an influence in the differential CSF t-tau and p-tau profiles observed between tauopathies and AD.

CSF p-tau levels (p-tau-181) have also been reported to be moderately increased in CJD [17, 105]. Although p-tau values in sCJD are only from marginal to slightly elevated, most likely reflecting basal phosphorylation of tau molecules released into the CSF as a consequence of neuronal damage, these alterations are subtype-dependent. In fact, sCJD subtypes VV2 and MV2K showed the highest p-tau levels positively correlating with the amount of tiny tau deposits in brain areas showing spongiform change [24]. In agreement with these observations higher p-tau levels were detected in PRNP codon 129 VV cases compared to MM and MV cases where prion type was unknown [27].

Compared to controls, slightly increased p-tau concentrations have been reported in DLB [17], an observation supported by meta-analysis studies [52]. However, a large amount of studies report normal p-tau concentrations [106–109]. While several studies detected similar concentrations between DLB, PD, and PDD groups [22, 110], other reports suggest that among the group of α-synuclein aggregation disorders, DLB patients show the highest levels of p-tau [59].

Although it is broadly accepted that p-tau levels in FTLD are lower than those reported in AD and similar to controls [111], it has been recently shown that CSF p-tau levels are positively correlated with postmortem tau pathology (cerebral tau burden) [112]. Another interesting finding of this study was the observation that CSF p-tau levels in FTLD-TDP were lower than those detected in FTLD-tau.

In contrast to t-tau, p-tau levels are not elevated in acute brain injury or in TBI [69, 71, 73]. These results support the idea that CSF t-tau and p-tau reflect different pathogenic processes occurring in the brain tissue. While t-tau would be associated to the degree of neuro-axonal damage, p-tau would mirror the presence of hyper-phosphorylated tau forms, and therefore, the presence of neurofibrillary tangles.

Interestingly, a straightforward association has been suggested between ischemic events, tau hyper-phosphorylation and the formation of NFT. In this regard, hyper-phosphorylated and truncated tau-forms, resembling those detected in AD, accumulate after a transient cerebral ischemia [113, 114]. In humans NFT pathology is detected in TBI, but presenting remarkable differences in terms of temporal and regional affection: in TBI, NFT are concentrated in the

superficial layers in the neocortex, whereas in AD they predominate in the deep layers [115, 116]. Additionally, in mouse model of repeated TBI, elevated p-tau without NFT formation was observed in aged mice overexpressing human tau [117]. Finally, the absence of altered p-tau levels in the CSF of acute brain damage could also be explained by the presence of different isoforms of aggregated tau. Indeed, this might also explain the unaltered CSF p-tau levels in tauopathies showing NFL pathology such as PSP [118].

3.3. P-tau/t-tau - (t-tau/p-tau) ratio

As described above, the partial overlap on t-tau levels observed in sCJD and AD cases decreases the specificity of tau quantification in the differential diagnostic context of both diseases. An interesting addition to the biomarker field was the observation that p-tau/t-tau ratio greatly improved the discrimination of sCJD cases, not only from AD, but also from other tauopathies showing increased t-tau levels. This finding was initially reported by Riemenschneider and colleagues in a small cohort of sCJD cases (n = 20) [119] and further validated by many independent studies in large sample populations [16, 120, 121]. Diagnostic parameters and cut-off values were calculated in a cohort of more than 1000 sCJD cases [22]. For the discrimination of sCJD from neurological controls and AD the area under the curves were from 0.996 and 0.990 respectively, indicating that p-tau/t-tau ratio is able to almost fully discriminate sCJD from non-CJD cases.

Finally, p-tau/t-tau ratio has been proved in independent studies to discriminate the two main forms of FTLD; FTLD with TAR DNA-binding protein 43 (TDP-43) inclusions (FTLD-TDP) and FTLD with tau inclusions (FTLD-tau), with reduced p-tau/t-tau ratio detected in cases with FTLD-TDP pathology [122, 123]. This goes in line with the recent observation that patients with primary progressive aphasia with a non-AD profile (presumably FTLD) were stratified in two clusters according to p-tau/t-tau ratio, possibly corresponding to FTDP-tau and FTDP-TDP pathologies [124].

3.4. Non-p-tau

Recently, an assay able to reliably measure CSF concentrations of non-phosphorylated tau (non-p-tau) has been developed. The assay specifically measures non-p-tau at epitopes 175, 181 or 231 [15]. The non-p-tau CSF levels in AD cases (at MCI or dementia stages) were increased compared to controls. Additionally, the authors did not find differences on non-p-tau levels between patients in the MCI and the dementia stages of AD, in agreement with the presence of increased t-tau concentrations in MCI [43, 46, 125].

One of the major handicaps in the use of t-tau and p-tau concentrations in the differential diagnosis of neurodegenerative dementias is the partial overlap on both biomarkers among several conditions [17, 22, 83]. Thus, it could be hypothesized that the comparative study of non-p-tau in diseases with brain injury (elevated t-tau), but differential tau pathology could improve the discrimination achieved by both t-tau and p-tau. In this regard, a recent study investigated if non-p-tau quantification could improve the current diagnostic performance of the AD-associated CSF biomarker panel (amyloid beta-42, t-tau and p-tau-181)

in differential diagnosis of four neurodegenerative dementias (AD, FTLD, DLB, CJD) [107]. While the authors concluded that non-p-tau quantification had no added diagnostic value as a CSF biomarker for the differential diagnosis of neurodegenerative dementia, it improved the discrimination of sCJD cases. Unfortunately, as t-tau levels were above the quantification limit in 17 out of 19 CJD cases analyzed in this study, no significant conclusions could be drawn on the differential diagnostic accuracy of both tests.

In summary, preliminary observations indicate that the non-p-tau assay may be an interesting additional tool for the study of the dissociation between neuronal damage and tau pathology in the brain and biological fluids of neurodegenerative disorders.

3.5. Tau truncated forms

A growing body of literature is pointing to tau fragments, produced by cleavage events, as major players in the onset and the progression of the pathology [126–129]. In AD brains, after an initial misfolding at early stages of the disease which involves the physical contact of the N-terminal region with the microtubule binding repeats, tau is cleaved first at residue D421 followed by cleavage at residue E391, while N-terminal cleavage appears in later stages of the disease [126, 130]. The differential enzymatic cleavages during the pathological process is mostly dependent on Caspases activation, which lead to the generation of several tau fragments, each displaying its own profile of neurotoxicity [131]. Additionally, Calpain proteases have been shown to produce a triplet of tau fragments spanning from 35 kDa to 15 kDa. Similarly to full length tau [132, 133], several reports have shown that tau fragments can be secreted and uptaken from cells and brain slices and mediate toxicity [134–136].

These and other findings led researchers to investigate the presence of tau fragments in CSF and other biological fluids as potential biomarkers for the differential diagnosis of tauopathies and associated diseases. In CSF, at least 10 fragments were characterized in AD by mass spectrometry [137]. The presence of the 20 kDa caspase-6 cleavage product of tau in the CSF of AD has been reported to be associated with brain pathology and was found to be increased with the severity of the disease and the overall measure of global cognition [138]. Other reports found a 26–28 kDa fragment in both AD and strokes patients [139]. Tau bands ranging from 20 to 40 kDa were found in AD and control CSF [140, 141], which corresponded to N-terminal and mid-domain fragments, while no C-terminal fragments were found. Therefore, biomarker-based diagnosis would strongly depend on the subset of tau species analyzed.

Tau fragments have been proposed as biomarkers not only for the discrimination of AD from controls, but also for the differential diagnosis within related neurodegenerative diseases. For instance, a divergent pattern of expression of different N-terminal tau fragments was found between AD and PSP, even though such kind of studies are limited by the frequently overlapping clinical diagnosis [142]. Nonetheless, the ratio between a 33 kDa and a 55 kDa fragment in CSF was proposed as a more specific and reliable biomarker for the diagnosis of PSP [63]. Moreover, in CSF derived from TBI patients, a 30–50 kDa tau fragment was found to correlate with the extent of axonal damage [143]. Lastly, in CSF derived from either lumbar or cervical puncture from amyotrophic lateral sclerosis (ALS) patients the neurotoxic 17 kDa fragment produced by calpain cleavage was found to be elevated compared to controls [144].

While no C-terminal tau fragment was detected in CSF, a combination of ELISA and mass spectrometry analysis [145] revealed the presence of a C-terminal tau fragments in serum derived from AD patients. The levels of this fragment inversely correlated with the Mattis Dementia Rating Scale, suggesting that the increase of the fragment in the serum might parallel the cognitive decline.

3.6. Tau-seeding-based assays

The development and implementation of seeding-based methodologies for disease diagnostic purposes is an emerging topic with demonstrated clinical applicability in the field of prion diseases due to the real-time quaking-induced conversion assay (RT-QuIC). This assay exploits the self-propagating replication capacity of the abnormally folded and pathogenic PrP (seed), which induce the misfolding of naive PrP molecules (template) into a similar pathogenic structure. This reaction can be amplified to detectable levels and quantified in real-time. Importantly, the use of CSF from prion disease cases as a seeding material in the RT-QuIC assay allows the discrimination of CJD from non-CJD cases with high diagnostic accuracy and almost full specificity [146, 147].

Although the precise mechanism of neurofibrillary tangle formation in the brain tissue is not fully understood, the observation of tau spreading implicates the presence of a prion-like pathogenesis, where abnormal tau forms may induce the misfolding of non-pathological forms in a regional-dependent manner. Therefore, the principles of the RT-QuIC assay could be applied to the amplification of tau pathological forms in biological tissues. Although, successful cell- and tissue-based tau seeding assays have been recently developed the presence of tau seeding activity in the CSF of a tau-related pathology has been only reported once. Saijo et al. developed a tau RT-QuIC based on the use of a 3-repeat tau fragment as a substrate, a tau isoform that preferentially accumulates in Pick bodies. The authors detected positive tau RT-QUIC signal in the CSF from Pick disease (PiD) cases, suggesting that this assay may be helpful in discriminating PiD and non-PiD cases [148].

4. Tau in blood-based biofluids

Although lumbar puncture is a routine technique in the diagnosis of neurological syndromes, it entails important side effects for the patient being headache and cranial nerves dysfunction the most frequent ones [149, 150]. Therefore, many efforts are focused to identify biomarkers in other body fluids. Among them, blood analysis has arisen as a promising and cost-effective tool to identify biomarker molecules out of the CSF. Besides avoiding side-effects associated to lumbar puncture, blood extraction is suitable to be practiced in ambulatory centers or in home visits for first disease screening. However, the blood-CSF barrier imposes a decrease in the concentration of brain-specific molecules in the blood compared to that found in the CSF, which creates the need to develop ultra-sensitive quantification methods [151]. Several works have investigated the use of amyloid-beta peptides levels in plasma as a biomarker candidate for AD, but little research is done for other proteins [152, 153].

Owing to the lack of high-sensitive techniques and the low amount of tau in blood compared to CSF, the initial measurement of tau in human plasma was technically complicated impeding the detection of this molecule in 80% of samples [154]. However, novel quantification methods were later developed to overcome this limitation. They include immunoassays based on carboxylated microsphere beads [155], digital array technology [156], immunomagnetic reduction assay [157, 158] and ultra-sensitive commercial ELISA kits [159]. This way, in the recent years, plasma tau has arisen as a promising biomarker in neurodegenerative conditions. Importantly, it does not show significant correlation with demographic parameters such as age, sex or educational level [160].

Although a study showed reduced plasma t-tau levels in AD patients compared to normal cognitive individuals [159], the current consensus data point toward the opposite direction. Indeed, in the blood-based diagnostics of AD, t-tau is the only significant biomarker in the discrimination of the disease, displaying an AD/control mean ratio between 1.5 and 4.5 [42, 161]. The use of an assay based on antibodies coupled to magnetic nanoparticles rendered very high values (>90%) of specificity and sensitivity when comparing healthy controls versus AD+MCI cases [157]. This method was subsequently validated in a study enrolling two independent cohorts, where those high levels of specificity and sensitivity were almost reached (>89%) in the combination of cohorts when comparing healthy with AD cases [162]. With these data, the authors concluded that the best performance of plasma t-tau in the AD diagnostics was in combination with plasma Amyloid beta-42 levels, in a similar manner than combination biomarkers increase the diagnostic accuracy of single measurement markers in the CSF [18].

In the differential diagnostic context, plasma t-tau also appeared elevated in AD compared to MCI. However, the overlap between groups hinders the clinical utility of plasma t-tau as a routine biomarker [163]. Plasma t-tau was not found increased in MCI cases that later developed AD compared to controls, neither in cases with pre-MCI stage of subjective cognitive decline (SCD) [164]. These findings suggest that plasma t-tau is a late marker of neuronal damage and cannot be used as a prognostic tool of the likelihood to develop AD-related dementia sensitivity of the methodologies is improved.

Plasma t-tau does not seem to be a good reporter of the tau pathology in AD brain, as no strong correlation between plasma and CSF t-tau could be soundly demonstrated so far in AD [163]. However, plasma and CSF t-tau appeared correlated in a very recent study performed in a cohort with various neurological syndromes [161]. On the other side, mild association of high plasma t-tau with AD-specific pathology cannot be discarded. Within the MCI group, those cases positive for amyloid beta-42 had elevated t-tau compared with those amyloid beta-42 negatives [163]. In addition, high plasma t-tau levels in AD patients are associated to rapid disease progression in late clinical stages, including cognitive impairment and brain dysfunction [163]. The detailed relationship between plasma t-tau and the pathological state of the brain during the course of the disease is not yet clear. The t-tau concentration in plasma has been associated to abnormal cortical thickness and memory performance in a cohort of MCI patients [165]. However, in another cohort of MCI and AD cases, plasma t-tau appeared unrelated to cortical thickness in AD-specific regions [166]. In the same study though, the authors did report a significant association of high plasma t-tau levels and reduced gray matter density.

Specific measurement of p-tau in plasma still represents a technical challenge. One of the first attempts to measure p-tau-231 in human plasma was based on a complex immunoassay using multi-arrayed fiber optics coupled to rolling circle amplification (a-EIMAF) [167]. Although the authors only measured 5 sCJD plasma samples and 5 controls, t-tau was increased in all the disease cases. By contrast, no differences between p-tau-231 levels were detected. Interestingly, a similar pattern of t-tau and p-tau-231 was found in the brain tissue. It should be noted that the authors used arbitrary units for p-tau-231 quantification due to technical impediment [167]. Very recently, fine quantification of plasma p-tau-181 has been possible using a novel immunoassay based on digital array technology that has been modified to detect this phosphorylated form. In an exploratory case–control study that included 3 small cohorts (<50 cases per cohort), AD, Down syndrome (DS), neurological controls and healthy controls were analyzed [168]. In general, p-tau-181 was specifically increased in AD and DS patients compared to controls. Correlation between age and p-tau-181 was found in the DS group, supporting the link between this protein and the presence of amyloid pathology. A striking correlation was also found between p-tau-181 levels in plasma and in CSF, in contrast to the weak or no correlation between CSF and plasma t-tau [160]. Therefore, it is possible that phosphorylated tau, in contrast to t-tau in blood, is only originated in the brain.

Besides plasma, the levels of t-tau and p-tau-181 have been recently evaluated in the serum of AD cases by real time Surface Plasmon Resonance. Both concentrations were increased in AD compared to controls, with a better performance of tau than p-tau-181. Tau was also significantly elevated in AD compared to MCI. Tau and p-tau-181 in serum appeared strongly correlated, which could mean un-specificity in the CSF-blood filtration of tau species [169]. Similar to plasma, serum tau levels also presented a negative correlation with scores of cognitive assessment (HMSE and MoCA).

Blood tau levels have also been investigated in rapid progressive dementias. One of the pioneering works reported an increase of t-tau levels in serum in CJD patients compared of those is serum of AD and other non-CJD rapid progressive dementias. In spite of the small number of cases analyzed (<15 per group), it provided a valid proof-of-concept toward measuring t-tau in blood to differentially diagnose CJD [170]. A very recent study has validated these data using a larger and autopsy confirmed cohort. The levels of plasma tau in sporadic CJD appeared more than 2-fold elevated compared to neurological controls and to AD. Genetic CJD cases also presented increased plasma tau compared to AD. Comparison among different subtypes of sCJD also revealed differences in plasma tau, which was higher in MM/MV1 and MM1 + 2 subtypes. On the opposite, the subtype MV2 (kuru plaque) presented the lowest levels of plasma tau among the disease group [161]. These results indicate that plasma t-tau may be also reflecting the subtype-specific hallmarks of sCJD pathology.

5. Tau in the evaluation of disease-modifying therapies

Several strategies have been considered in order to prevent tau deposition. Compounds inhibiting tau aggregation [171], stimulating immune system against misfolded and

phosphorylated tau, as well as inhibiting of kinases responsible for tau hyper-phosphorylation, especially glycogen synthase kinase-3, have been proposed [172–174]. Therefore, tau and p-tau quantification in biological fluids is emerging as a potential tool in the evaluation of disease-modifying therapies. On one hand, alterations in p-tau levels would be informative of the phosphorylation and aggregation state of tau in the brain tissue. On the other hand, therapeutic approaches preventing neuronal damage would also alter the levels of t-tau protein in the CSF.

Interestingly, decreased CSF p-tau levels have been reported in patients treated with bapineuzumab, an antibody capable of binding to soluble and fibrillary forms of amyloid beta despite clinical trials do not lead to clinical benefit for intravenous bapineuzumab treatment [175].

However, as this research field is in its early phases, longitudinal studies are required to definitely demonstrate the relationship between temporal alterations in tau levels and clinical outcome. Additionally, as the effect of disease-modifying therapies on CSF biomarkers may be influenced by the mechanism of action of the therapeutic compound, alternative biomarkers should be used in order to assess the complete panel of hallmarks associated to the neurodegenerative process.

6. Conclusion

CSF t-tau and p-tau concentrations display good sensitivity and specificity in the discrimination of AD patients from non-demented control cases and a high diagnostic accuracy in the discrimination of sCJD cases. Both biomarkers become useful in the identification of patients at risk of progression to AD. The partial overlap between t-tau and p-tau levels among several neurodegenerative dementias indicates that more specific biomarkers are required in order to improve the accuracy in the differential diagnostic context. Alternative tau-based approaches have been recently developed and form the basis of the second-generation tau assays. On one side, the use of composite biomarkers, the development of non-p-tau assays and tau seeding methodologies, and the detection of tau truncated forms and alternative phosphorylation sites are promising alternatives that need further research to maximize their potential as diagnostic and prognostic tools. On the other side, the quantification of tau in blood-based fluids is gaining experimental momentum due to the advantages of using blood instead of CSF and to the implementation of high-sensitivity tests that can detect scarce tau amounts in plasma and serum. Several contradictory findings in the field might be related to the use of differential methodologies, which in some of the cases are not yet fully implemented and validated in large and independent cohorts.

Finally, the clinical diagnostic utility of tau measurements is complemented by the role of this protein as a reporter of the degree of neuro-axonal damage in the brain and the pathological hyper-phosphorylation tau state, which is specifically present in tauopathies. Since we are in the dawning of second-generation tau assays, future studies are necessary to validate them in larger and independent cohorts of patients in order to prove their clinical utility while they

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	Total tau	*Phospho-tau*	*Non-phospho-tau*
Cerebrospinal fluid			
Alzheimer's disease	++	++	+
Parkinson's disease	=	=	NA
Parkinson's disease dementia	+	=	NA
Dementia with Lewy bodies	+	=	=
Creutzleft-Jakob disease	+++	+	+++
Frontotemporal dementia	+	=	=
Vascular dementia	+	=	NA
Amyotrophic lateral sclerosis	+	=	NA
Normal pressure hydrocephalus	+	=	NA
Plasma			
Alzheimer's disease	+	++	NA
Creutzfeldt-Jakob disease	+++	=	NA
Serum			
Alzheimer's disease	+	++	NA
Creutzfeldt-Jakob disease	+++	NA	NA

=	Unchanged
+	Slightly increased
++	Increased
+++	Highly increased
NA	Not analysed

Table 1. Tau levels in the biological fluids of major neurodegenerative diseases and associated disorders compared to control cases.

might provide important clues toward understanding the molecular events taking place in neurodegenerative processes.

A summary of the findings on tau-related biomarkers in the CSF and blood of neurodegenerative dementias is shown in **Table 1**.

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Chapter 5

Tau in Tauopathies That Leads to Cognitive Disorders and in Cancer

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Additional information is available at the end of the chapter

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Abstract

Tau is a copious microtubule-associated protein mainly expressed in neurons; it is also expressed in non-neuronal cells. Tauopathies are neurodegenerative diseases occurring mostly within the neuronal and glial cells of the central nervous system with a conspicuous tau pathology. In tauopathies, soluble tau disconnects from microtubules and forms abnormal, aggregated filamentous assemblies of hyperphosphorylated tau. Genetic, pathological and biochemical analyses have also proved that tau protein plays a major role in the pathogenesis of several tauopathies. Cognitive disorders are a type of psychological disorders that mainly distress observation, learning, memory, and problem elucidating. Among different cognitive disorders like amnesia, dementia, and delirium tauopathies mainly involve in dementia. Though tau is a neuronal protein, it is also expressed in various non-neuronal cells, like those of the liver, kidney and muscle. The activity of non-neuronal tau, especially in cancer cells, still needs to be elucidated; tau might have significant functions in non-neuronal cells. This chapter describes the associations between tauopathies and cancer.

Keywords: tau, tauopathies, cancer, Alzheimer's disease, microtubule, phosphorylation

1. Introduction

The microtubule-associated protein tau was originally identified as a heat-stable protein that was co-purified with tubulin [1] and is solely expressed in higher eukaryotes [2–4]. Its main functions include controlling microtubule assembly [1, 5, 6], contributing to the polymerization of microtubules [7] and acting as a parameter of axonal transport [8] and axonal diameter [9]. Tau protein is also involved in the formation polarity during neuromas and in neurodegeneration [10]. It also acts as a protein framework to control the signaling pathways. Phosphorylation is the most common post-translation modification of tau protein. Hyperphosphorylation of tau

protein is detected in neurofibrillary tangles (NFTs). NFTs are noticeable in many age-dependent diseases, which are collectively called tauopathies. Tau was not only observed in the nucleoli of non-dividing cells but also in high amounts in the nuclei of cancerous cells that specified a precise protagonist of tau in dividing cells [11]. Hence, tau might have some important functions in fast-dividing cells, which in turn may have an effect on cancer pathogenesis.

In addition to neurons, tau expression has been noticed in human breast, prostate, gastric, colorectal and pancreatic cancer cell lines and tissues [12–18]. Tau is also found in patients with twisted tubulofilamentous of inclusion-body myositis [19]. The activity of non-neuronal tau, especially in cancer cells, still needs to be exemplified. The hyperphosphorylation of tau leads to Alzheimer's disease (AD) and tumor suppressor protein pRB, as well as different cell cycle activators like Cdk4, Cdk2, cyclin D, cyclin B and PCNA are present in the neurons of AD patients; this indicates re-commencement of the cell cycle, which may be a mechanism of neurodegeneration [20]. There are more associations between tauopathies and cancer, as high levels of cancer-related proteins like Fos, Jun and BRCA1 are found in AD [21, 22]. Cancer pathogenesis and tauopathies are also linked with respect to signal transduction, where the prolyl isomerase, Pin1, acts as a main factor [23]. Tauopathies also leads to cognitive discrepancies in for AD.

Tau protein activity is predominantly controlled by its phosphorylation. Two important aspects of cancer, cell signaling pathway and cell cycle progression, can be modulated by tau. Tau might work as a possible modulator of the efficacy of cancer chemotherapy drugs. In some previous experiments involving tau in different cancers, a connection between tau expression and drug resistance was noted [12, 14, 24–27], as a competition between tau and the drugs for microtubule-binding sites occurred. Deregulation of Pin1 can be a crucial protagonist in the pathogenesis of tauopathies and cancer and might be the basis for remarkable new therapies in the future [23]. Finally, there could be a good liaison between age-related tauopathies that leads to dementia that is significant category of cognitive disorders and cancer, mainly because both involve aberrant tau phosphorylation.

2. Tau in tauopathies

The main roles of tau protein are stimulating microtubule assembly and maintaining microtubule stability; these are regulated by its phosphorylation level. The preeminent activity of tau is maintained by its regular phosphorylation level, that is, 2–3 mol phosphate/mol of the protein [28]. The unusual functions of tau protein might be defined by this phosphorylation as well. Tau hyperphosphorylation reduces the microtubule binding and microtubule assembly-forming activity of tau [29, 30]. In case of in vitro experiments, cleaved tau has a high tendency to unfasten from microtubules and subsequently, to aggregate [31].

2.1. Tau gene

A particular gene, MAPT, that resides on chromosome 17q21 encodes tau protein [32]. The size of this gene is more than 50 kb and contains two differently modified haplotypes, H1 and H2 [33, 34]. Because of alternative splicing, several high and low molecular weight isoforms of tau are engendered. Normally, six isoforms of 352–441 amino acids are articulated in tau in the central nervous system (**Figure 1**), which are differentiated by the presence or absence of exons 2, 3 and 10 [3]. Exon 10-containing isoforms are known as four-repeat or 4R isoforms, whereas isoforms excluding exon 10 are known as three-repeat or 3R isoforms.

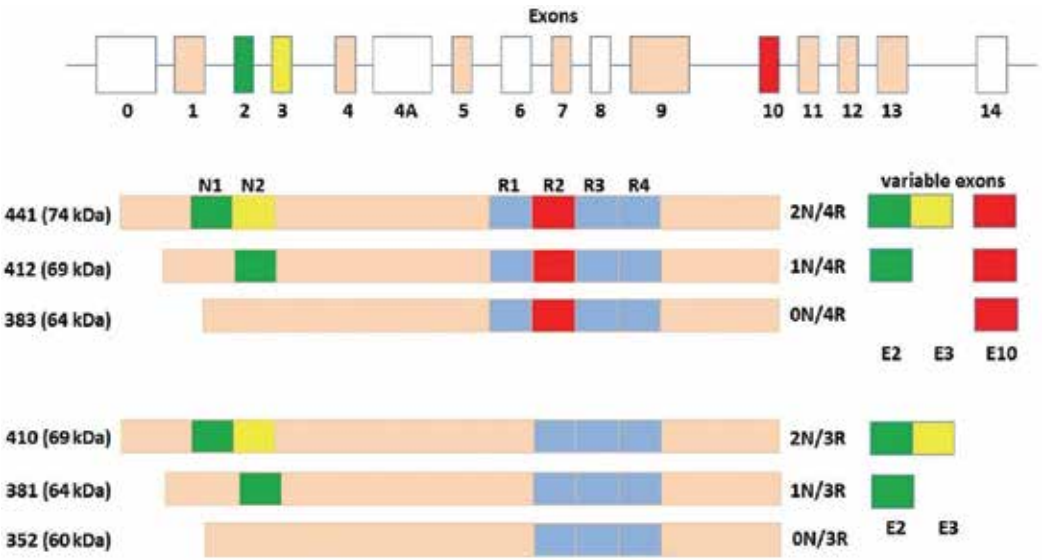

Figure 1. Graphic representation of human tau gene.

2.1.1. Post-translation of tau

There may be several types of post-translation modifications of tau protein, of which phosphorylation is the most common. Phosphorylation occurs when a phosphate group is added by esterification to one of the three amino acids, serine (S), threonine (T) and tyrosine (Y). Increase in phosphorylation decreases the affinity of tau toward microtubules and finally destabilizes cytoskeleton. There are 85 recognized phosphorylation sites described in human AD brain tissue. Among them, 53% phosphorylation sites of tau [45] are serine, 41% sites [41] are threonine while only 6% sites [5] are tyrosine [35–37]. Tau protein also comprises 11 recognized O-glycosylation sites, where the covalent attachment of oligosaccharides to a protein occurs [38]; 12 glycation sites, where non-enzymatic protein glycosylation is routinely detected in mature tissues [39–41], 1 prolyl-isomerization site, where the reaction that relocates the protein disulfide bonds occurs [42, 43]; 3 tau truncation sites, which improve the tau aggregation ability and implement neuronal apoptosis [44–46]; 4 tau nitration sites, where nitrogen oxide adjuncts to the tyrosine of an organic molecule for tau aggregation [47]; 8 tau polyamination sites, which are involved in the NFT formation process [48, 49]; 3 sites of ubiquitination, which is subordinately implicated in tau pathology [50, 51]; 1 site of sumoylation and 1 site of oxidation, which stabilizes ubiquitination and is associated in tau lesion development, respectively [52–55]; and lastly 2 sites of self-aggregation, which reconciles cell toxicity to prime for AD [56]. All of the post-translation modifications are shown in **Figure 2**. Phosphorylation impacts tau's solubility localization, and role and connections, and vulnerability to other post-translational modifications. Additionally, the hyperphosphorylation of tau simulates pathological stoichiometric tau phosphorylation and replicates the structural and functional characteristics of AD [57]. Several phosphorylated sites explicit to diseased tau were discovered by the analysis of soluble and insoluble tau fractions using mass spectrometry [58]. Tau ensures that the axonal microtubules work properly, and lets the neurons function normally, whereas

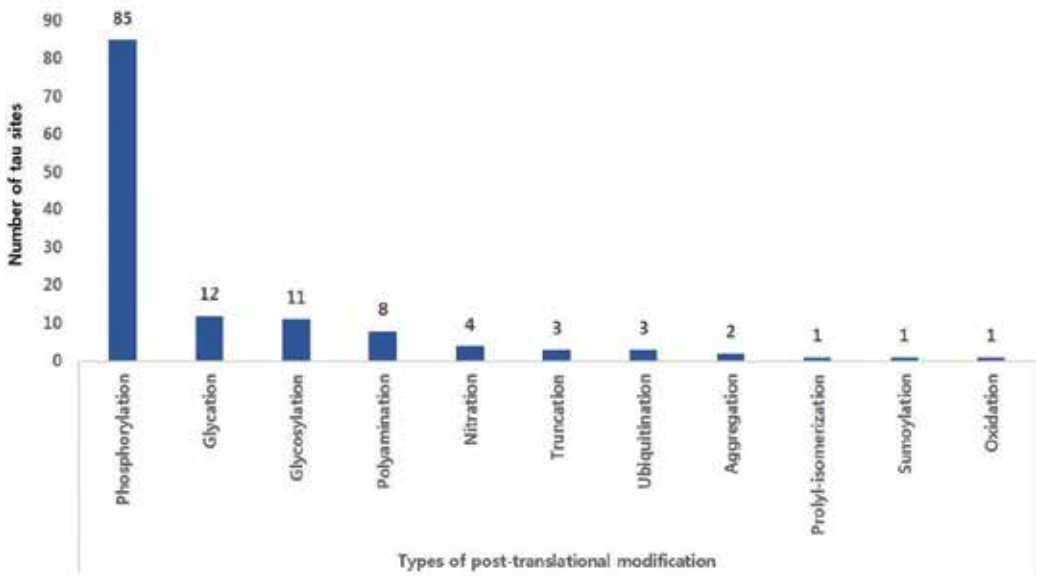

Figure 2. Number of post-translation modifications of tau protein in function.

hyperphosphorylated tau cannot ensure a well-organized microtubule binding and leads to neuronal loss due to the disassembly of microtubules.

2.2. Tauopathies

Neurodegenerative diseases that are caused by abnormally phosphorylated tau mainly in older people are collectively known as tauopathies [59]. In tauopathies, such as AD, tau is uncharacteristically hyperphosphorylated and amassed as NFTs of paired helical filaments (PHFs) [60–65]. The main obsessive mediator of the most prevalent tauopathy, AD, is misfolded tau [66]. Besides AD, several other neuronal diseases such as frontotemporal dementia, Pick's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are also related to microtubule-binding protein tau [67, 68], and these types of central nervous system disorders are called tauopathies. The brains of patients with tauopathies consist of insoluble tau deposition, and the fibrils involved, which are located mainly in the cell bodies and neuronal dendrites, are called as NFTs [69]. Though the reasons of tau aggregation are not clearly identified, the post-translation modification of tau, mainly, hyperphosphorylation, is one of the main reasons for all tauopathies. Tau is phosphorylated at various serine and threonine residues, and hyperphosphorylation subsequently reduces the binding abilities of microtubules [30, 70–72] and increases aggregation [41, 73].

A few tauopathies are briefly described below (**Table 1**).

2.2.1. Alzheimer's disease

AD is the most common type of dementia accounting for anywhere between 50 and 80% of all dementias and can cause a treacherous decline in cognition day by day. Clinically, AD is

Disease	References
Alzheimer's disease	[66, 67, 74]
Down's syndrome	[75–77]
Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17)	[78–80]
Pick's disease	[81–84]
Progressive supranuclear palsy (PSP)	[85–88]
Creutzfeldt-Jakob disease	[89, 90]
Dementia pugilistica	[91, 92]
Inclusion-body myositis	[19, 93–95]
Gerstmann-Sträussler-Scheinker disease (GSS)	[96, 97]
Amyotrophic lateral sclerosis/Parkinsonism-dementia complex	[98]
Argyrophilic grain dementia	[82, 99, 100]
Corticobasal degeneration (CBD)	[101–104]
Diffuse neurofibrillary tangles with calcification	[105, 106]
Hallervorden–Spatz disease	[107, 108]
Multiple system atrophy (MSA)	[109, 110]
Niemann-Pick disease, type C	[111–113]
Progressive subcortical gliosis	[114]
Myotonic dystrophy	[115]

Table 1. List of neurodegenerative disorders that are categorized as tauopathies.

identified by the examination of senile plaques of extracellular Aβ-amyloid peptide deposits and NFTs of intraneuronal tau deposits [116]. AD is also observed in neuropil threads and senile plaques consisting of dystrophic neurites [117]. Tau biochemical analysis revealed that all of the six isoforms of tau are present in AD and that the filaments of NFTs are in a paired helical filamentous form or in twisted ribbons at some places. The apolipoprotein E-4 allele genetically amends periodic AD [118].

2.2.2. Progressive supranuclear palsy

PSP is a neurological syndrome characterized by postural instability and mild dementia, where tangles are present mainly in the subcortical and cortical areas of the brain. PSP is caused by the accretion of NFTs and is a four-repeat tauopathy [119]. It has been reported that a mutation of the tau gene may cause autosomal dominant PSP; environmental risk factors are not involved in PSP. In sporadic cases, the H1 MAPT haplotype has been constantly connected with PSP [119], whereas a different haplotype, H2, seems to be defensive against PSP [120].

2.2.3. Pick's disease

Pick's disease is an infrequent dementia of older people that affects the frontal lobes of the brain and causes speech complications like aphasia, and behavior problems, ultimately leading to death. Pick's disease is a sporadic 3R tauopathy, where insoluble tau accumulates

mainly in neuronal cells and in glial cells, such as prickle-shaped astrocytes and twisted bodies [121]. Like PSP, Pick's disease is also associated with a mutation in the tau gene. However, Pick's disease is not a distinct entity but one of the subtypes of the variety of diseases associated with temporal dementia [122].

2.2.4. Frontotemporal dementia with Parkinsonism associated with chromosome 17 (FTDP-17)

Frontotemporal dementia with Parkinsonism associated with chromosome 17 (FTDP-17) is a neurological disorder that is a part of frontotemporal dementia, categorized by a damage of the neuron in the frontal and temporal lobes of the brain. A loss of these cells can affect personality, behavior, speech and cause motor disturbances. Mutations in the tau gene can cause this dementia. 32 tau gene mutations have been recognized in over 100 families of this syndrome [123]. Tau gene mutations associated with FTDP-17 cause anomalous filament development and an amassing of tau in neuronal and glial cells in the cerebral cortex and in the nuclei of subcortical cells. Tau mutations alter tau isoforms in FTDP-17. The mechanisms of the modifications that lead to neuronal death are yet to be discovered.

2.2.5. Corticobasal degeneration

Corticobasal degeneration (CBD) is an adult variable dementia and neurodegenerative syndrome. This is a sporadic disease accounting for one per million cases of dementia per year; the incidence of CBD is ten times lesser than that of Parkinson's disease [124]. In case of CBD, filamentous inclusions in neurons and glia having selective accumulation of hyperphosphorylated four microtubule-binding repeat tau (4R-tau) are seen [125]. The tau H1 MAPT haplotype is also stalwartly related with CBD pathology, just as it is with PSP [120].

3. Tau in cancer

Tau expression has also been noticed in different non-neuronal cells like those of the liver, kidney, muscle and so on [126, 127] Tau protein has also been expressed in human breast, prostate, gastric and pancreatic cancer cell lines and tissues [12–16]. Tau is also found in patients with twisted tubulofilaments of inclusion-body myositis [19].

As both cancer and AD are age-related diseases, and as both diseases occur mainly in developed countries with similar dietary habits, there might be some correlation between the two diseases. Additionally, tau-positive and tau-negative cancer cells show different results after treatment with chemotherapeutic agents like paclitaxel [14].

In case of breast cancer, 52% patients are tau negative [14]. An approximately same result (57%) of tau expression in breast cancer was found in a research by a different group [128]. There are a lot of experiments based on breast cancer that show different percentages of tau negative. In case of gastric cancer, 30% patients are tau negative [15], whereas 25.7% patients are tau negative in case of ovarian cancer [25]. These results suggest that tau protein expression may be diverse for different cancer sites. The causes of different cell lines expressed as tau positive or negative are not clear enough. In case of prostate cancer, androgen-independent prostate lines

show a considerably higher level of tau than androgen-dependent cells lines. Even androgen-independent derivative cell line isolated from androgen-dependent line shows higher amount of tau than that of the original cells. Also, in case of ovarian cancer cells, endometrioid carcinoma cell types express higher levels of tau protein compared to other cells. Estrogen also regulates tau protein expression [129]. A more extensive analysis will be required to confirm all of these causes of tau expression level of different cell lines.

Tau escalates the deceiving and reconnection of isolated breast tumor cells, and circulatory tumor cells might be responsible for increased risk of disease repetition. That is why the pathological assessment of tau may be useful for patients by diminishing metastasis through circulatory tumor cells mobilization [130].

Heat shock protein (Hsp90) inhibitors are used as possible cancer treatment agents as several cancer-related proteins become stable by cooperating with Hsp90. Numerous Hsp90 inhibitors reduced tau phosphorylation at different sites of phosphorylation in cells overexpressing mutated human tau [131–134].

Pin1 (peptidyl-prolyl cis/trans isomerase (PPIase)) bonds to phosphorylated tau on the Thr231-pro site and catalyzes the isomerization of pSer/Thr-pro motifs, to prompt conformational changes in tau. These changes keep back the ability of phosphorylated tau to bind microtubules and inspire microtubule-binding abilities, thereby dephosphorylating tau protein via its phosphatase, the protein phosphatase 2 (PP2A) [135]. It is noteworthy that Pin1 is overexpressed in various types of human cancers and is also an outstanding prognostic marker in different cancers [136–138]. Pin1 is a molecular target for cancer therapeutics, as its inhibition in cancer cells can elicit apoptosis and conquer the renovated phenotype [139–141].

The deficiency of active Pin1 is responsible for unusual tau accumulation whereas Pin1 controls cell cycle and is essential for cell division. Pin1 overexpression increases oncogenesis by different cell signaling pathways. There might have been an antithetical association between tauopathies and cancer explained by Pin1 [142].

Many proline-directed protein kinases, such as cyclin-dependent kinases (CDKs), mitogen-activated protein kinase (MAPKs), glycogen synthesis kinases (GSKs) and PP2A, govern the reversible phosphorylation of tau [143–145].

Tau has some roles in signal transduction. There is a high volume of proline residues found in different domains of tau [146] that can interrelate with Src homology 3 (SH3) domain [147]. Tau can also interrelate with the SH3 domain of Src, Fyn and Lck, as revealed by the Glutathione S-transferase (GST) fusion binding assay [148]. The bonding of tau to microtubules has a significant effect on the tau-Fyn interactions, as observed by the biochemical analysis of tau-Fyn binding affinity [149]. Tau could encourage the activity of Src family kinases to measure tau's binding affinity for microtubules, thus resulting in tyrosine phosphorylation. In taxol-stabilized microtubules, Fyn can perform tyrosine phosphorylation without tau; phosphorylation of tubulin increases drastically if tau is added [150]. Hence, the relationship between tau and non-microtubule proteins might have a possibly noteworthy functional significance.

Initially, tau was isolated from the brain, but shortly after that, tau availability was not limited to neurons. In one of the initial experiments, non-neuronal tau from both primary human monocytes

and U297 lymphoma cells were studied, and both total and phosphor-specific tau were observed [151]. Several other experiments also exposed the availability of tau in different cell lines and tissues. Some of those experiments were very brief and only a northern or western blot was done to show the availability of tau mRNA or protein, respectively, from the liver and kidney of mice and other tissues of rats [126, 127]. Some of the experiments detected multiple tau isoforms and pointed out the correspondence between non-neuronal tau and neuronal tau [152], whereas others showed the microtubule-binding properties of tau from hepatoma and fibroblast cells [153]. From these experiments, it is clear that tau from both neuronal and non-neuronal cells might show similar properties. In one experiment using several human cell types including HeLa cells, lymphocytes and non-transformed skin fibroblasts, tau was not only observed in the nucleoli of non-dividing cells but also observed in higher amounts in the nuclei of cancerous cells that specified a precise protagonist of tau in dividing cells [11]. Hence, tau might have some important functions in fast-dividing cells, which might have an effect on cancer.

Tau might work as a possible modulator of drug resistance. Microtubule-targeting drug estramustine-resistant [154] E4 cells expressed a massive amount of tau at both the mRNA and the protein levels, unlike DU145 cells [13]. This experiment exposed significance of the incidence of tau in non-neuronal cells; this might have a connection with signal transduction and tau's microtubule-binding properties. The expression of tau is considerably diverse in cases of residual disease or in those with a pathological complete response (pCR) in patients with breast cancer undergoing chemotherapy by the microtubule-depolymerizing drug, paclitaxel. The residual disease group expressed more tau than the pCR group [14]. siRNA knockdown tau is more vulnerable to paclitaxel treatment than the wild-type tau in case of breast cancer cells [14, 26]. A nearly similar report was published, about the relationship between tau and paclitaxel resistance in case of gastric cancer [15].

As hyperphosphorylation of tau leads to AD, and tumor suppressor pRB protein as well as different cell cycle activators like Cdk4, Cdk2, cyclin D, cyclin B and PCNA are also present in the neurons of patients with AD, there might be an insinuation of the re-commencement of the cell cycle, which could be a mechanism of neurodegeneration [20]. In case of other neurodegenerative disorders that might be caused by tau protein including FTDP-17, PSP and CBD, these cell cycle activators were found [155]. Tau phosphorylation occurred at disease-relevant sites of primary rat neurons after insertion of oncogenes [156]. This is suggested by the fact that abnormal tau-related diseases are linked to cell cycle markers in several diseases, including cancer. The aged control mouse does not express the increase of the cell cycle marker, PCNA and cyclin D; this was responsible for the sign of neurodegeneration [157]. For normal human tau-expressing transgenic mice, increased tau phosphorylation occurred, along with insoluble tau being found in the brains of aged mice [157]. This suggests that irregular cell cycle re-entry might explain the presence of tau. CNS tissue from the *Drosophila* model used to study neurodegenerative diseases exhibited an increase in the cell cycle markers, PCNA and phosphor-histone 3, as well as neuronal loss [158], which is also evidence that tau drives cell cycle re-entry. The visible neuronal loss in *Drosophila* for either wild-type or mutant tau was overturned by hindering the mammalian target-of-rapamycin (mTOR) pathway, as well as by obstructing the cell cycle in different ways [158]. This finding also links cell signaling with tau-activated neurodegeneration. There are further associations between AD and cancer, as high levels of cancer-related proteins like Fos, Jun and BRCA1 are found in AD [21, 22].

Overexpression of Pin1, which is responsible for some types of cancer, works together with tau in a phosphorylation-dependent way to carry out tau phosphorylation at Thr231 [159]. Brains of patients with AD comprise less Pin1 than aged-matched normal brains; hyperphosphorylation of tau, behavioral defects as well as other forms of neurodegeneration might have occurred, owing to the loss of Pin1 [160]. When one copy of the p73 gene, a p53 family member that regulates Pin1 [161], was missing, thus leaving only one efficient copy, age-related neurodegeneration and tau hyperphosphorylation were induced [162]. Although tau influences neuronal death, its mechanism for doing so is not clear.

Two important properties of cancer, cell signaling pathway and cell cycle progression, can be modulated by tau. As both AD and most cancers are primarily observed in aged populations, the role of tau in cancer cells may be linked with tauopathies.

Patients with AD have a lower risk of different cancers. The genes that are overexpressed in AD and Parkinson's disease-type CNS diseases were downregulated in different cancers like lung, colon and prostate cancer and vice versa [163].

4. Tau in chemotherapy

Folic acid (also called folate or vitamin B9) intensities can plummet due to the influence of certain chemotherapy drugs used for cancer treatment. Chemotherapy-initiated folic acid insufficiency prompts abnormal tau phosphorylation, which can lead to different tauopathies like AD [164].

Paclitaxel is one of the most important chemotherapy drugs for cancer treatment; it binds to beta-tubulin in the same place as tau protein. Cancer cells with a low tau expression show a higher sensitivity to paclitaxel, whereas those with a high expression of tau display a resistance to paclitaxel-related chemotherapy. In case of breast cancer, low tau expressions are favorable for paclitaxel administration during chemotherapy.

Tau-negative expression can be used to select gastric cancer patients for paclitaxel treatment, on the basis whether paclitaxel is more functional in cells with low or no tau expression [165]. Tau expression analysis should be considered for taxane-based chemotherapy for some types of bladder cancer, as tumors with low tau expression display an enhanced response to chemotherapy [166]. Tau expression is associated with the sensitivity of breast cancer cells to taxane-based chemotherapy; patients with low or no tau expression should be more responsive to chemotherapy than patients with high expression of tau [24, 167]. Tau expression is also a potential marker for response to chemotherapy and subsequent survival in lung, ovarian, pancreatic and prostate cancer.

Nowadays, some drugs used for the treatment of cancer are also used for the treatment of different neurological disorders like Parkinson's disease and AD. Nilotinib is an FDA-approved protein tyrosine kinase inhibitor (TKI), which is used for the treatment of chronic myeloid leukemia. It also targets AD, which produces neuroinflammation and misfolded proteins, to ultimately reduce cognitive damage. In Parkinson's disease, nilotinib triggers autophagy to remove hyperphosphorylated tau from the brain before they accumulate as plaques [168, 169].

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Chapter 6

Re-Framing and Re-Thinking Dementia in the Correctional Setting

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Additional information is available at the end of the chapter

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Abstract

Overall, the populations of Western countries are ageing, and new technologies in forensic science, changes in prosecution and sentencing laws, alongside reduced options for early release, have contributed to the growth of the older prisoner population. This increase in the ageing population in the correctional setting has given rise to increasingly complex healthcare needs in the prisoner population who present with poorer physical, social and mental health than the general population. Prisons have not been developed for older people or their healthcare, or for management of declining cognitive abilities associated with dementia. This leaves the older prisoner with chronic health problems vulnerable to poorer health outcomes in this setting. Healthcare services within the correctional environment needs to match that in the general community and this requires the development of policies to support staff to put processes in place that will improve health outcomes for prisoners.

Keywords: correctional setting, dementia, healthy prison, human rights, older prisoner, policy agenda, prisoner

1. Introduction

The percentage of the population in the over 65 year age group is estimated to double by the year 2055. This increase in life expectancy is related to developments around improved education, health and public safety [1]. Internationally, all countries are experiencing increasing growth in the population aged over 65 years and in turn there is an expected rise in chronic diseases including dementia [2]. Dementia is a growing challenge for society, and is expected to increase further in coming decades [3]. In the general population of those people aged 65 years and older, dementia is recognised as the leading reason for disability [3].

Dementia is a chronic condition represented by impaired functions of the brain with the affected areas being memory, cognitive skills, perception, behaviour, language, mobility and personality [3, 4]. Another area impacted by the development of dementia is executive function, causing problems with word-finding, judgement and reasoning [5]. These impairments are irreversible and generally have a gradual onset and progression, leading to a decline in the person's ability to perform self-care activities [3, 4].

Due to modern technologies and changes in sentencing requirements there has been an increase in the number of people entering the correctional environment and an increase in admissions of older people, which is expected to continue rising in correlation with the increased ageing population in the general community [6, 7]. Being classified as old in the correctional setting occurs at a younger age than in the general population and with this comes the incidence of chronic diseases and dementia as found in the general community, but at a younger age [8]. Prisoners have poorer health status than the general community due to their pre-incarceration lifestyle which increases their health risk resulting in poor health outcomes [9].

Identifying dementia in the early stages provides the opportunity to put strategies and supports in place with the person, while they are still able, and allows the person to be informed about their diagnosis [10]. Being informed about a diagnosis of dementia provides a chance for the person to make decisions about their care in the future and their continued wellbeing [10]. Early identification and diagnosis in the correctional setting presents the opportunity to build awareness of staff and other prisoners about the condition and its progression [10]. Even though healthcare providers have acknowledged that early identification of dementia is important, about two thirds of those with dementia die without it being diagnosed [11, 12]. This means that many people will never receive important interventions in the early stages, or have the opportunity to prioritise their care into the future [11].

There is minimal information around policies, organisational systems and practices in relation to management of prisoners with cognitive impairment and dementia, and evidence shows that this section of the community is marginalised and victimised. There is growing urgency to improve access by prisoners to appropriate healthcare for screening and management of cognitive impairment, as well as general health promotion to improve long-term outcomes. The World Health Organisation guide for prison health suggests adopting a simple model for correctional settings to create a healthy prison and provides a resource for prisons that are struggling to address the increasing older prisoner population [13].

This chapter highlights the issue generally and sets out strategies for organisations to use in identifying dementia and developing a healthier correctional environment which will lead to improved health outcomes for prisoners and also for staff and for the communities where these prisoners will be released.

1.1. Definitions

Correctional facilities are where people are housed when they have been accused or convicted of breaking the law by committing crimes in a country, and the criminal justice system has

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deemed they are dangerous to the public [14]. They are placed in correctional facilities to be segregated, to protect the population of that country from their actions and to maintain societal laws [14]. There are many different terms used across the world to refer to the correctional environment including corrections, correctional setting, correctional facility, correctional institution, prison, gaol, jail, lock-up, penal institution, penitentiary and incarceration [15].

There are many different terms used to describe the people who reside in correctional facilities including prisoner, crim, criminal, inmate, offender, convict, con, incarcerated, gaolbird [16].

The morbidity classification of an aged or elderly prisoner commences at 50 years whereas in the broader population group the morbidity classification begins at 60–65 years of age which is an equivalent disparity of 10 years [8, 17–19], therefore someone 50 years old is classified as being aged in the correctional setting. This difference in age is related to lifestyle factors including minimal medical care, substance misuse, low education levels prior to the prisoner entering the correctional environment, as well as the effect of life in prison with isolation from family and threats of violence [18, 20].

Dementia has been defined by the World Health Organisation [4] (p. 2) as "a syndrome, usually of a chronic or progressive nature, caused by a variety of brain illnesses that affect memory, thinking, behaviour and ability to perform everyday activities [9]." The impairment that this causes is permanent and not reversible, resulting in the person not being able to live independently [3, 4].

Cognitive impairment is where the person is unable to make everyday decisions, has problems with remembering things, being unable to concentrate on activities or learn new things [21]. Cognitive impairment can be an early sign for the development of dementia and has many differing causes [21].

2. Current policy agenda

The World Health Organisation has developed a prison health guide [13], 'Health In Prisons', to firstly set out the critical requirements in health service provision and delivery of care, including information around standards in prison health. Secondly, it argues that prisoners should receive health care that is comparable to the general community and cites several international standards to support this entitlement. Thirdly, the guide highlights best practice based on the idea that there should not be any discrimination against prisoners based on their legal situation. Furthermore, it argues that prisoners have the right to receive the same quality and level of healthcare as the general population in the country [13, 22].

The World Health Organisation [4] has identified that the incidence of dementia is increasing at an alarming rate across the world and therefore all countries need to place dementia on the public health agenda. Many countries have developed plans and policies for addressing the increasing concerns relating to dementia, including Australia, England, Scotland, France, South Korea, Norway, Denmark, Netherlands, Japan, United States of America and Canada [23].

However, these plans and policies concentrate on the general community and do not translate into the correctional setting or provide any plans for moving into this environment.

Australia has developed the 'Corrections Ageing Prisoner and Offender Policy Framework 2015-20', which identifies that ageing prisoners have varying individual and system needs, and these needs should both be considered [24]. There are four fundamental principles characterised: supporting age-appropriate regimens and accommodation, enhancing health and wellbeing, tailored age and interest-relevant programs and building strong partnerships [24]. Situated under these principles there are four key priority areas. The first requires support for staff to ensure they are delivering evidence-based best practice within the facility as well as system enhancement. Secondly, prisoners require access to age appropriate services for their health and well-being. The third priority is about building staff capacity to ensure the workforce is assessing and supporting common ageing conditions. Finally, the fourth provision requires of monitoring of ageing demographics to ensure all prisoners and staff needs are being addressed in a timely manner [24].

3. Demographics/epidemiology

Overall, the populations of Western countries are ageing, and it has been suggested new technologies in forensic science, changes in prosecution and sentencing laws, alongside reduced options for early release, have contributed to the growth of the older prisoner population [6, 7]. Australian population statistics show the numbers of Australians aged 50 years and over increased by 36.8% in the period 2000–2010 [25, 26]. However, there was an increase of 70.4% in prisoners aged 50–54 years, 79.7% in prisoners aged 55–59 years, 81.8% in prisoners aged 60–64 years and 141.7% increase for the over 65 year old group from the year 2000 to 2012 [26]. This increase in the number of older prisoners has been identified across the world [27]. Accompanying this there is an expected rise in the rate of chronic disease including cognitive impairment and dementia in correlation to the rise in the general population [25, 28].

The World Alzheimer Report 2016 [29] identified in 2016 that there were approximately 46.8 million people across the world with dementia and this is expected to increase by the year 2050 to 131.5 million people. Alzheimer's Disease International [29] recognised that different income level countries have different levels of identification of dementia. For example in low and middle income countries there are only 10% of people with diagnosed dementia, whereas in high income countries this rises to about 50% being diagnosed [29].

Approximately 13% of the general US population aged over 65 years have dementia whereas in the prisoner population it can be as high as 44% [30]. Baldwin and Leete [31] reported that a UK survey of prison inmates provided evidence that 15% of those surveyed exhibited signs of cognitive impairment. This was then used as an indication that there could be many unrecognised instances of dementia in prisons [31]. Correctional settings have not been prepared to address the needs of older, infirm or disabled prisoners which create a strain on staff [31]. For instance, it is now recognised that correctional services staff are not trained to identify

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a person with a cognitive impairment or care for someone who is disabled, rather, they are employed to manage prisoners' behaviour [31].

Despite the fact that an increased awareness of the ageing population and dementia has been a major focus of literature on older people, there is minimal documentation about how this is impacting the correctional setting [5]. Maschi et al. [30] (p. 442) state that there is 'no national study to estimate prevalence of dementia among the U.S. prison population'. Williams et al. [32] also identified that there has been minimal research into the prevalence of dementia in the correctional setting, and based on other data, they expect cognitive impairment to be high and unrecognised in the older prisoner population. There is limited research into the early identification of dementia in the prisoner population, with correctional healthcare services having a strong focus on acute healthcare issues rather than long term preventive measures [33]. This correctional setting has given rise to increasingly complex healthcare needs in the prisoner population which is directly linked to the increase in the ageing population in this setting [34].

4. Community and correctional settings

4.1. Individual (national framework and health status)

A high proportion of those people who enter the correctional environment are from disadvantaged and/or minority groups in society, with the majority of the marginalised being well represented and generally from a particular socioeconomic quintile [35]. Those people who become involved in the criminal justice system have a higher incidence of health problems, such as untreated chronic conditions and mental illness, than the general population [35, 36]. It is well documented that people from low socioeconomic lifestyles have a high incidence of unhealthy behaviours such as alcohol and substance misuse, smoking, poor nutrition and living conditions and they rarely visit healthcare services [35, 37]. Health conditions such as mental illness and some unhealthy choices and behaviours, for example alcohol and illicit substance misuse place people at greater risk of arrest and once they are incarcerated, they sometimes enter an overcrowded and at times violent environment [36]. These lifestyle factors prior to incarceration and then within the correctional environment creates negative effects on the mental health of the prisoners due to overcrowding, isolation, lack of mental stimulation, lack of privacy, and separation from family or supports, which in turn puts prisoners at greater risk of developing dementia [17, 35].

Prisoners who have early stages of dementia are treated the same as the rest of the inmates within the correctional environment which causes additional problems. For example, a person with dementia is unable to follow simple instructions or directions from correctional staff which can result in or to lead punishment for non-compliance [31]. This subsequently increases the prisoner's confusion, leading to an exacerbation of the dementia symptoms and processes [5, 31]. It was also identified that the dementia process could cause confusion for a prisoner around social standards or customs in the correctional setting.

Baldwin and Leete [31] acknowledge that a person with dementia in the correctional setting is vulnerable to abuse and bullying from other prisoners. Cognitive impairment is an early identifier for dementia, and failure to identify cognitive impairment early in prisoners could lead to adverse health outcomes including victimisation, the inability to conform with complex instructions, and poor judgement resulting in disciplinary actions [30, 32]. This is supported by other studies which acknowledge that older prisoners who have dementia are at a greater risk of becoming victims of violence, bullying and victimisation [5, 38].

4.2. Correctional setting

Prisons exist for three reasons; to provide safety for the community by removing someone who has demonstrated criminal activity from society, as a form of punishment for these activities and lastly for rehabilitation prior to returning to the community [39]. Prisons therefore have not been developed for a person's healthcare, or for management of the declining cognitive function which occurs with dementia [39, 40]. This leaves the older prisoner with cognitive impairment and dementia vulnerable to poorer health outcomes in a correctional setting [40].

Prisons have not been designed to accommodate older or infirm prisoners, therefore inflicting further punishment if the prisoner is unable to navigate the facility due to cognitive impairment or dementia [30, 31, 41]. Older prisoners are not able to easily access bathroom facilities, climb up to top bunks or attend some exercise sessions [31, 41]. Equipment to support the older, frail prisoner is not generally available in this setting and activities are not structured for the older person with reduced cognitive or physical abilities [18, 41]. The inflexible environment of the correctional setting could also intensify the loss of independence and functional ability of the older prisoner [41]. The older prisoner may present with multiple and complex healthcare needs, which are difficult to manage in an unprepared setting [41]. Prisoners are at increased risk of developing depression which can be exacerbated by the lack of stimulation and distance from family and support networks [31].

In Australian prisons, the rate of older prisoners is increasing faster than the same age in the general population, and there has been a substantial increase in the number of older prisoners in the correctional system during the decade between 2000 and 2010 [10, 25]. This increase in the number of older prisoners has been identified across the world [27]. For example, England and Wales report a 74% increase in older prisoners in the past decade and the United States reports the number has tripled in the same time period [7].

United States citizens 65 years and older who have dementia represent about 13% of the general population, and the prisoner representation can be as high as 44% [30]. In the United Kingdom a survey on prison inmates provided evidence that 15% of those surveyed exhibited signs of cognitive impairment that had not been previously identified. These findings were then used as an indication that there could be many unrecognised instances of dementia in prisons [31]. In the United States there are prisoners with dementia who have been neglected, due to being incarcerated in facilities where medical and mental health care for this group of the population is sub-optimal [30].

Due to the structured routine of life in a correctional facility, a person with dementia may not be identified early or easily and the routines in the correctional setting can mask the signs and symptoms of dementia [10, 18]. Prisoners are not expected to coordinate their daily routine or act independently and the inability to do this, because of the dementia process, may not be recognised [10]. They may therefore not be identified as having any cognitive impairment until their behaviour begins to clash with expectations of the correctional environment [10].

Not being identified as having dementia until the late stages means that strategies or treatment cannot be put in place during the early stages to slow or relieve symptoms [10]. As the disease progresses the older prisoner will develop problems following instructions which could lead to punishment which will in turn further impact on their health [10]. As the process of the disease advances the affected person will also develop problems with being able to socialise with others and undertaking general activities of daily living such as performing hygiene needs [10]. The inability to understand and perform general tasks could also lead to being reprimanded or punished and therefore will adversely impact on the physical and mental health of the person [10]. Failure to identify cognitive impairment and dementia in prisoners could lead to such adverse outcomes as victimisation, the inability to conform to complex instructions, and poor judgement resulting in disciplinary actions [30, 32]. This is further supported by other authors who state this lack in understanding may lead to the older prisoner with dementia becoming vulnerable to abuse and bullying from younger prisoners [18, 38].

If the correctional environment is not designed for prisoners with cognitive impairment and dementia, they will find it takes a greater effort to navigate their way around it, and they will be at greater risk of confusion and becoming lost in their surroundings [42–44]. This suggests the reduced independence caused by confusion has an impact on the person's sense of identity and can lead to an exacerbation of the progress of dementia [42–44]. Those with dementia have been identified as 'among the most marginalised, socially excluded and highly stigmatised groups in society' [42] (p. 188). Prisoners are a marginalised and socially excluded group because they are placed in an environment which has been developed to disempower, control and put the prisoner in a submissive position [33].

4.3. Case studies (globally)

There is minimal research around dementia screening and management in the correctional environment, however some prisons have implemented or are developing processes for older prisoners.

Fishkill, in New York (United States of America) has created a dementia specific unit to provide accommodation for dementia prisoners from the state's prisons, which is attached to the prison's medical centre [10, 25]. Staff are required to attend 40 hours of training, designed by the Alzheimer's Association, to assist them in working with prisoners in this unit [10]. The supposition is that dementia-specific staff training provides a way to create knowledgeable staff and reduce the occurrence of confusion or anxiety in prisoners with dementia [10].

The California Men's Colony (Unites States of America) was developed for any prisoner with a severe cognitive impairment to reduce the incidence of victimisation, and meet the needs

of this group of prisoners [10]. Prisoners need to meet special requirements for entry into this facility, with dementia being one of the requirements [10]. The facility offers a 'Special Needs Program for Inmate-Patients with Dementia (SNPID)' which supports prisoners by modifying either their social or physical environment [10, 45]. This program includes the use of specially selected prisoners to provide support to the prisoner with dementia and ultimately improving their quality of life [10, 45].

Training of prisoners to become carers has been used as a strategy in Queensland (Australia) by providing Carers Certificate 2 training to selected prisoners to assist with older prisoner care [46]. This provides extended care for the prisoner with cognitive impairment when needed, while also providing the prisoner carer with a potential career on discharge from prison [46]. These carers work under the direction of a registered nurse to ensure safe and quality healthcare is provided.

Long Bay Correctional Complex in Sydney (Australia) is developing access to allied health professionals who specialise in areas of need for prisoners with dementia [10]. They will provide long term supported care in the correctional health service, which will include an '…aged-care offender's independent living in segregation from the mainstream prison, with support from a disability service…' [10] (p. 15).

4.4. Community settings

There have been various strategies for early identification and support for people in the general community with cognitive impairment and dementia for some time, however this has not translated into the prison setting. Specialised tools are used in the community to assess a person's functional abilities as these skills are the first ones affected by cognitive impairment and dementia [5]. Two of the community tools are 'activities of daily living' (ADLs) and 'instrumental activities of daily living' (IADLs). A person in a correctional environment would not be responsible for developing or using these skills so an alternative tool has been developed in the United States of America called 'prison activities of daily living' (PADLs) [5]. Although this tool has been identified by a couple of authors it does not appear to have been picked up in other countries. Each country and each correctional facility will have slightly different processes and these could be used to modify the PADLs to suit their specific facility.

In Australia, 'The National Framework for Action on Dementia', which aimed to make dementia a national priority, was developed to support communities to provide assistance to carers and those in the community with dementia [23]. A national framework for action was agreed upon by Australian Health Ministers and this framework listed five priority areas [3]. These priority action areas were: 'care and support services, access and equality, information and education, research and workforce and training strategies' [3]. Even though this was developed for the general Australian population, the correctional setting is yet to follow these recommendations [10]. In England a national dementia strategy was developed to provide support for early diagnosis and intervention, and Scotland developed a dementia strategy to achieve similar outcomes [23]. In the United States of America preventing and reducing dementia has been identified as a 'national public health priority' [30].

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5. Healthcare in correctional settings

5.1. Prisoners access to healthcare is a human right

The question has been raised about whether it is appropriate to continue to hold someone in prison if they no longer remember their criminal act due to dementia [47]. Dementia can contribute to a prisoner having no knowledge about his/her wrong doing and the loss of the ability to understand this [31]. There is also the situation where a prisoner was initially aware of their guilt when admitted to the correctional facility, however in time they no longer have an understanding of this or their surroundings [31]. In all of these situations there is no opportunity for rehabilitation, which is the main reason for incarceration prior to release back into society [31].

Compassionate release from prison revolves around four different points: 'the chance of recidivism, the rights of the victim, the costs involved in continued incarceration versus the cost of external healthcare, and the continued welfare of the prisoner with dementia' [31]. This raised the question of the ethics of keeping a prisoner, whose psychological and physical needs cannot be met, in prison [31].

Older prisoners are more costly as they require resources that are more expensive compared to prisoners who are younger and generally healthier [48]. One of the increased resources needed is increased healthcare generally due to a lack of healthcare throughout their lives [48]. Older prisoners have a higher incidence of physical and mental health issues than those in the community who are the same age and therefore need ready access to healthcare services [48, 49].

Prisons were initially designed for young people, with narrow staircases and cement buildings and floors which can be harsh on old bodies [50]. Prison healthcare systems were initially designed for young and healthy men, therefore older females and males from marginalised backgrounds and/or minority groups, who have higher incidences of chronic conditions, have different healthcare needs which can challenge the traditional models of care [51].

Many older prisoners have chronic medical conditions. Approximately 95% of prisoners will eventually be released back into society, therefore proper management of these conditions in the correctional setting will reduce the costs and the impact on communities when prisoners are released [32]. Even though being incarcerated could be the optimal time to identify and mange health problems, this is not occurring adequately or consistently across correctional facilities internationally [49]. The guidelines of many countries state that healthcare provision to prisoners should be to the same standard as the general population, however this has not occurred in many prison healthcare services, with frequent lapses in care [19, 49].

As the correctional population is becoming older, increasingly release is through death, and therefore there is a growing need for end of life options in this environment, making it difficult for correctional services to meet the special needs of the ageing population while remaining humane [52]. In some countries there is a movement toward penal harm which means that disciplinary measures, which extend to the healthcare clinic, are the focus in correctional

facilities [53]. This penal harm also occurs when correctional staff feel that policies of the facility and security override the need for medical attention [53]. When this occurs the quality of the healthcare provided can deteriorate significantly and can be seen as standard care for the facility even though it is well below what is provided in the general community [53].

Of prisoners aged between 50 and 54 years, about 50% had mental health problems, and only one third of these people would have adequate access to treatment during the time they were in prison [30]. Although there is a section in the US constitution protecting against cruel punishment, and supporting the rights of prisoners to appropriate medical care, many criminal justice system healthcare providers are not prepared to support the needs of older prisoners in a cost- effective way [32, 40]. Williams et al. [32] and Ahalt et al. [40] identified that healthcare systems within the prison setting increasingly need to provide healthcare for rising chronic conditions as the population in correctional facilities becomes older.

5.2. Individual (determinants of health)

People within the correctional setting have poorer social, education and economic circumstances which impact on their determinants of health. For example, being in an environment not designed for older people with aged conditions, the socioeconomic indicators demonstrate most have a low education level, are homeless, generally unemployed and have substance misuse [20, 25, 54]. A person's lifestyle, geographical location, employment status and social connections strongly influence their health, with studies establishing the links between health, poverty and social exclusion [35]. Those incarcerated in a correctional setting are at a higher risk of developing dementia and/or related problems due to the isolation of the setting, being exposed to violence, at times being in overcrowded facilities as well as being separated from their families [33]. Older prisoner's health is vastly poorer than those of a comparable age residing in the community. It has been highlighted that, of prisoners in the over 60 years age group, 85% had chronic disease, and in particular a high incidence of mental illness, which was found to be five times greater than a comparable sample group in the community [18].

Those who become incarcerated have higher rates of substance misuse and chronic diseases, including those affecting mental health, and, if these are not recognised, treated and managed in the correctional environment before the prisoner is released, there will be an increased burden on the community [55]. There is also evidence of a cycle of reoffending caused by links between the determinants of health, such as employment and housing, once as person is released from prison, with a high number of these people becoming homeless [35].

Older prisoners entering a correctional setting, where the majority of inmates are young and can be quite violent, are becoming more vulnerable and at risk of violent episodes from those more physically fit [52]. Health disparities and poorer health outcomes occur where appropriate healthcare is not provided to individuals in the correctional environment, which not only affects the person with dementia but also the prisoners around them, as well as the community they will be released back into [55].

Health promotion is an important aspect of providing healthcare and has been a growing trend internationally. Health promotion activities are the foundation of the WHO guide to prison health which also encompasses the Ottawa Charter for Health Promotion and the Declaration of the Alma-Ata [56–58]. 'Peace, shelter, education, food, income, a stable ecosystem, sustainable resources, social justice and equity' are critical to a person's health and are the foundation for the Primary Health Care principles [57]. The principles acknowledge that the Health Promotion approach is not restricted to just the individual but also applies to the setting or environment, and highlights practices to reduce the impact of the 'wicked' problems within communities and/or populations [59].

For a prisoner to feel 'at peace' they need to be feeling safe and not be in fear or stressed about their wellbeing in the environment they are in [56]. Being in an environment where a person's circumstances create stress over an extended period can lead to feelings of insecurity, for prolonged periods of time can be both physically and emotionally harmful [60]. If a person has long periods of feeling insecure or anxious, accompanied by being socially isolated and with poor self-esteem, they will have an increased incidence of mental illness. Not only does this increase psychological problems, it also leads to increased death at an early age [60]. These problems are recognised in greater numbers across industrial countries in the section of the population classified as low socioeconomic, which includes the correctional population [60]. Therefore unless healthcare in the correctional setting is supported by using guidelines such as the World Health Organisation prison health guide, prisoners will not be able to achieve the Primary Health Care and Health Promotion approaches and principles such as achieving peace.

Social isolation will and has a great impact on a person's wellbeing and creates barriers to being in a place where they are feeling at peace [60]. Being excluded from social interactions and distanced from family and loved ones will also create stress and feelings of unease leading to health problems and premature mortality [60]. This social isolation can be harder on some sections of the community, including the older prisoner population, and even on release they remain quite vulnerable [60]. There is a greater risk of early death in people who are stigmatised by their position, such as being a prisoner, and being looked down upon, along with exclusion from society, can have a significant impact on a person's health [60]. Furthermore, if prison healthcare and management do not address these issues and develop policies for healthy prisons, there will be an increase in deaths within this particular population group.

5.3. Correctional healthcare services (incorporation of health performance framework)

Prisoners within the correctional setting are seen as being in communities which are isolated and self-contained, away from the general population and the public health umbrella [61]. As a consequence, many opportunities for health improvement have been missed for both the individual and the community inside and outside the prison [61]. The health status of prisoners does not match their counterparts in the community for physical, social and mental wellbeing, resulting in a much poorer health status and outcomes [17, 18, 54].

Correctional healthcare services are responsible for the provision of care to prisoners and are the key personnel to support those with cognitive impairment and dementia [62]. The increase in the numbers of older prisoners, and their higher incidence of chronic disease and disability, are challenging and place a burden on correctional healthcare service providers who are generally not educated in aged care [40]. Therefore, where there are prisoners with multiple comorbidities, and especially for prisoners with mental health or cognitive impairment such as dementia and who have a reduced capacity to articulate their health problems, this can lead to under diagnosis of conditions/illness.. This is compounded by the key system issue of the regime in the correctional setting. Furthermore, as these regimes have not been developed with consideration of older prisoners with frailer and poorer health, many conditions and illnesses go unrecognised. More recently, overcrowding within correctional settings has compounded the complexities in delivering best practice healthcare, service provision and diagnosis of people with cognitive impairment [19].

Correctional healthcare services have a strong focus on acute healthcare issues rather than long term preventive measures [33]. In fact, correctional healthcare services are in an optimal position to deliver primary healthcare services that can be a disease prevention and health promotion service that is equivalent to that received on the outside [9]. If this style of healthcare is delivered within the correctional setting not only will it reduce the impact on communities once prisoners have been released, it will also provide optimal care within the national health performance framework and provide equivalent care to the community [9, 54].

It has been identified that prisoner's healthcare needs can be complex, and many are too extensive for prison healthcare services to manage [33]. In Australia, this leads to the health system performance in the correctional setting not meeting the requirements of the National Health Performance Framework [54]. This causes inequity across the range of patient care needs because the service provided within the correctional environment is vastly different to that in the general community [18, 54].

Correctional facilities were not designed for prisoners who are dependent on others for care, creating challenges for correctional healthcare services in identifying and supporting those with cognitive impairment and dementia [63]. This leads to incidences where care needs have gone unrecognised and health needs have been unmet [63]. There is very little information in the literature about early screening, identification and support of prisoners with cognitive impairments or dementia, and as a consequence there is little evidence to direct practice around this vulnerable group in the correctional setting.

Effective healthcare provision in the correctional environment can be obstructed due to the routine of the prison, correctional staff unavailability, time constraints and demands from prisoners [62]. There are barriers for nurses to develop therapeutic relationships with those they are caring for due to correctional requirements and the physical environment which can affect nurse-patient relationship building [64]. Correctional health clinic attendance is dependent on prisoners being able to attend, and this can be restricted by correctional services procedures and constraints [34, 62]. This creates a competition between the custody aspects of the correctional environment and the caring aspects, at times providing barriers to care and limiting nurse's autonomy [64]. A key point from the World Health Organisation

guide for prison health is that healthcare staff within the correctional setting need to have professional independence and this should be to the same level as healthcare staff in the community [22].

Healthcare needs of prisoners and care delivery by healthcare professionals is affected adversely by the culture in the correctional environment and the tension this creates can affect the recruitment and retention of nursing staff in the prison [62]. Due to staffing retention issues, nurses may undertake longer or double shifts to ensure healthcare coverage which means spending longer hours behind bars, and this can lead to similar feelings to the prisoners of isolation and segregation from the community which could lead to mental illness such as depression [64]. Nurses working in the correctional environment can feel marginalised by other staff such as doctors who are in attendance for a short time, and who instruct the nurses on what to do without really understanding the complexities of setting and without being with the prisoners for long periods of time [64]. Correctional officers, although in attendance for similar periods of time, have a vastly different role and do not have the same pressures as the nurse who is expected to sort out the health problems of the prisoners [64]. Innovative delivery of healthcare in the correctional setting is often obstructed and the initiation and ongoing management of these resources is held back by environmental procedures [62].

In Australia each state and territory government is responsible for the healthcare provided in their correctional facilities [3]. As a result there are variations between jurisdictions about how and what healthcare service is provided [3]. The differences in healthcare provision and the function of clinics can range both between and within states and territories [3, 34]. Some jurisdictions will provide allied health and mental health services within the prison healthcare setting, while others will use external providers [3]. While there is restricted access to different allied healthcare professionals, there are challenges with retention and recruitment of staff [34]. There is limited information about the differences between prison healthcare in the different states in Australia, and how they identify and support prisoners with cognitive impairment and dementia in their jurisdictions.

5.4. Case study (international initiatives)

California Men's Colony (CMC) provides an environment with areas specifically for those inmates with moderate to severe dementia and provides tailored programs for those with cognitive impairment [7]. This prison identified that there was a need to assist prisoners with severe cognitive impairment in order to reduce the incidence of victimisation and meet the needs of this group of prisoners [10]. The outcome of these programs has provided evidence that there is an improvement in social skills, attention levels and depression [7]. They also have a program where they buddy a prisoner without dementia with one that has dementia [7]. The prisoner buddies need to have a record of good behaviour, and receive training from the Alzheimer's Association so they can provide care for those with dementia and protect them from victimisation and bullying [7, 10].

Onomichi prison has a ward for older prisoners which provides nutritional support, and they changed the requirement that prisoners march in formation so that it wasn't as strict as other areas in the prison [65]. This environment was designed for prisoners who are not very

mobile, with ramps and hand rails being provided instead of stairs, and they have customised their wash rooms to accommodate the less mobile [7].

Fishkill Correctional facility in New York provides a unit for inmates who have been identified with cognitive impairment, and once admitted to the unit, there is a policy of regular assessment [7]. Apart from the commonly used assessment tools for cognitive impairment they also use 'Early Warning Signs' and 'Dementia Symptoms and Behaviour Triggers' [7]. All staff working in this facility are chosen from a pool of people who want to work there rather than being allocated to this facility, and they all must complete a 40-hour program of training developed and delivered by the Alzheimer's Association [7, 10].

Long Bay Correctional Complex in Sydney provides a program that collaborates with agencies specialising in dementia care to deliver better services to prisoners with dementia and cognitive impairment [10]. Some of these are the provision of access to allied health professionals who specialise in areas of need for these prisoners, long term supported care in the hospital facility, an aged-care offender's area of independent living that is separate to the mainstream prison with support from disability services [10]. A program is being developed to support appropriate aged care placement within the correctional setting, and collaboration on the development of processes for identification and assessment of prisoners with dementia as well as their management [10].

The state of Texas in the United States of America has geriatric units that have been designed for prisoners who are 60 years and older to provide more support for these prisoners with the activities of daily living [18]. They also have a geriatric unit for prisoners that is higher level and arranges access for the prisoners in this unit to specialist services for their higher acuity health needs such as dialysis and physiotherapy [18].

6. Environmental and sustainable practice approaches in correctional settings

6.1. Building competencies and workforce capacity

The World Health Organisation [4] (p. 3) states that 'Capacity-building of the workforce is essential to improve knowledge and awareness of the benefits of a coordinated response to care'. Correctional healthcare services have the opportunity to provide screening and treatment for a section of the population recognised as marginalised where healthcare is involved [61]. Providing services using standardised clinical guidelines will ensure the healthcare provided is of the same standard of care provided in the general community, and does not set lower standards of care for prisoners [61]. Developing agreements between correctional healthcare and correctional services to reduce the barriers that currently exist between healthcare and security will provide a more streamlined standard of care [61]. Ensuring all staff within the facility where there are prisoners identified as having cognitive impairment or dementia have education on recognition and management of dementia will reduce the vulnerability while in prison [61]. These actions will support the National Health Performance

Framework by addressing Health System Performance to provide improved 'effectiveness, safety, responsiveness, continuity of care, accessibility, efficiency and sustainability' [54].

Best practice management recognises early identification of dementia as being important, and also specific training in dementia care and support for correctional staff [10]. It is suggested that dementia training should incorporate information on helping staff to understand what dementia is and signs of its development, as well as how it can impact the person with dementia and those they are living with [10]. If staff are adequately informed and trained this could lead to early identification of the person with dementia, which can ultimately lead to early interventions and support being provided [10]. Feczko [5] supports this by acknowledging that correctional staff need to be trained in identifying the early stages of dementia, and how to recognise a prisoner's inability to undertake basic tasks rather than staff focusing on behaviour problems. It has also been identified that correctional officers need education and training to help them understand that if a prisoner is not following an order or direction it may not mean they are deliberately being disobedient, rather it may be due to their deteriorating cognitive abilities through the dementia process [52]. Prison health staff are not trained in aged care or early identification and care support for those with cognitive impairment and dementia, therefore specific training will assist those predominantly responsible for prisoner health to care for this vulnerable group [32].

The other aspect of training and support for correctional and healthcare staff is to ensure those working closely with people who have dementia are provided regular debrief sessions to safeguard their own wellbeing [10]. This will then link into the World Health Organisation prison health guide where health promotion and management is needed for correctional staff to reduce stress and to maintain the workforce [66]. Developing resources for health promotion should not only encompass prisoner care, it should also develop a partnership to provide for staff across the facility [66]. There can be high sick leave in some correctional settings and if staff members feel that they have a health promotion service available to them through work this could lead to them feeling more fulfilled in their employment and therefore lead to reduced sick days [66].

Other strategies to improve workforce capacity within the correctional setting are modifications or adaptions in the correctional environment which can help to avoid disruptive or unacceptable behaviour from a person with dementia. Meanwhile, if prisoner behaviour becomes easier to manage, the staff will have a reduced burden within their work shifts [10]. This modification could be as simple as a process change to provide carers within corrections by training selected prisoners to be support people for the prisoner with dementia [10].

6.2. Re-framing of practice to improve quality of life for prisoners

The development of policies and procedures for health checks, screening and assessment on admission and at regular intervals, along with the use of risk reduction program such as 'Your Brain Matters', will help in supporting and educating healthcare staff to provide quality care to prisoners that matches services provided in the community [1]. The World Health Organisation guide for prison health provides advice around the need for development of

health policies in prisons which are integrated into the health policy of the nation [22]. The development of these policies and procedures will provide staff with resources to support decision making around dementia in prisoners and present a structure for initial screening and regular follow up to ensure those with cognitive impairment and dementia do not miss out on early interventions to improve the progress of their health and outcomes. This is supported by Hayton in the World Health Organisation guide for prison health, where it is stated that there need to be regular assessments and screening with prevention strategies and health promotion included [67].

Policies and procedures can be developed to identify the specific age group where these screenings should begin and the staff member responsible for the identification. For example the correctional officer may identify that a specific prisoner who did not raise any flags in their admission screen is demonstrating behaviour that may show the early development of cognitive impairment. This correctional officer would then arrange for a referral to the nurses at the health clinic who could undertake a more comprehensive assessment, and then if the prisoner meet certain requirements as per the policy and procedure, they are referred to a geriatrician or medical practitioner who can provide a diagnosis. Once a diagnosis has been made, strategies developed with an individual plan of care for the prisoner to ensure the remainder of their time behind bars is managed in a safe manner free from victimisation.

Cashin et al. [41] states that another option is to develop a facility within a prison that simulates a hostel environment which provides housing for the aged prisoner in a more cost effective environment. These facilities should be developed to be similar to the community aged care centre and use trained younger inmates as care assistants, therefore reducing the staffing costs [41]. These carers would receive formal aged care training which can lead to a formal qualification for use once released from prison [41]. These trained carers would be supervised by qualified healthcare professionals who can observe the standard of care they provide as well as their level of skill development [41]. This provides the older prisoner with personalised care not previously available in a general prison, as well as providing the care assistant with a role within the prison that can translate to employment once released [41].

The older offender who has dementia may not be able to stand trial. However if their crime has been serious or involved violence they need to be placed under supervision in a facility that can accommodate their diminished mental capacity, to protect other prisoners and wider community [38]. It is recommended a secure unit be provided for the older adult with dementia to provide security and appropriate healthcare without the physical restraints imposed in the acute care setting, therefore not compromising safety and providing a comfortable environment [38]. This environment needs to be staffed by people trained in the care of these prisoners and how to address any incidents which may arise [38].

Another strategy is to collaborate with specialists in the field of aged and dementia care for support and education program development (for example Alzheimer's Association, geriatricians, physiotherapists, occupational therapists, carer supports and training). These specialists can help to develop the polices for identification and support for both the prisoners and staff as well as specific staff training programs to skill them in aged and dementia care. Dementia specific training provided to all staff working in the correctional environment where there are

potentially prisoners with cognitive impairment and dementia, strengthens the workforce by ensuring they have the capacity to work safely in this environment with minimal stress.

There may be the need to redevelop areas of the correctional environment to accommodate older and infirm prisoners. This may mean that organisations need to modify environments in areas where dementia prisoners, those at risk of dementia or cognitive impairment are housed to reduce poor behaviours as well as poor outcomes. If the facility is of a substantial age then modification could be difficult therefore simple actions would be around clear signs and directions, which could assist the prisoner with dementia in identifying their specific cell, where to go for meals and hygiene needs. It may also mean these prisoners are housed in an area with no or minimal stairs and that bunk beds are not used as the old, infirm prisoner who will have difficulty climbing up onto them.

6.3. Developing a healthy prisons approach

The World Health Organisation (WHO) was the first to discuss the promotion of health in prisons, for not just prisoners but for correctional and healthcare staff as well [13]. Their 'Health in prisons' publication, developed as a guide to prison health, that there needs to be a focus on 'health promotion' and 'health protection' which can be successful within the correctional environment [13]. The guide provides recommendations on how to develop a healthier correctional environment for both prisoners, staff and the environment which will also reduce the amount of harm in these settings [13]. The guide explains the fundamental steps that need to be included when developing health and health promotion in prisons [13, 68]. It states that all staff need to be involved from senior management down, and to make it sustainable there need to be links between the correctional healthcare service and healthcare in the community [13, 68]. This will then ensure that all interested parties are involved in the process, including prisoners, community healthcare in the local vicinity, politicians, staff and management [13, 68]. There needs to be a shift in perception around corrections and health so that creating a healthy prison is supporting the public not just those that are incarcerated [68].

Being able to create a healthy correctional environment using the whole prison approach is not always clear and can be quite difficult in areas that are resource-poor [68]. For example low and middle income countries may not have the resources to manage change in the correctional environment using a whole prison approach to develop health promoting prisons. There are many models for health promotion but there are few publications that provide direction to prison staff and administrators around this process [68]. One model that has been designed to guide correctional organisations in developing healthy prisons is the TECH model. This model was designed following the World Health Organisation guide for health in prisons [13, 68]. The TECH model is described as a way to improve health in any country no matter the level of resources they have and is about health promoting approaches using four domains that move across long term chronic care to short term acute care [68]. The TECH model uses the World Health Organisation guide for prison health as a foundation in its development, and it also meets the requirements of the Primary Health Care principles within the 'Declaration of Alma-Ata' and the Ottawa Charter for Health Promotion with both documents developed by the World Health Organisation to guide and direct health internationally [57, 58].

The first of the four domains is 'T: test and treat infectious diseases and provide vaccinations, if available'. This guides prisons to screen and treat for infectious diseases [68]. These infectious diseases include sexually transmitted infections and, diseases contracted as a result of substance abuse which has a high incidence in prison populations [68]. Depending on the location of the correctional facility there may be infectious diseases endemic in the location and therefore identifying and treating would provide optimal outcomes, not only for the facility but also the community the prisoners will eventually be released back into [68]. After this initial identification and treatment, arranging childhood vaccinations where appropriate will provide important cover of some conditions which could be transmitted to visitors, children and correctional staff [68]. Once these two actions have been completed undertaking any further immunisation as part of prevention and age specific for the older population will reduce the opportunity of diseases being spread through the correctional population [68].

The second domain is 'E: Environmental modification to prevent disease transmission' which includes not only the physical environment but also factors such as insects which may cause the transmission of disease [68]. For this there may need to be a program of spraying the area for insects especially if there are areas of stagnant water which is a good breeding area for insects such as mosquitos [68]. A survey of the physical environment is needed to identify if there is anything present that could be a source of infection transmission such as home-made tattoo equipment [68]. Another consideration would be the provision of condoms, and although management may not want to acknowledge it, consensual or non-consensual sexual activity does occur and providing protection will reduce the transmission of sexually transmitted infections [68]. Another environmental impact on health is the move to banning smoking in correctional facilities which will have a long term impact on health, and improved nutrition can improve health without being too costly [68]. Longer term planning for environmental modification should be considered especially where overcrowding will impact both the physical and mental health of the prisoners [68].

The third domain is 'C: Chronic disease identification and treatment'. Because the ageing population in the correctional setting is increasing so is the incidence of chronic disease [68]. Once chronic diseases are identified their treatment can be reasonably low cost and many can be improved by improving the prisoner's nutrition and increasing opportunities for exercise [68]. Mental health problems in this older group in the prison are also higher than the general community population and can worsen in a correctional setting if not identified or treated in a timely manner [68]. Therefore screening when on admittance and early treatment can reduce the impact on prisoners and improve health outcomes [68]. Once screening has identified health issues then a treatment plan can be developed for the individual targeting the specific needs of the prisoner and therefore reducing the potential of increased costs for unmanaged chronic health conditions [68].

The fourth domain is 'H: Health maintenance and health education'. This domain is about maintenance of the actions taken during the previous domains to develop a healthy prison [68]. Therefore this domain is about continuing to provide screening as well as chronic disease management and ongoing management and treatment of infectious diseases [68]. This continued management is required so the incidence of infectious diseases and chronic health

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conditions does not increase in a closed environment such as a correctional setting [68]. Being in close confines with multiple other prisoners means that if there is an infectious disease present it will move through the prisoner population fairly quickly, making it more costly to treat in the long term [68]. This affect both prisoners and the correctional service officers working with them by putting staff at risk of contracting the infectious disease and potentially taking it home to their families [68]. Management incudes education which should be undertaken regularly for both prisoners and staff [68]. Education for prisoners needs to be conducted regularly to ensure those with short sentences do not miss out on important information about health education that will improve their own and community health outcomes [68]. One option is for peer educators within the prisoner population to educate other prisoners in a culturally appropriate way and who, after release, can become community educators [68]. Peer educators are a cost effective way to ensure interested parties receive the correct and timely education where it is needed [68].

This TECH model of four domains provides information to be used by any correctional facility in any country and is not dependent on being in a higher income country. Each of the four domains explains aspects of health that need to be considered with minimal or no financial impact of the facility. It has been designed to develop a 'healthy prison' using the 'World Health Organisation guide to the essentials in prison health' as the foundation, providing whole prison health for prisoners and staff [13]. Providing education and optimal healthcare services in a correctional setting moves the organisation from just thinking about health in their prison to being a healthy prison [13, 68].

There are many different suggestions around building a healthy prison, ranging from major structural changes to policy development and procedural changes. A 'whole-prison approach' identifies initiatives in other areas of the community and adapts them to the correctional environment [9]. Some of the other programs that could inform this approach are 'Healthy Hospitals', 'Dementia Friendly Community', 'Healthy Cities/Towns' which all have components that could be adapted to the correctional environment [9]. All these programs have provided development across multiple domains to achieve their health outcomes and therefore the approach should be taken across the entire correctional facility [9]. Health promotion is an important aspect of healthcare in any community and if this direction is used in the correctional setting then diseases and disorders will be identified in a timely manner to allow early treatment, as well as support through to and past release from prison. To ensure this approach is successful there must be development of an assessment process which can incorporate all interested parties to ensure it encompasses all needs [9]. This also means there must be a system in place to manage and develop the change that is required to move the correctional facility from its current practices and systems to working with external stakeholders, for example including community and industry partners, to provide a system wide approach to health care and promotion. This is important as it not only focuses on health promotion for the prisoner but is also inclusive of the health of staff to ensure it is underpinned by the core principles of health promotion [35]. This is a systems approach where responsibility is not exclusively given to the healthcare service within the correctional setting but is shared by other areas of the system working together to provide a healthy prison [35].

7. Policy to practice recommendations

7.1. Prisoner/individual

- Policies developed for screening prisoners on admission for cognitive impairment and then regular health checks with an annual cognitive impairment screen
- If a prisoner is suspected of cognitive impairment on admission then allocation to a designated safe area with further assessments and referrals to follow.
- Development of activities and work in which older and infirm prisoners are able to participate.
- Development of a program for screened prisoners to become buddies or carers for those unable to care for themselves (potentially where the carers could do further study and receive a certificate at the end of their time in prison for potential employment prospects on release).
- Development of a discharge policy for prisoners with cognitive impairment or dementia back into the community where there are designated supports in place for the prisoner, their carer and the community (for example ensuring medical and community supports are in place).

7.2. Management/systems

- Policy development
    - Between general correctional services and correctional healthcare services to provide timely healthcare when needed and streamline prisoner access.
    - For processes in areas where prisoners with cognitive impairment and dementia are located to enable recognition and management strategies, as well as resources for support.
    - Adopting the World Health Organisation's guide to Health in prisons standards and principles.
- Improved coordination and communication between general correctional services and correctional healthcare services to avoid cancellation of health appointments outside of the prison or specialist visitors into the prison.
- Development of a regular training schedule for all staff working in areas where there are, or may be, prisoners with cognitive impairment. This should be developed by accessing organisations that specialise in the areas of aged care and dementia care.
- Support process developed for regular staff debriefs as well as ad hoc sessions after an incident.

7.3. Workforce

Correctional employees

- Training and education for all correctional employees including:
  - What is cognitive impairment and dementia?
  - Resources to identify strategies for identification and referral, as well as behaviour management.
  - Specific aged care and support for frail and aged prisoners.

Healthcare employees

- Training and education in aged care including:
  - Comorbidities in the older prison population.
  - Early identification assessment including screening tools
  - Management and treatment of dementia.
- Development of partnerships with organisations who manage aged and dementia care in the community.

7.4. Environment/setting

- Modification of a specific setting or area in a timely manner for older prisoners with aged specific healthcare issues or cognitive impairment.

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Chapter 7

Effective Restorative Home Support for Older People Living with Dementia and Their Caregivers: A New Zealand Case Study

Annie Weir

Additional information is available at the end of the chapter

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Abstract

Home support programmes provide services to enhance the well-being of both people living with dementia and their family/caregivers. There is limited research into the effectiveness of these home support programmes. This chapter reports on a small-scale study undertaken in New Zealand aimed at identifying factors that constitute effective restorative home support services for people living with dementia and their caregivers. A restorative home support approach aims to meet an individual's daily needs as well as promoting activity and independence. Data collection was undertaken in two phases, firstly, an international literature review identified a range of positive outcomes for participants of restorative home support programmes, such as improving functional outcomes, improving quality of life and reduced rates of institutionalism. Secondly, mixed methods were used to elicit views of multiple stakeholders. Quantitative survey data was reported using descriptive statistics and thematic pattern analysis was performed on the qualitative data. Ten key factors of effective home support services were identified under three broad categories: Client and Caregivers, Community and Organisational. These findings raise issues around what constitutes effective restorative home support and may inform debate internationally and lead to better outcomes for clients and their caregivers.

Keywords: effective restorative home support, dementia, mixed methods, client-focused, community

1. Introduction

New Zealand society, like much of the developed world, is experiencing a steady increase in the number of older people within the community living with dementia. Internationally, the

number of people affected by dementia is anticipated to rise exponentially as the world population ages. Global improvements in health care and living standards have contributed to people living longer, and this represents a significant challenge to health and social services [1]. A recent World Alzheimer Report noted that in high income countries approximately half the people living with dementia receive a diagnosis and in middle and low income countries under 10% receive a diagnosis [2]. With increased awareness of dementia in communities, it is likely to lead to more cases of dementia diagnosis. It is estimated that 46.8 million people worldwide are living with dementia and that this number is likely to increase to 131.5 million in 2050 [2].

Due to limited resources and policy development, the provision of services for individuals living with dementia in many developing countries is minimal. In contrast, many developed countries have formulated, or are in the process of developing, policies and services aimed at supporting the needs of individuals living with dementia and their family/caregivers. While the management of dementia care varies globally, home-based support is typically a leading component of government policy as it is viewed as a cost effective support measure [3, 4].

Dementia is not a single disease, it is caused by a variety of brain illnesses that affect memory, thinking, behaviour and ability to perform everyday activities, and is usually of a chronic progressive nature [3]. Dementia is a costly condition from its social, economic, and health dimensions, and numerous nations are formulating strategies such as home support to manage this development such as the provision of home support [1].

Although the levels of provision and nature community-based services vary between nations, the challenges faced by each government in maintaining and improving services, in the context of a rapidly ageing population and changing expectations, remain similar [5]. Community-based services for people living with dementia include home support services offering assistance with domestic tasks, meals, transport, medication administration, and personal care; day programme services that provide leisure, learning and respite activities; support groups in dementia education initiatives; and range of medical support services. International research reveals that the provision of quality community-based services for people with dementia can postpone the need for institutionalised care [6].

Traditionally, home support services for older adults have often emphasised well-meaning dependency model service provision and encourage maintenance and support only [7]. Under this model, as support workers and allied health staff held a task orientated attitude that prioritising getting the job done and doing as much as they could for the client. The service orientation often lacked an emphasis on the promotion of healthy daily routines, exercise, social interaction, autonomy and assisting individuals to undertake the own daily needs [5].

Recent progressive changes in home support practices are, in part, grounded in the developments that occurred over the past three decades in the care of people living with disabilities [8]. Today the concepts of normalisation, engagement with the community, and empowerment, permeated approaches to the management of people with intellectual, psychiatric and physical needs. A number of developed countries propose that home support services catering for the needs of older adults required a similar progressive change of attitude [8] and following this trend a number of new models of care have been developed. Examples of home support models focused on optimising client functioning and independence, is an integrated

component of service provision, include the (primarily) Australian-based active service model [9], the United Kingdom-(UK) based reablement programme [10] and the United States of America (USA) restorative model [11].

The next section details international research findings: investigating the impact of restorative care initiatives, the needs of family caregivers supporting someone living with dementia, and the needs of paid caregivers supporting someone living with dementia.

1.1. Restorative care

International research assessing the impact of restorative care programmes has largely been undertaken in the United States of America (US) and focused upon older adults living within a residential care settings – the results have identified a range of positive outcomes for participants including maintaining and improving functional outcomes, improved quality of life and independence, and psychological gains; a range of positive outcomes for caregivers have also been identified including increased satisfaction and knowledge of restorative care, and increased outcome expectations [12].

A small number of international studies have investigated the impact of restorative care within a community setting. An Australian-based study compared the outcomes of 100 older adults aged 60+ years (without a dementia condition) who participated in a short-term restorative home-care programme directed at optimising functioning, promoting healthy ageing and encouraging the self-management of chronic diseases; with 100 older adults who received the usual home-care services [8]. Research participants were interviewed at the commencement of the programme and at a 3 month and 1 year follow-up. The research found that individuals participating in the restorative programme showed improvements on all personal outcome measures compared with the control group. The researchers commented that "participants who received restorative home care showed greater improvement in their self-care, home management and mobility scores" ([8], p. 198).

A US-based study paired 691 older adults aged 65+ years, without a severe cognitive impairment, and receiving a restorative home care programme through a single restorative staffing unit; with 691 similar aged/gendered adults receiving the 'usual' home care programme across five other staffing units [11]. All support staff (restorative and non-restorative) were employed by the same provider. The research identified that older adults participating in the restorative home care programme were significantly more likely to remain living at home and to have a reduced likelihood of visiting an emergency department. The restorative care participants also showed higher levels of self-care, home management and mobility. The researchers commented that the success of the restorative model was supported by an "enhanced sense of teamwork and improved coordination among the home care staff, the reorientation toward maximizing patients' functional independence, and the inclusion of patients, families and home care staff in setting goals" ([11], p. 2104).

A United Kingdom (UK) based study evaluated the impact of a home support programme that incorporated restorative care elements [13]. The experiences of 29 older adults recently discharged from hospital and supplied with a follow-up 6 week restorative home support programme, were compared with a control group of 25 (similar) older adults receiving the conventional community

support services. The home support participants were found to have spent fewer days in hospital and more days at home over a subsequent 12 months following the intervention.

A narrative review was undertaken in 2015 of four prevalent models of home support for community dwelling persons living with dementia, The four models included: Case Management (may increase use of community-based services and delay institutional care; Integrated Care (results in greater use of community-based services, decrease in hospital days, however, the clinical effects are unknown); Consumer Directed Care (known to increase satisfaction with services and have little effect on clinical outcomes); Restorative Home Care models research has demonstrated that an individual's functions and quality of life improve, however, there is very limited research that has included people living with dementia. It was also noted there is a dearth of research that compares the outcomes and impact of models of care for people living with dementia and their family/caregivers [14].

Evaluations on restorative home support services have identified advantage in providing timely interventions, education and assistive technologies to encourage older people to develop increased levels of independence and activity [5].

1.2. Caregivers supporting someone living with dementia

Globally, care from relatives, including partners, children and extended family provides the foundation of support for people living with dementia [15]. Research has identified that caregivers looking after a family member with dementia are in most need of extra support [16].

Some researchers have contended that policy makers and health service providers often give little recognition to the vast savings they achieve through dementia care services being provided free of charge by family (and friend) caregivers [17]. A European study evaluated the experiences of family caregivers across five European Union countries and found that caregivers looking after an individual with severe dementia typically spent in excess of 10 hours daily in caring tasks and one-third of all caregivers devoted 14 hours or more each day to caring tasks [15]. The research also revealed that while it is commonly understood that cognitive problems – memory and confusion- are known to be associated with the onset of dementia, many carers were unaware of the behavioural symptoms such as aggression and personality changes which often occur and can cause the person with dementia to behave out of character; and create a great deal of stress and challenge for caregivers [15].

Among some researchers and policy analysts there has been a call for a "fundamental re-orientation towards caregivers and caregiver supports… beginning with viewing caregivers as a critical health human resource in a system that [increasingly] depends on their contributions in order to function" ([17], p. 103). This re-orientation recognises that with a growing older-adult population, the health system in many developed nations will increasingly be reliant upon family members to provide the first level of care for people living with dementia.

Peter Stoltz and colleagues [18] reviewed the international literature identifying the needs of family members who care for an elderly person living at home (the majority of studies involved family members caring for a dementia-affected person) and found strong evidence showing that family-based caregivers: have a variety of learning needs about their family member's

condition; wish to network in groups with other caregiver peers, for social and/or learning needs; desire periodic respite from their caregiving responsibilities; often experience a range of negative emotions associated with their caregiving responsibilities – typically feelings of burden, stress and worry; fear social isolation both for themselves and their family member.

While caregivers valued the external support provided to them and their dementia-affected family member, many studies revealed that caregivers often experienced support services has been 'given' to them, rather than being negotiated and individually tailored to meet their needs; and while such forms of support were often well intended, it was not always appropriate for the cared-for the person's or caregiver's needs [18].

Similar findings were identified by Siobhan Reilly and colleagues [19] from the Cochrane Collaboration in their review of the dementia research literature commenting that:

"Services are often organisationally highly fragmented, coming from a wide range of sources both formal and informal, including from health and social care services, family, friends and neighbours. As a consequence the picture of resource provision for the older person may be a series of piecemeal contributions from a range of different services, with no one having an unambiguous responsibility for taking a broader view of need beyond their own particular remit. Assessment and care plans tend, therefore, to be 'service oriented' rather than 'client-centred', piecemeal and not holistic, defining needs in terms of available services of care rather than individual problems" ([19], p. 3).

A Canadian study evaluating the experiences of family members caring for a person with dementia also identified a need for an integrated continuing care model that included the person living with dementia and the caregiver as partners in care. The researchers reported that the provision of appropriate and consistent support services – assistance with personal care, meals, homemaking and respite – were very influential in extending the period of time that family caregivers could maintain care within the family residence [20].

A recent Irish review explored the concept of respite care and how it relates to people with dementia and their caregivers. It is widely recognised that respite gives the carer a physical break and consequently a mental break from the person living with dementia. The researchers noted that respite can be viewed as both as service and an outcome. They argued there is a lack of clarity around the concept of respite and it is currently only understood in relation to the carer experience and consequently that this is potentially harmful to both planning and delivery of person-centred dementia care. They further suggested that a name change from respite care to restorative care in order to highlight the significance of offering mutual, individualised health and social services that will enhance care relationships [21].

1.3. Paid home support staff working with someone living with dementia

The Canadian study also identified that the high turnover of professional and non-regulated home support personnel could often lead to an inconsistency of service provision [20]. Other issues affecting the standard of service provision provided by support staff included limited training, lower wages than colleagues in an acute care settings, few benefits and limited supervision [22].

2. The New Zealand context

This section consists of three parts: Part one reports on the New Zealand policy environment that has shaped government responses and subsequently social service providers' responses to older people living with dementia and their caregivers. Part two examines New Zealand research on the restorative model. Part three reports on research undertaken on home support staff.

2.1. Policy environment

The latest 'Economic Impact of Dementia' report authored by Deloitte [23] and commissioned by Alzheimers New Zealand, suggests there will be approximately 170,000 New Zealanders living with dementia by 2050, up around 300 percent on current figures of 62,000. The report highlights the significant economic impact of dementia with the costs of supporting dementia diagnosed people could reach nearly $5 billion by 2050. It is suggested that new models of care that delay entry into residential care have the potential net benefit of $22 million a month, leading to substantial savings over time. The economic impact report is a key information source on the size and scale of the dementia challenge in New Zealand and is used to inform decision-making around dementia policy [23].

The New Zealand policy framework for senior home-based support is primarily founded upon two Government strategy documents: the Ministry of Social Development's New Zealand 'Positive Ageing Strategy, 2001' and the Ministry of Health's 'Health of Older People Strategy, 2002'. The Positive Ageing Strategy promotes the concept of positive ageing, affirms the value of older members of society, and highlights the importance of issues such as access to health services, financial security, independent living, the physical environment and personal safety. The Health of Older People Strategy details an integrated continuum of care, which seeks to ensure that all relevant health and disability services are coordinated in such a way that older peoples' needs are appropriately met "at the right time, in the right place and from the right provider" [24].

In recognition of the increasing challenge of burgeoning numbers of older adults diagnosed with dementia, the New Zealand Ministry of Health released in 2013 the 'New Zealand Dementia Care Framework' to initiate and coordinate dementia services for people living with dementia in the caregivers/families [25].

The vision of the framework is to ensure: people living with dementia, their family are valued partners in an integrated health and support system. They are supported throughout their journey with dementia, to enable them to maintain and maximise their abilities, optimise their sense of well-being and have control over their circumstances [25]. While the national framework recognises that many individuals living with dementia may ultimately require residential care facilities, the framework actively promotes community-based services that support those individuals living with dementia to remain living at home and home-based support services are a central component of this approach. The Framework is not directly based upon the restorative model of care, it does advocate for a person-centred and people directed approach that includes many restorative like principles ensuring that people living with dementia and the families/caregivers are respected, valued and are engaged partners in care planning, receive clear communications and education that enable them to be engaged at all levels of decision-making, and able to self-determine many aspects of their lives [25].

2.2. Restorative model

Research undertaken in 2012, compared the experiences of almost 600 older people at risk of permanent institutionalisation: one half were provided with the usual level of support care and the other half were provided with a strong care-management intervention designed to facilitate independent living [26]. Individuals were tested at 3, 6, 12, 18 and 24 months; and the results showed that older people receiving the care-management intervention had a significantly reduced rate of permanent institutionalisation and risk of mortality. The authors suggested that the intervention benefits could also be due to a "higher level of coordinated care, which offered more comprehensive support and early crisis resolution" and an improved "relationship between the participants care manager and GP" ([26], p. 726).

A recent randomised trial of restorative home care for frail older people undertaken by a team of researchers at the University of Auckland, aimed to "establish the effectiveness of a restorative home support service on institutional-free survival in frail older people referred for need assessment." ([27], p. 27). A secondary outcome of the research was that the health of the informal caregiver was also investigated. Their trial concluded that restorative home care may reduce mortality in older people, potentially lower the rate of institutionalisation, as well as improve carer's well-being ([27], p. 33).

An Auckland based study evaluated the impact of a restorative home care service for older adults aged 65+ years in the Auckland region [28]. Older adults and their caregivers were identified via a home care agency and a clustered randomly to receive a restorative home care intervention (n = 93) or the usual home care support service (n = 93). In contrast to the traditional home support service, the restorative home care programme was more flexible in its delivery and focused upon promoting functional status and improved quality of life. The research findings revealed that older adults participating in the restorative-based programme demonstrated a significant improvement in health related quality of life and there was some evidence of improvement in social contact. Key aspects of the intervention contributing to these findings included: "goal facilitation and development of personalised support plans, the coordinators enhanced input and support, and improved training for support workers" ([28], p. ii).

2.3. Home support staff

While paid caregivers are essential to the provision of home support services, there are ongoing difficulties in recruiting and retaining good staff due to poor working conditions and inadequate training opportunities. The Auckland based study [28] also evaluated the experiences of support staff engaged in the controlled trial in Auckland that allocated 93 older adults and their caregivers to a restorative home care intervention, with a similar sized group receiving the usual home care support. The research findings revealed that the restorative intervention had a substantial positive impact on the participating staffs sense of job satisfaction – primarily due to an improved provision of training, increased support and supervision, and more flexibility in work tasks. This improvement in caregiver work satisfaction lead to a substantial reduction in the turnover of staff participating in the restorative intervention. The researchers noted that in spite of the improvements achieved through the restorative intervention, a majority of staff identified issues in relation to their working conditions including low wages, no reimbursement for travel time between client visits and a lack of guaranteed work hours [28].

Throughout New Zealand there are 22 Alzheimers Societies whose role is to promote education and awareness, and to provide support and advocacy for people with dementia and their caregivers. Kirkman [29] surveyed and collected interview data from 48 women employed as community workers with Alzheimers Societies throughout New Zealand. Despite their low pay, part-time work and the lack of recognition of their professional qualifications, many workers were satisfied with their role as they felt they were making a difference for people with dementia and their families. Overall, Kirkman found a "gendered" patterning of paid and unpaid care for people with dementia commenting that this "reflects the traditional view that women are carers both inside families and outside them as well" and that "what is needed as we plan for the dementia epidemic' is recognition of the value of the work that women have done as paid and unpaid cares" ([29], p. 14).

In New Zealand home support services are predominately offered by non-government organisations (NGOs) that offer a range of home support services (from personal care to respite care for carers). The NGOs often have receive government funding for eligible clients Needs Assessment and Service Coordination Co-ordination service (NASC) via the District Health Boards who are funded by the Ministry of Health. Additionally, NGOs attract self-funded clients. NGOs are guided by the implementation of the New Zealand Dementia Care Framework [25].

3. Research on factors that constitute effective home support services for people living with dementia and their caregivers

Impact Research New Zealand was commissioned by Presbyterian Support Northern (PSN), a large NGO delivering social services to the upper half of the North Island in New Zealand to undertake research aimed at identifying: What factors constitute effective restorative home support services for people with dementia and their caregivers? How do these factors integrate into the National Dementia Care Framework?

3.1. Research design

A case study design was undertaken, data was collected from key sites in the upper half of the North Island. Case studies allow researchers to focus on the case, in this instance on key Enliven sites in the upper North Island. Case study allows for a holistic and real world approach ([30], p. 4).

In an attempt to answer the overarching research question the research, a mixed methods were utilised [31]. Two stages of data collection were employed to identify the key factors that constitute effective restorative home support services for people living with dementia and caregivers.

In stage one, a literature review was undertaken to identify the research evidence for best practice in home support care. A literature review is a critical examination of the research evidence and enables researchers to place their research question in context with previous research findings, refine research methods and analysis, avoid unnecessary replication of previous studies, and build upon previous research evidence [32]. A combination of New Zealand and international research literature was incorporated into the review, with a particular focus upon home support services incorporating restorative care principles. International research

evidence was gathered from countries with similar social dynamics to New Zealand including Australia, the United Kingdom, the United States and Canada. In addition to providing an overview of best practice elements, the review helped inform the questions for the fieldwork.

In stage two, mixed methods using a combination of qualitative and quantitative methods were used to gather a comprehensive range of data from Enliven clients and the caregivers/families, Enliven home support staff and senior managers, along with key stakeholders in the community who are recognised as experts in the field of dementia care home support services and social/health policy implementation were invited to participate in the research. Qualitative research methods used in the project included semi-structured telephone and focus groups interviews. Semi-structured interviews allow research participants to liberally discuss their thoughts, feeling and experiences about a particular research topic. This process enables researchers to gain rich insights into the 'meaning' individuals formulate about their experiences. Focus groups are an effective means of gathering data across a group of people – this process helps to identify differences and similarities in people's experience and opinions through discussion and participant interaction. Quantitative research methods used in the project included the administration of a paper-based survey questionnaire. Questionnaires are an efficient method for capturing data from a range of key informants in different locations.

3.2. Study setting

Enliven first delivered restorative home- support services under the Community First restorative model established in Hamilton in 2002, as a Ministry of Health funded 'Ageing in Place' pilot programme. In 2009, Enliven was successful in securing a contract to deliver Auckland District Health Board's Enhanced Home Support Services for people over 65 years. This contract introduced a (restorative-like) strengths-based approach promoting client independence using formal goal setting and flexible packages of funding to ensure a right place and right time experience for older people.

Over time Enliven restorative home support services have progressively been expanded across the PSN region to include five DHB areas: Auckland, Counties Manukau, Waikato, Lakes, and Bay of Plenty. During this time Enliven has continued to build capacity to support clients who might otherwise be in residential care to remain in their own homes, and this encompasses people living with various high and complex needs including dementia.

Additionally, Enliven has incorporated restorative principles within its day programmes – as a component of socialisation and mobility goals, as well as providing mental stimulation and general enjoyment. Day programmes also assist caregiver needs and stress, through providing respite time.

3.3. Sampling, recruitment of participants and data collection methods

Fieldwork data gathering methods included: telephone and face-to-face semi structured interviews; focus group interviews, and the administration of a paper-based questionnaire. Research participants included: a selection of Enliven clients diagnosed with dementia and their families/caregivers; a selection of Enliven managers and staff; as well as a number of key community stakeholders. All participants were nominated by Enliven senior managers and each data collection method selected for the different groups under study were agreed to as

being appropriate and would provide the researchers with sufficient data to answer the overarching research question.

3.4. Ethical considerations

Impact Research NZ has a code of ethics that is in line with the Association of Social Science Researcher (ASSR) standards and requires that work is carried out with professionalism, integrity, good judgement, and in a way that contributes positively.

The researchers were experienced in conducting sensitive enquiry with vulnerable people. The researchers acknowledged that some people living with dementia and their families/caregivers have experienced distress and care was taken to not inadvertently cause harm or distress in any way to those taking part.

Due to the variable capabilities of some people living with dementia, clients were informed that the telephone interview and questionnaire could be completed by the client living with dementia, the client's primary caregiver/family, or a combination of both. All interviews were recorded and transcribed.

Participants were informed both verbally and in writing about the purpose of the research, the names of the researchers/agency conducting the research, and contact details of responsible persons for questions and/or complaints. An explanation of what involvement entailed, their right not to participate and to withdraw their consent, their access to the information they gave, and to receive a summary of the research results, was provided. Informed consent was gained from all participants prior to data collection and their right to cease the interview at any time was reiterated at the commencement. All interviews were recorded and transcribed.

Care has been taken to preserve the anonymity of participants by removing any identifiable information and ensuring that information is not linked to any individual participants or organisations. Researchers have adhered to the 'duty of confidentiality', which means that no identifying information from participants has been shared with other parties. Any third parties who may be given access to research data (the transcriber) was asked to sign a confidentiality agreement.

All hard copy data was kept in locked storage at Impact Research NZ premises and was only be accessible to Impact Research NZ researchers. All electronic data, including any digital recordings of interviews, were password protected and only accessible to Impact Research NZ researchers. All data is kept for at least 3 years following the completion of the project and then destroyed.

3.5. Analysis

The range of data collection methods used allowed for triangulation of the common themes across the data set. A thematic pattern analysis was performed on the qualitative data from telephone and face-to-face interviews, focus group interviews, and responses to open-ended questionnaire questions. This process involved reading the transcripts and comments to establish keywords and emerging themes, and repeat readings to check and refine established themes. Themes are then organised into broad categories and selected quotes from respondents' accounts are used to illustrate the themes. Care is taken to de-identify individual quotes to protect participant anonymity. Analysis of the data using constant comparison between cases provides a distillation of

Participants	Number of participants identified	Number of participants	Participant selection criteria	Data collection methods All interviews were semi-structured
Enliven clients diagnosed with dementia and their family/ caregivers	30	22	• Clients with early onset dementia through to moderate dementia. Clients new to the Enliven service and clients who had been receiving Enliven services for some time. • Clients situated in city, town and rural settings. • Clients from various ethnicities such as Māori, Pacific, European and Asian.	Telephone interviews elicited information on how well the service is being received and what could be improved. Paper-based questionnaire covered: demographics age, ethnicity, sex, geographic location, length of time since dementia diagnosis, length of time with home-support. Additionally, 10 closed questions using a five point Likert scale covered: the care plan, aspects of service delivery, and suggestions for improvements.
Enliven home support staff	15	10	Enliven Area Managers were asked to nominate 15 Enliven staff – team leaders and home support staff – to participate in focus group interviews	Staff focus groups held in two city locations: Auckland and Hamilton. The interviews covered their views on the provision of restorative care, what works well, challenges, training, data collection and reporting, how the service could be improved.
Enliven managers	7	7	General Manager Enliven Enliven Area Managers	Face-to-face interview 40–60 minutes covered the strategic direction of restorative care Telephone interviews of 40–60 minutes duration covering implementation, strategic overview, the factors that make up effective restorative, issues of culturally appropriate care, staff recruitment and retention, training, funding issues, quality measures for home support, and potential future service developments
Key stakeholders	11	11	Community services – Age Concern, Senior Line, Alzheimers Auckland. DHB services – Gerontology services (×2), Assessment services, Mental Health Services for Older People, Dementia Services Project, Access Network, Community Geriatric Services. MoH – Needs Assessment and Service Coordination Agency.	Telephone interviews or face-to-face interviews Stakeholder interviews explored a range of home support issues including how best to meet the current needs of people living with dementia and their families through home support, best practice in provision of home support, the need for essential/specialist staff training; and the projected future needs of this client group. All interviews were recorded and transcribed

Table 1. Summary of participants numbers, selection criteria and data collection methods.

participants' experiential knowledge. Augmenting the interpretation of these findings is a critical commentary drawn from the research literature relating to the features of effective home support services for people living with dementia and their families/caregivers.

Quantitative data gathered from the client questionnaires was entered into an Excel database for statistical analysis and used to generate descriptive tables and figures. Quality checks were undertaken to ensure the data was complete, free of distortions and ready for analysis. Data was then entered into our Excel database to generate descriptive statistics (**Table 1**).

4. Research findings

Ten key factors supporting effective restorative home support services for people living with dementia and their caregivers were identified and these are factors are grouped under three primary headings: Clients and Caregivers, Community, and Organisational. The subsequent discussion section will detail how these factors are consistent with the research literature and fit within the national dementia care framework.

4.1. Clients and caregivers

The majority of clients were aged between 75 and 94 years (36% aged 75–84 years and 36% aged 85–94 years), were female and identified as New Zealand European. The over representation of female clients is consistent with New Zealand females living longer than males. One third of clients had been diagnosed with dementia for over 3 years, almost half diagnosed for 1–3 years, and the remainder for 1 year or less. Just over half of clients had received home support care for 1 year or more. Dementia impacted 'moderately' on one-half of clients and 'significantly' on one-third of clients.

The majority of clients lived with family/caregivers, while a few clients with early onset dementia lived on their own with home support services being an essential component of their ability to remain living independently. All clients had received a NASC assessment that allowed them to access government-funded services from Enliven and linked to goals in an agreed care plan. The majority of clients received Enliven home support services on a daily basis.

The objective of Enliven home services is to support clients to remain living in their own home for as long as possible and with the greatest amount of dignity and independence that their circumstances allow, and this goal was highly valued by clients, caregivers, staff and key stakeholders alike. While all parties recognised that dementia was a progressive illness; there was a strong desire for clients to be supported to live at home, as long as the primary caregiver/family was able to cope with the situation and the client's safety was not compromised.

Factor 1: Client outcomes.

Effective home support services for people living with dementia ensure that the needs of the client are upheld at all times, that clients are treated with respect, that client outcomes are integrated into realistic service care-plan goals, and that caregivers/family are included in service planning.

Enliven places clients and their caregivers/families at the centre of their service provision. The aim of Enliven restorative home support services is to achieve client outcomes that assist clients to remain living in their own home and to maintain physical, cognitive and social wellbeing. A majority of clients/caregivers identified four aspects of the Enliven service that were most

important to them: their relationship with home support staff, the capability and professionalism of home support staff, the liaison/communication across home support staff (and Enliven), and the service care-plan developed with the service coordinator. Clients and caregivers wish to be treated with dignity, and to ensure that the client is viewed as a total person, e.g. someone who has had a full life, with rich experiences and capabilities. Clients and caregivers discussed the importance of home support staff liaising with one another (often through the client's log book), to ensure that all staff were kept updated of any developments in the client's life.

A number of clients, caregivers and key stakeholders also remarked on the importance of the client's service-plan having some flexibility built into it, so that support workers have opportunities to undertake alternative (appropriate) tasks for the client as required; a number also recommended that a small proportion of the client's home support time be specifically allocated for the client's/caregiver(s) discretion, to be used as they think most appropriate.

Factor 2: Caregiver needs.

Effective home support services for people living with dementia recognise that the primary caregiver(s) of a person living with dementia (often) require regular periods of respite if they are to sustain their role, and require consistent communication from support workers and other Enliven staff regarding their loved-one's experience/condition.

Caregivers remarked that they strongly valued opportunities to have a period of time out from their loved one; as this provided them with an opportunity to undertake other necessary tasks, maintain relationships with family and friends, and to have some personal time. Similarly, key stakeholders and staff commented on the importance of the primary caregiver's role, commenting that many home support clients living with dementia were only able to remain living at home due to the commitment of their caregiver (along with the provision of various support services). An integrated dementia care service supporting people living with dementia to remain in their own homes needs to provide appropriate levels of support for clients and caregivers alike.

Caregivers also reported on the importance of being regularly updated by home support staff (and other Enliven staff as appropriate) about their loved-one's day/experience and any other issues that may arise during the provision of home support services. For example, caregivers expressed a strong desire to be informed on how their loved one responded during the support worker's visit and for support staff to also communicate this information with each other (for the client's benefit).

Factor 3: Cultural issues.

Effective home support services for people living with dementia recognise the cultural need of clients and their caregivers/families.

The PSN Enliven geographical region covers a wide mix of culturally diverse populations. As a consequence, each of the regional managers has worked very hard to develop service and staff capacity to meet the particular cultural needs of their area. Service coordinators endeavour, when possible, to match support workers with clients of the same ethnicity. A client reported on the value of this approach when English was a second language. Key stakeholders also discussed the importance of developing culturally sensitive services that respect the ethnic needs of clients and their caregivers/families.

4.2. Community

Factor 4: Dementia education.

Effective home support services for people living with dementia provide caregivers/families and clients with educational dementia-based resources and opportunities to attend educational programmes.

Numerous key stakeholders and staff discussed the importance of dementia education for clients and their caregivers/families during all stages of the client's condition. While Alzheimers NZ are the national provider of dementia-related education, there is opportunity for Enliven to work with Alzheimers NZ to expand this service for Enliven clients and their caregivers/families. A staff member remarked that if Enliven employed its own dementia care specialist, then the organisation would be in a position to deliver dementia education programmes as a component of its integrated dementia care service.

With systematic dementia-care training opportunities, Enliven staff, at all levels of the organisation, would be in a stronger position to provide clients and their caregivers/families with dementia-related information. Staff would also be better positioned to know where to refer clients to for other allied support services.

Factor 5: Comprehensive community-based integrated dementia care services.

Effective home support services for people living with dementia are integrated into regional DHB-initiated dementia care pathways and are predicated upon clients receiving a specialised Needs Assessment and Service Coordination (NASC) assessment.

Key stakeholders and Enliven senior managerial staff discussed the importance of people living with dementia receiving a specialised dementia assessment as early into their condition as possible. An early diagnosis of dementia provides the dementia-affected person and their family with an enhanced opportunity to understand the cognitive and behavioural changes that are occurring, and increased opportunities to access available medical and social support services in an integrated manner.

Effective home support services for people living with dementia are (as funding allows) integrated into a comprehensive range of community-based services.

Enliven has developed a range of initiatives to support older adults within the community, including day programmes, walking groups, swimming groups, café conversation groups, men's groups, interactions with church volunteer groups, and home-share care programmes (to name a few). Staff and key stakeholders remarked that these community-based services are formulated to promote restorative-care for client wellbeing through physical and cognitive stimulation, and social connectedness within the community – and that there were opportunities for home support clients to more fully engage with these services.

4.3. Organisational

Factor 6: Organisational leadership.

Effective home support services for people living with dementia requires organisational leadership that maintains a strategic vision incorporating the principles of restorative care, familiarity with the

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national dementia care framework, promotes staff education and training in dementia care, and maintains strong relationships with key regional stakeholder organisations.

Enliven was viewed by many clients, caregivers and key stakeholders as a leading provider of home support services. To be a leading provider of restorative home support services for people living with dementia and their caregivers/families; Enliven leadership will need to ensure a strategic vision linking to appropriate policies and resources that facilitate the best services for dementia clients and their caregivers/families. Senior staff will also need to effectively share this vision/initiative with Enliven staff at all levels of the organisation.

A number of staff noted that in order for Enliven to strengthen its position as a leading provider of community services to people living with dementia at home, senior management will need to increase expertise in dementia care, and that a specialist dementia-care position could be created to provide training and support for staff, thus building staff capacity. It was also noted by staff that given the limited budget for home support staff training, senior management will need to be innovative in the way they utilise (existing) resources to achieve best practice goals.

Staff and key stakeholders discussed the importance of Enliven maintaining relationships with key regional stakeholder organisations, e.g. DHB, MOH, NASC, Alzheimers NZ, community health professionals and community groups. Many staff and key stakeholders remarked that Enliven is well positioned to engage with emerging DHB-facilitated dementia care pathways and to promote integrated community-based services for people living with dementia.

Factor 7: Workforce capability and development.

Home Support Care: Effective home support services for people living with dementia employ home support staff with a positive and respectful attitude towards clients/caregivers and are well-trained in home support care for people living with dementia and their caregivers.

A majority of clients and caregivers remarked that the qualities and skills of the support worker staff they interacted with was an important feature of the Enliven home support service: for example, the support worker's ability to understand of the client's needs, the manner in which they interacted with the client, their ability to communicate clearly with the client/caregiver(s), their knowledge of the client (e.g. what the client likes, their past and preferences); alongside the support worker's competency in undertaking various domestic, housekeeping and personal tasks. Effective home support staff also liaise with other home support staff who are working with the client (often through the client logbook), to ensure important client-related information is passed on, and that clients and caregivers are not required to repeat themselves for every new worker.

Restorative Care: Effective home support services for people living with dementia ensure staff at all levels of the organisation receive education and training in restorative care.

Enliven has a strong tradition of training staff in restorative care principles and there was an acknowledgement from staff that ongoing monitoring of restorative practices was required to uphold the quality of Enliven service provision. Key stakeholders also acknowledged that many aspects of the restorative care model are a feature of the national dementia care framework – although it must be noted that the national framework does not use the terminology 'restorative care'.

Dementia Care: Effective home support services for people living with dementia ensure that home support staff and service coordinators receive training in dementia care and participate in regular case-review meetings to discuss client management issues.

Enliven staff at all levels of the organisation strongly supported an expansion of staff training opportunities in dementia care; with many recommending the employment of a dementia care specialist to work directly with senior staff and service coordinators, and to overview support worker training and case-review meetings. A majority of key stakeholders remarked on the growing importance of dementia trained, and well supervised/supported, home support personnel.

A majority of respondents, across all respondent groupings, discussed the importance of consistent staffing personnel for people living with dementia and the difficulties it can cause when clients are faced with changing staff personnel. While many home support staff had worked for Enliven for many years, Enliven managers acknowledged that the service experienced a turnover of home support staff and that this situation created ongoing difficulties in maintaining staff training levels/requirements.

Managers and key stakeholders identified a range of factors that impact upon home support staff retention rates including a modest pay rate, split and reduced working hours, unreliable income (due to clients being absent), and transport issues. Managers also acknowledged that home support work can be a difficult and that not everyone is suited to assisting clients with personal hygiene tasks, cleaning, and dealing with challenging client behaviours.

The Enliven service covers a range of diverse ethnic communities across the greater Auckland, Waikato and Bay of Plenty regions. As a consequence, Enliven actively endeavours to maintain an ethnically diverse home support staff group, and service coordinators attempt to meet clients' various language and cultural needs.

Factor 8: Organisational database.

Client Data: Effective home support services for people living with dementia require an organisational database that identifies and tracks clients living with dementia.

Currently, the Enliven home support client database is able to identify the number of home support clients presenting with a diagnoses of dementia; it cannot however, detail dementia-diagnosed clients across age and ethnicity groupings. The database is also not updated of changes in a client's dementia condition over time. Senior managers and service coordinators, along with DHB funders, need to be able to track client details to ensure that clients are receiving appropriate services. Being able to access and track client data, enables senior managers to monitor changes in client population demographics, and therefore to be able to employ staff and develop services to match the client population.

Staff Data: Effective home support services for people living with dementia require an organisational database that identifies and tracks the number of dementia-affected clients each support worker is engaged with, and the level of dementia-care training each support worker has undertaken.

Currently, the Enliven home support database is not able to accurately identify the number of home support clients living with dementia each support worker has on their caseload and the range of services these clients are receiving. Senior managers and service coordinators, along

with DHB funders, need to be able to track support worker case-load details to ensure that clients are receiving appropriate service provision from well trained staff. It was noted that Enliven intended to upgrade its current databases as funds became available.

Factor 9: Organisational communication.

Effective home support for people living with dementia requires the service provider to maintain good communication processes with clients and their caregivers/families.

Many caregivers commented on the importance of being able to communicate effectively with home support staff and service coordinators when various care issues arose. Key stakeholders also remarked on the significance of clients and caregivers being able to approach service providers, and the importance of having well developed mechanisms to collect client and caregiver feedback.

Factor 10: Organisational Evaluation.

Effective home support for people living with dementia requires the service provider to undertake regular service evaluations.

All managers stressed the importance of Enliven's commitment to evaluating its provision of home support services. Service assessment took a range of forms including informal evaluation undertaken through client, caregiver/family and staff feedback. Regular Formal evaluations are undertaken through service coordinator case-reviews and service Results Based Assessment (RBA) evaluation. All key stakeholders remarked on the importance of service providers evaluating service delivery.

5. Discussion

This section details the principal conclusions arising from the research findings and the research literature. It commences with an overview of the context that dementia services currently exist within. It then features central components of best practice in delivering home support for people living with dementia and their caregivers.

As the post Second World War baby boomer population progressively ages and New Zealanders live longer, the demand for older adult support services will continue to grow. While residential facilities for seniors, including hospital-affiliated residences, will meet a proportion of this demand; it is home support services assisting older people to remain living in their own home (in conjunction with other community-based services supporting quality of life) that will service much of this need. The popularity of non-residential support is driven by the wish of many older adults to remain living within their own home for as long as possible, and by governmental policy supporting this preference as a cost effective (budgetary) option.

The national dementia care framework is predicated upon the best practice principles of providing proactive, accessible and integrated services that are flexible and client-centred [25]. Over the past decade, Enliven has integrated the principles of restorative care into its home support services. There is a great deal of commonality between the principles of restorative care and the national dementia care framework principles. Both models advocate for client-centred services

that are flexible in delivery; that set (manageable) goals for clients that encourage physical, mental and social stimulation; empower clients and their families to maintain control over their circumstances; and maximise client's abilities and sense of wellbeing.

5.1. Staff training in dementia care

With the increasing number of home support clients presenting with dementia-related symptoms, there was agreement from home support staff, managers and key stakeholders, that home support staff working with a person living with dementia require specialised training in dementia care. This finding is strongly supported by the research literature, with numerous studies revealing that the quality of care provided to people living with dementia is, in part, predicated upon the level of specialised dementia-care training staff receive [18, 19].

A number of staff and key stakeholders remarked that, in their opinion, DHBs had a responsibility to supply service providers with adequate levels of funding to ensure that home support staff dementia-care training requirements were met.

5.2. Integrated Community-Based Dementia Care Services

5.2.1. Client needs

Alongside the two primary community care services of home support services and community day programmes; Enliven has also developed a number of other community-based initiatives to support older adults within the community, including walking groups, swimming groups, café conversation groups, men's groups, interactions with church volunteer groups. All these community-based services are designed to promote the restorative care principles of maintaining client wellbeing through physical and cognitive stimulation, social connectedness within the community, and support to maintain independence within the home.

The international research literature supports the remarks of many key stakeholders and staff that a comprehensive range of community-based services supplied to people living with dementia, has the potential to slow dementia symptoms and to prolong the period of time these individuals can remain in non-residential care [5, 8, 11, 13].

5.2.2. Caregiver needs

The research literature is unequivocal in its finding that the length of time that a person living with dementia can remain in their own home is frequently dependent upon the capacity of a key individual, or individuals, to maintain a primary caregiver role, and that the provision of community support services may often be as important for the caregiver and it is for the client [17, 33]. This position was strongly supported by comments from participants in this study.

Caregivers remarked that they valued the opportunity to have a period of time out from their loved one; as this gave them, as the primary caregiver, an opportunity to undertake other necessary tasks, maintain relationships with family and friends, and to have a personal break. Caregivers remarked that home support services helped to reduce their levels of stress and to sustain their role as a caregiver.

Similarly, all managers, staff and key stakeholders commented on the importance of the primary caregiver's role, remarking that many home support clients living with dementia were only able to remain living at home due to the commitment of their caregiver, along with the provision of Enliven services.

5.2.3. Dementia education

Numerous key stakeholders and staff participating in this study discussed the importance dementia education for people living with dementia, and their caregivers/families. This finding is strongly supported by the research literature and also a key component of the national dementia care framework [19, 25].

While Alzheimers NZ are funded to be the primarily New Zealand provider of dementia-related education, there is opportunity for Enliven to work with Alzheimers NZ to expand this service for Enliven clients and their caregiver/families – with the organisation providing exclusive educational services for Enliven clients.

5.2.4. Leadership

Many Enliven senior managers are members of regional social service and/or dementia care networks – some of these networks are working with local DHBs to plan regional dementia service provision. International research shows that the greater the integration of clients services the better the general outcomes for clients [19], and this finding is a central principle of the national dementia care framework i.e. requesting local services to work more closely together for the benefit of the client. These dynamic supports Enliven senior and middle management initiating and maintaining links with key stakeholder organisations within their region.

5.2.5. Funding

Key stakeholders and Enliven managerial staff identified that that the home support industry suffers from a high turnover of staff due to funding issues. Similar findings have been found in New Zealand [30] and overseas [19]. Enliven staff identified a range of financial/organisational factors impacting upon home support personnel retention rates, including a modest pay rate, split and difficult working hours, unreliable income due to staff not being paid if the client was absent, and transport issues.

Many clients and caregivers participating in this study remarked that they valued building a relationship with their home support staff and found it very frustrating when they were presented with a high turnover of home support personnel. Home support staff are often the 'face' of the organisation and Enliven is therefore judged by the quality and consistency of its support staff.

5.2.6. Evaluation

Enliven has good service evaluation processes in place. International research highlights the importance of service evaluation [7, 12] and this theme is incorporated into the national dementia care framework [25]. All managers stressed the importance of Enliven's commitment to evaluating the quality and appropriateness of its home support services. Service evaluation took

a range of forms including informal and formal evaluation processes. Informal evaluation is undertaken though client and caregiver/family feedback, along with support worker comment. Formal evaluation is undertaken through regular service coordinator assessments with clients and caregivers/families (every 3–12 months depending upon need) and service RBA evaluation.

6. Conclusion

While dementia is an escalating global problem and governments look to how best to meet the increasing demand on their public health and social services, some local solutions may influence future decision making. This research highlighted how a local provider sought to find its own solution to the question: 'What are the factors that constitute an effective restorative home support service for people living with dementia and their families/caregivers?' A review of their current design and delivery of home support for people living with dementia and their caregivers led to the identification of 10 factors influencing the delivery of effective home support for their clients and their caregivers. These factors may have implications internationally, as we look to provide globally best practice in home support. These implications may include: policy and practice that keep the needs and well-being of the dementia diagnosed person and their caregiver central to all decision making and keeping track of their progression; the provision of adequate funding to ensure a skilled workforce to meet the home support demand; acknowledging clients' ethnic diversity and responding in appropriate ways; and further investigation into a range of home support models to ensure appropriate integrated quality community services.

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Chapter 8

The Hypothalamus in Alzheimer's Disease: A Golgi and Electron and Microscope Study

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease is a progressive irreversible neurodegenerative disorder, characterized by gradual decline of mental faculties including learning capacity, emotional and behavioral alterations, serious decline of motor skills, and dysfunction of the autonomic nervous system with disruption of circadian rhythms. Among the potential modifiable risk factors diabetes and obesity may play a considerable role in the pathogenetic background of the disease. We describe some of the morphological alterations of the hypothalamic nuclei in early cases of Alzheimer's disease, using silver impregnation techniques and electron microscopy. The morphological and morphometric study revealed substantial decrease of the neuronal population, which was particularly marked in the suprachiasmatic, the supraoptic and the paraventricular nuclei of the hypothalamus. The silver staining demonstrated an obvious shortage of the dendritic arborization of neurons, associated with marked spinal pathology and axonal dystrophy. It must be underlined that Alzheimer's pathology, such as neuritic plaques and neurofibrillary degeneration was minimal in hypothalamus in comparison with other areas of the brain. Mitochondrial alterations and fragmentation of Golgi complex were observed by electron microscopy in a substantial number of neurons and astrocytes in the hypothalamic nuclei. The hypothalamic pathology may be related to instability of autonomic regulation which occurs gradually in Alzheimer's disease.

Keywords: Alzheimer's disease, hypothalamus, Golgi staining, electron microscopy, autonomic dysfunction

1. Introduction

Alzheimer's disease (AD) is a progressive devastating non reversible neurodegenerative disorder of the central nervous system, which has been recognized as the most common cause of serious cognitive decline in elderly people resulting in profound dementia [1, 2] with no effective therapy [3]. It is reasonable that AD induces a huge social burden and has a serious economic impact, since it starts frequently as mild cognitive impairment, resulting eventually in dementia, as the time advances [4, 5], affecting over 26 million people worldwide [6, 7].

The pathogenesis of AD involves a considerable number of cellular and molecular underlying mechanisms, as well as many genetic or acquired overlapping risk factors [8], such as diabetes, obesity and psychosocial stress, which although are among the modifiable factors, may contribute substantially in the rapid mental deterioration, aggravating the clinical phenomenology of the disease [9].

A substantial number of clinical observations and laboratory investigations plead in favor of brain injury [8], stress [10–12], or stress-related psychiatric disorders [13, 14], type 2 diabetes [15, 16] insulin resistance [17, 18], inflammation [19] and depression [12, 20] as probable causative factors in the pathogenetic spectrum of AD [21].

The neuropathological profile of AD includes the formation of neuritic plaques, the neurofibrillary degeneration in the form of tangles of highly phosphorylated tau proteins, the dendritic alterations, the spinal pathology, the marked alterations of dendritic spines, the dramatic reduce of the number of synapses, the substantial neuronal loss [22, 23], which is quite prominent mostly in limbic structures and selectively in various areas of the cortex of the brain hemispheres, as well as the phenomena of inflammation [24]. The prolonged gathering of the Aβ peptide in the brain activates microglial cells and pericytes reasonably, inducing neuroinflammation, which participates obviously in the ongoing pathogenic cascade of AD [24]. Coarse aggregations of Aβ amyloid peptide in the brain may consequently promote degenerations of neurons and astrocytes, which are particularly sensitive in changes of protein homeostasis, energy decline and oxidative stress [25]. The vascular factor is an additional component of the pathogenetic cascade of AD, since the disruption of the BBB and the alterations of the brain capillaries [26, 27] could lead to infiltration of the perivascular space by immune cells, promoting reasonably the exacerbation of inflammatory reactions [24].

The initial clinical manifestations of AD are subtle. However, as the time advances progressive memory and learning impairment [28], language disturbances, visuospatial disorientation, ideomotor apraxia, behavioral disturbances, depressive symptoms [29–32], personality changes [33–35], and a multitude of non-cognitive symptoms, such as sleep disruption, circadian dysrhythmia, changes in body weight and autonomic dysfunction progressively establish as principal dominant deficits in AD [36]. Sleep disturbances, on the other hand, might have a negative impact on the amyloid burden and the cognitive capacity of the patients, though the etiopathogenic mechanisms of the sporadic cases of AD remain yet unclear.

Many hypotheses have been submitted concerning the various mechanisms of the pathogenetic process of AD, based mostly on the neuropathological investigation and the experimental models of AD. Moreover the genetic investigation of the familial AD underline the heterogenetic character of AD, though the clinical investigation suggests that the disease at the advanced stages follows a common pathway with many other degenerative conditions of the brain [37, 38].

The oxidative stress correlated with the cortical and subcortical deposits of Aβ peptide can obviously play an important pathogenetic role in AD [39, 40]. In addition, the marked mitochondrial alterations in neurons and glial cells in cortical and subcortical structures and in cerebellum [40, 41], which are mostly observed in dendrites deprived of spines, may contribute in shaping the pathogenetic pattern of the disease. On the other hand electron microscopy in early cases of AD revealed fragmentation of the cisternae of Golgi apparatus [42] even in areas where the characteristic Alzheimer's pathology was unremarkable. The morphological alteration of Golgi complex may be associated with the impairment of protein trafficking, acting as an additional pathogenetic component of AD. It is well recognized that Golgi complex is of instrumental importance in sorting and trafficking of the plasma proteins toward their final membranic target [43].

The autonomic nervous system participates in the brain dysfunction in case of AD either in the form of autonomic hyperactivity or of autonomic failure under the influence of strong exterior emotional inputs. The hypothalamus, the principal autonomic center is involved in advanced stages of AD [44–49], whereas the suprachiasmatic nucleus (SCN), which is the main circadian pacemaker, undergoes several continuous alterations during the course of the disease [50]. The activation of the hypothalamic-pituitary-adrenal (HPA) pathway by exterior stimuli, inducing stress increase substantially the glucocorticoid release [49], which may modify the emotional and autonomic reactions of the patients who suffer from AD.

The modification of the volume of the third ventricle in AD may be considered as an evidence of the involvement of the hypothalamus, which would undergo pathological alterations in AD [51, 52], that may have a different molecular and cellular character in comparison with those observed in the hippocampus and in the cortex of the brain hemispheres [53], since hypothalamic plaques are not associated with increased gliosis or prominent disruption of the neuropile [53]. In addition the majority of diffuse plaques in the hypothalamus in case of AD may be labeled with an antiserum to the Aβ peptide, of the beta-amyloid precursor proteins (beta APPs), whereas Aβ peptide-immunoreactive plaques are rather uncommon in the hypothalamus of patients without AD [54]. It was also noticed that the neurofibrillary degeneration in the hypothalamus involves primarily those neurons that are associated with cortical areas which show prominent Alzheimer's pathology [53].

Following our previous study [54] on the morphological alterations of the hypothalamus in AD, in this study we attempted to describe some additional morphological findings, concerning the hypothalamic nuclei and the dendritic and spinal pathology in early cases of Alzheimer's disease.

2. Material and methods

2.1. Material

The morphological study of the hypothalamus concerns 14 autopsy cases of patients suffered from AD [54], at early stages according NINCDS-ADRDA criteria [55] and Braak and Braak staging [56] (**Table 1**). Twelve additional intact brains of apparently healthy individuals, who died accidentally, were used as normal controls [54].

Samples from the hypothalamus were excised and processed for electron microscopy and silver impregnation techniques including rapid Golgi's method, Rio Hortega's and Bodian's techniques [57, 58].

2.2. Methods

2.2.1. Electron microscopy

For the electron microscopy the fixation of the specimens was performed in Sotelo's fixing solution, according to method, which was described in previous article [54]. Then they were post-fixed in 1% osmium tetroxide, dehydrated in graded alcohol solutions and propylene oxide [54]. Thin sections were cut in a Reichert ultratome, contrasted with uranyl acetate and lead citrate and studied in a Zeiss 9aS electron microscope [54].

Gender	Age at death	Duration of the disease	Length of brain fixation in months	Braak and Braak stage
M	55 y	3 y	1	II/III
F	62 y	28 mo	1	II/III
M	63 y	37 mo	1	II
F	66 y	40 mo	1	II/III
M	72 y	3 y	1	III
M	74 y	38 mo	1	II/III
F	75 y	42 mo	1	II/III
F	76 y	46 mo	1	III
M	78 y	42 mo	1	II/III
F	80 y	2 y	1	II/III
M	78 y	42 mo	1	II/III
F	76 y	36 mo	1	III
M	54 y	2 y	1	III
M	65 y	37 mo	1	II/III

The hypothalamus was excised and studied from 1974 to 2011.
AD: Alzheimer's disease, F: female, M: male. Fixation for silver impregnation techniques.

Table 1. List of the AD brains.

2.2.2. Light microscope

2.2.2.1. Silver impregnation techniques

For the rapid Golgi staining, the hypothalamus, after 1 month's fixation in fresh prepared formalin, was immersed in potassium dichromate for 10 days and in 1% silver nitrate for additional 10 days. Following dehydration in graded alcohol solutions, the specimens were embedded in paraffin and cut, some of them at 100 μ and some at 25 μ, alternatively [54]. Sections of 25 μ were stained also with methylene blue, according to Golgi-Nissl method [57–60]. All the sections were mounted in Entellan (Merck-Millipore, Darmstadt, Germany), between two cover slips and studied in a Zeiss Axiolab Photomicroscope, equipped with digital camera and computer.

We studied extensively the suprachiasmatic (SCN), the supraoptic (SON) and the paraventricular nuclei (PVN) of the hypothalamus [45]. The volume of the nuclei was estimated according to Cavalieri principle [61, 62]. We described the type of dendritic arborization, the morphology of the dendritic branches and spines, and then we estimated the number of dendritic branches, as well as the spinal density, on sections stained according to rapid Golgi, and Golgi-Nissl methods.

2.2.3. Morphometry

Morphometric studies were performed with an image analyzer (Image J program). The mean surface area of the neurons, as well as the dendritic arborization, was calculated in silver staining [63]. The morphology of the soma and the dendrites was estimated on the basis of the criteria posed by Jacobs et al. [64], concerning the quality of staining of dendrites and the contrast between neurons and neuropile.

The estimation of the in space distribution of the dendritic branches was performed in a centrifugal way according to Uylings et al. [65]. We estimated the diameter of the soma, the length of the dendrites, the number and the type of the dendritic branches, the length of dendritic segments per dendritic order and the spinal density per segment, given that each dendrite which arises from the neuronal body up to the first bifurcation is considered as first-order dendritic branch.

For the quantitation we applied Image J program, which was properly adjusted for the used microscope (Carl Zeiss Axiolab Photomicroscope). The dendritic arborization was assessed on the basis of the method of concentric cycles introduced by Sholl [66].

The dendritic spines were counted on three sequent segments of the dendritic field. The first segment, 20–30 μm in length, was located on the primary dendrite, the second segment, 20–30 μm in length, on the secondary one and the third segment of 40–50 μm, on the tertiary dendrite.

At the level of electron microscopy we applied the stereological estimation introduced by Nyengaard [67] and West [68–70]. We estimated the number, the length, the surface area, the volume and the spatial distribution for the mitochondria [54, 70] and for the cisternae and the vesicles of the Golgi complex [71].

We estimated also the mean nuclear area, the dendritic profiles of the neurons [72], the spinal density per dendritic segment, the areas of the pre- and postsynaptic terminals [73–75] and the number of synaptic vesicles per presynaptic component [54, 75].

The statistical evaluation of the data was based on the Student t tests. P-values below 0.05 were considered statistically significant, and those bellow 0.01, highly significant.

3. Results

3.1. Silver impregnation technique

From the anatomical point of view the human hypothalamus is extended from the level of lamina terminalis anteriorly to a level through the posterior commissure and the posterior edge of the mammillary bodies, posteriorly. Using the silver impregnation techniques, including Golgi-Nissl method, we could clearly visualize the neuronal population of the hypothalamic nuclei. We studied all the hypothalamic nuclei extensively; however we focused our description particularly on the suprachiasmatic (SCN), the supraoptic (SON) and the paraventricular nuclei (PVN).

In rapid Golgi method, the morphological and morphometric study of the neurons, demonstrated a considerable decrease of the number of neurons, and a substantial loss of dendritic branches in the patients who suffered from AD (**Figures 1** and **2**), as compared with normal controls (**Figures 3** and **4**). Abbreviation of the dendritic arborization was prominent mostly in the neurons of suprachiasmatic nucleus (SCN) which was associated with marked decrease in the number of dendritic spines (**Figures 5** and **6**), in comparison with the normal control brains (**Figure 7**). The same morphological alterations concerning the dendritic branches and the spines were also observed in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus in AD (**Figure 8**).

The morphometric estimation of the dendritic spines of the neurons of the SCN and SON revealed a dramatic decrease of their number in AD brains in comparison with normal controls (**Figure 9**)

3.2. Electron microscopy

Detailed study on electron microscope revealed marked morphological changes of the neuronal dendrites, which were prominent mostly in the secondary and tertiary dendritic branches of a considerable neuronal population of the suprachiasmatic (SCN), supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus of patients who suffered from AD. Marked decrease in spine density was noticed in the dendritic branches of the neuronal networks of the hypothalamic nuclei, a phenomenon, which was particularly prominent in the suprachiasmatic nucleus. Small spines and giant spines were also observed in a considerable number of neurons of the suprachiasmatic nucleus. Many large and giant dendritic spines were observed, which included multivesicular bodies.

http://dx.doi.org/10.5772/intechopen.75887

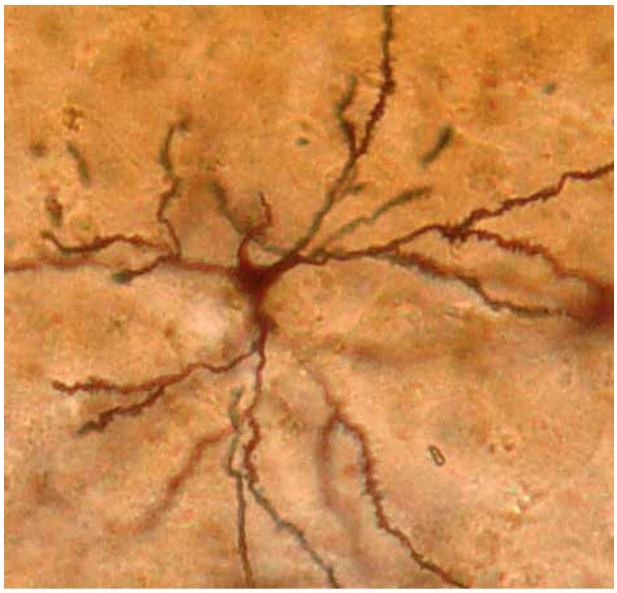

Figure 1. Neuron of the SCN nucleus in AD brain. Golgi staining 1200X.

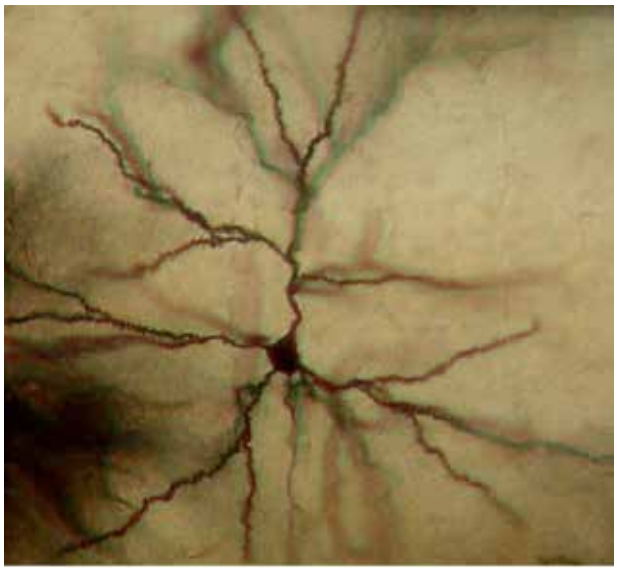

Figure 2. Neuron of SCN of the hypothalamus in a case of AD. The loss of the dendritic branches is obvious. Golgi staining, magnification 1200×.

Mitochondrial pathology was observed in many dendritic profiles in the suprachiasmatic and the paraventricular hypothalamic nuclei, of AD brains. The most frequent findings were the disruption of the cristae and the accumulation either fibrillary or osmiophilic material in the

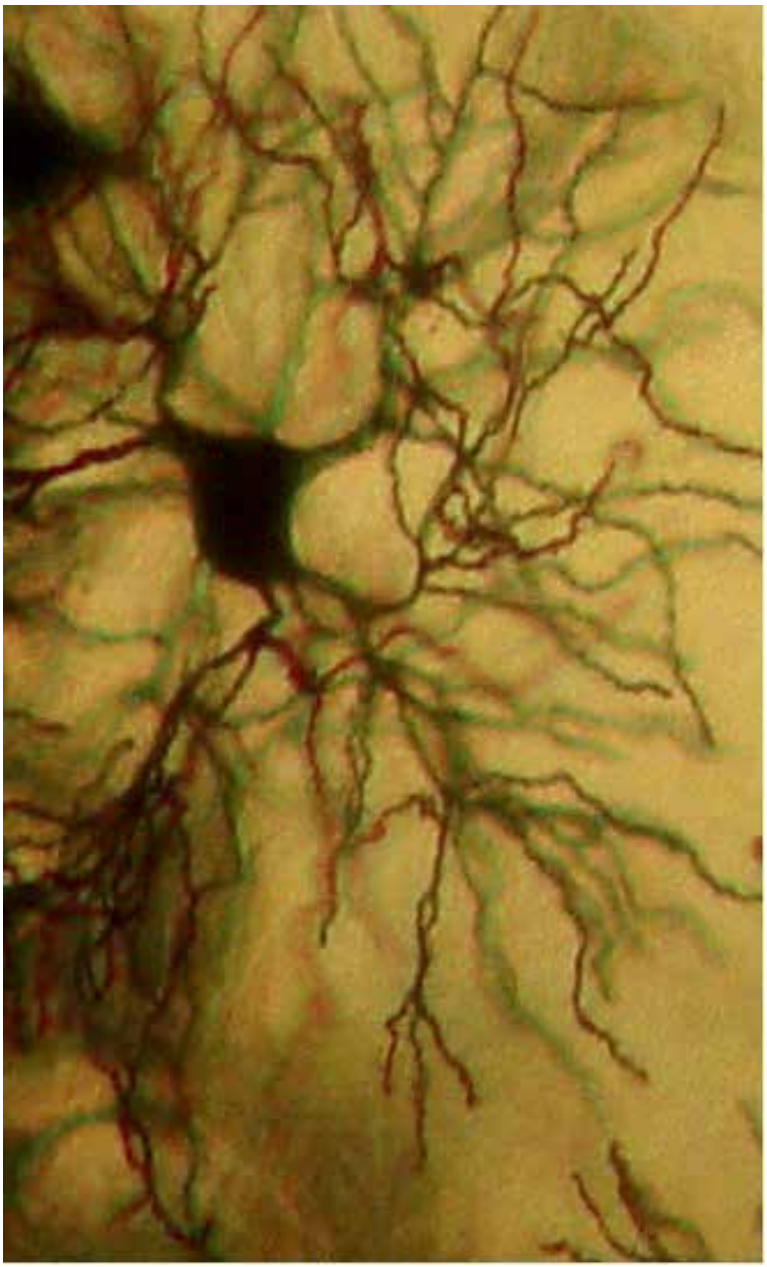

Figure 3. Neuron of the SCN of the hypothalamus of a normal brain aged 75 years.

mitochondria (**Figure 8**). The polymorphism of the mitochondria was also impressive, some of them being giant and very elongated and some being small and round.

The morphometric estimation of the mitochondria in the soma, the dendrites and the dendritic spines of a substantial number of neurons of the suprachiasmatic nucleus in AD brains

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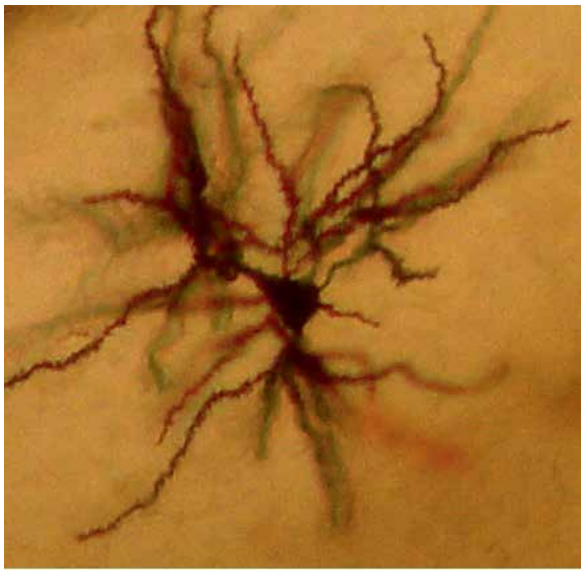

Figure 4. Neuron of the SON of the hypothalamus of a normal brain aged 80 years. The dendritic branches have numerous spines. Golgi staining, magnification 1200×.

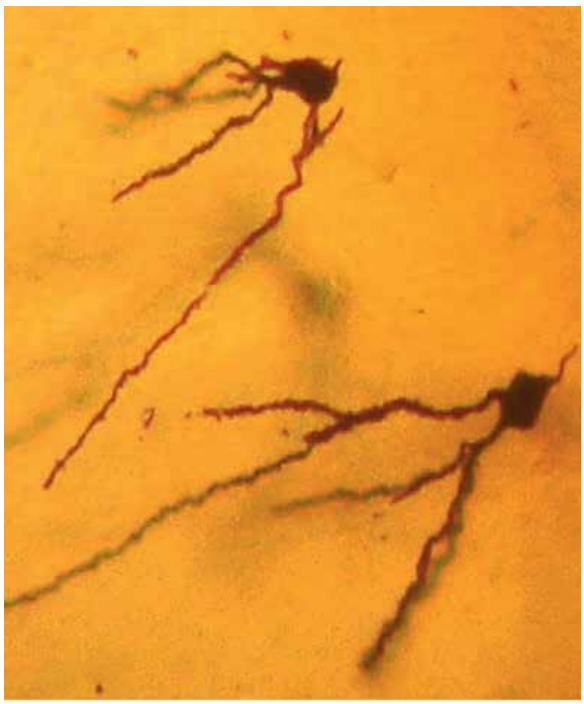

Figure 5. Abbreviation of the dendritic arborization is prominent in the neurons of suprachiasmatic nucleus (SCN) which is associated with marked decrease in the number of dendritic spines. Golgi staining, magnification 1200×.

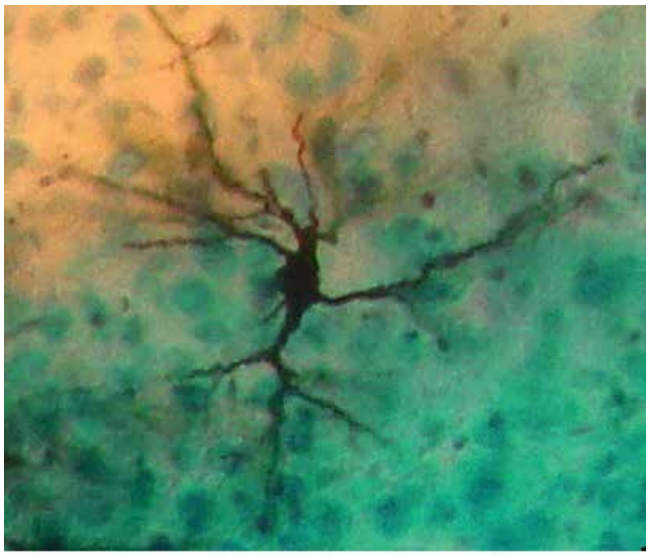

Figure 6. Neuron of the SCN of the hypothalamus of a case of AD. The abbreviation of the dendritic arborization and the poverty of dendritic spines is obvious. Golgi-Nissl staining, magnification 1200×.

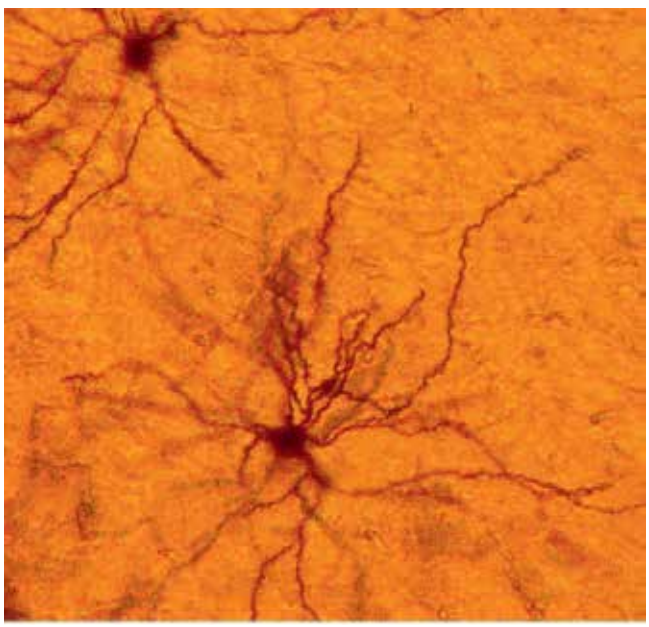

Figure 7. Neuron of the SCN of the hypothalamus of a normal brain 80 years. The dendritic branches are covered by spines. Golgi staining, magnification 1200×.

revealed that they have an average diameter of 440 ± 250 nm and a mean axial ratio of 1.7 ± 0.2. (**Figure 10**). In the same area the ellipsoid mitochondria of the dendritic spines of normal control brains have an average diameter of 650 ± 250 nm and a mean axial ratio of 1.9 ± 0.2., though the round mitochondria have a mean diameter of 350 nm. The mitochondrial cristae in

http://dx.doi.org/10.5772/intechopen.75887

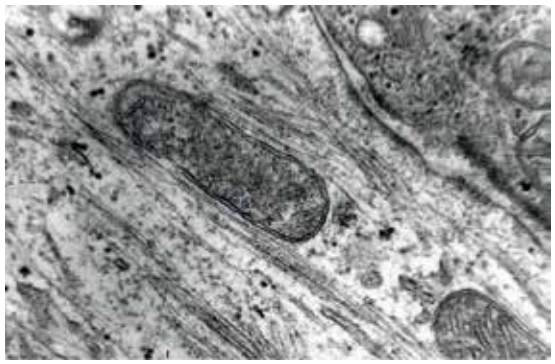

Figure 8. Mitochondrial alterations of a dendritic profile of a neuron of SCN of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000×.

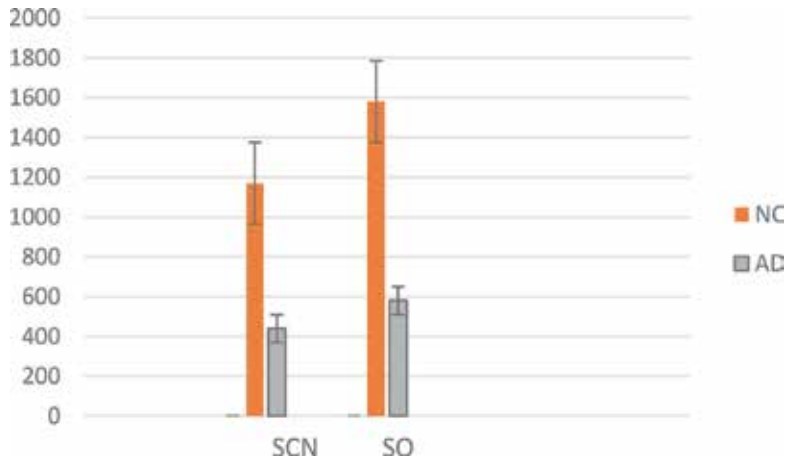

Figure 9. Average dendritic spines per dendritic arbor in SCN and SO neurons, based on measurements of 100 neurons ($p < 0.005$). AD: Alzheimer's disease, NC: normal control, SCN: suprachiasmatic nucleus, SO: supraoptic nucleus.

Figure 10. Mean diameter (in nm) of mitochondria in neurons of suprachiasmatic nucleus, based on estimation of 500 mitochondria ($p < 0.05$). AD, Alzheimer's disease; NC, normal control.

AD brains demonstrated serious changes such as disorientation, fragmentation and globular deformation. Mitochondrial alteration was also a frequent phenomenon in numerous astrocytes and pericytes in AD brains.

In a substantial number of neurons of the suprachiasmatic and paraventricular nuclei of the hypothalamus the Golgi apparatus appeared to be fragmented and atrophic (**Figure 11**). It was noticed that the atrophy or the fragmentation of Golgi apparatus (**Figure 12**) and the mitochondrial alterations coexisted with dendritic and spinal pathology in the majority of neurons.

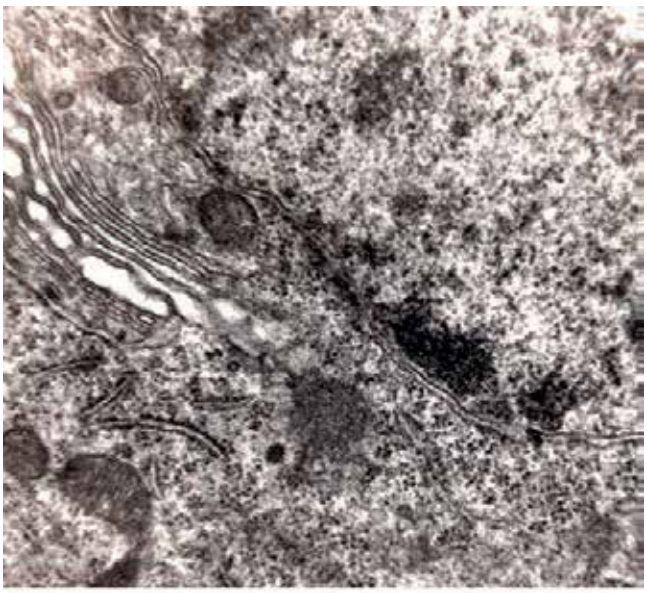

Figure 11. Alteration of Golgi apparatus of a neuron of the SCN nucleus of the hypothalamus of a case of AD. Electron micrograph, magnification 124,000×.

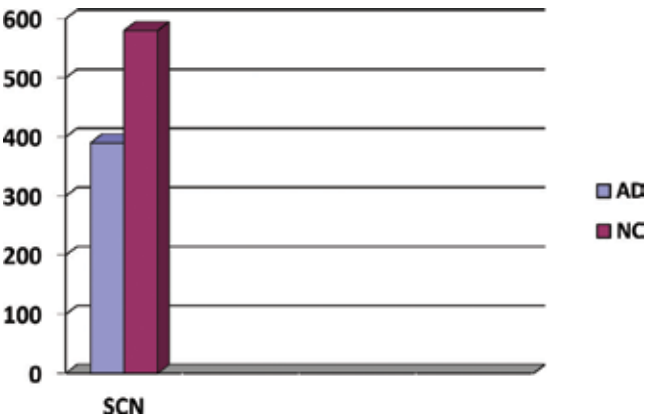

Figure 12. The volume of Golgi apparatus in nm^3. Based on measurements of 100 neurons of SCN ($P < 0.005$). AD, Alzheimer's disease; NC: normal control, SCN, suprachiasmatic nucleus.

4. Discussion

Hypothalamus is a crucial brain region for the regulation of substantial homeostatic functions, including the circadian rhythms and the sleep–wake cycle. In Alzheimer's disease and other neurodegenerative disorders [76–78] several hypothalamic nuclei are affected. It seems that the hypothalamic nuclei are not involved simultaneously at the early stages of AD. The suprachiasmatic nucleus seems to be more seriously affected than the others in aging [76]. In previous studies, it was clearly revealed that the total cell population in the suprachiasmatic nucleus is substantially decreased in aging and dramatically in AD [78] in which the hypothalamic dysfunction is closely related to sleep disturbances [79].

The hypothalamic nuclei seem to be involved with various severities in the neurodegenerative process, which progressively results in AD. In addition, the correlation of the alterations of the neuronal dendrites in the hypothalamic nuclei with those seen in the neocortex and the cerebellum, results in concluding that the hypothalamic alterations are modest in comparison with those, which are established in the acoustic area of the cortex, the visual cortex, the prefrontal areas and the cerebellar cortex [80–83].

The fact that the hypothalamus is the essential subcortical center of the homeostatic and autonomic processes, may explain the reason why some nuclei such as the supraoptic and the periventricular ones reserve substantial synaptic density, even in the advanced stages of AD, in correlation with other subcortical and neocortical neurons,.

However, the suprachiasmatic nucleus demonstrated more severe dendritic alterations and synaptic loss than the supraoptic and paraventricular nuclei, a fact which might explain the phenomenon of desynchronization of circadian rhythms in the majority of the patients, who suffer from AD [84] or cognitive decline [85] in the spectrum of other degenerative conditions of the brain [86], given that suprachiasmatic nucleus is of crucial importance for the generation and synchronization of circadian rhythms in man [86, 87]. It is reported that changes of the circadian rhythm (CR), arterial blood pressure and circadian temperature may occur in AD patients [88], especially during the night time [89–91]. Changes also of the melatonin levels are not an unusual phenomenon in advanced senility and AD [92–94]. Sundown syndrome on the other hand, frequently associated with increased motor activity is a rather common condition in advanced AD cases [95].

In a large number of neurons of the hypothalamic nuclei mitochondrial alterations were seen mostly in the soma and the dendrites. Mitochondria play an essential role in the energy supply of the cell, which is crucial in the alteration of reduction-oxidation potential of the cell, in the formation of free radicals, in scavenging activity, as well as in the intracellular calcium control and the activation of apoptotic cascade [96–98]. Normally the mitochondria are numerous in the dendritic profiles and the axons, which have a continuous increased activity during the neuronal interactions. Mitochondrial density is also substantially high in the synaptic components, since mitochondria are the main energy generators for the ceaseless activity of the synapses.

Mitochondrial dysfunction may play an important role for enhancing the neurotoxicity of the Aβ peptide, though increased mitochondrial proteostasis may reduce amyloid-β

proteotoxicity [99, 100]. In addition, impaired mitochondrial biogenesis contributes to mitochondrial dysfunction [101], which is directly associated with the oxidative stress, the main activator of the pathogenic cascade of AD [101–103].

Mitochondrial motility and accumulation are related to the functional state of the neuron, since mitochondria are transported to regions where necessity for energy is particularly high, as it occurs in the dendritic and axonal profiles and the synapses [103–105]. The shape and size of mitochondria are not stable, since they undergo continual fission and fusion which are necessary for cell survival and harmonious adaptation to changing conditions. Recent studies reported increased mitochondrial fission and decreased fusion, due to increased Aβ peptide interaction with the mitochondrial fission protein Drp 1, inducing increased mitochondrial fragmentation, impaired axonal transport of mitochondria and synaptic degeneration in AD [106, 107]. The consequence of the dynamic fusion and fission processes is the eventual mitophagy of the damaged mitochondria.

Nevertheless, a considerable diminution of the mitochondria is also seen in aging-related neurodegeneration [97, 98], as well as in the early stages of AD, when the mental decline is subtly detected [107]. In normal brains, few spines only contain small round mitochondria in contrast to dendritic branches which mostly include large mitochondria that become numerous during synaptogenesis and in various conditions of hormonal disequilibrium [104, 106]. In AD, marked morphological changes of the mitochondria have been observed in neurons, which show an extensive loss of dendritic spines, associated with giant spines, distortion of spines and synaptic loss. The association of mitochondrial pathology with the synaptic loss is reasonably attributed to a sharp decrease of energy supply by the defected mitochondria [106, 108], a fact which occurs even at the initial stages of AD, when the typical Alzheimer pathology, consisted of the neuritic plaques and the neurofibrillary tangles is still minimal [109, 110].

The mitochondrial pathology, which is observed in the neurons of the hypothalamic nuclei are additional evidences of the causative role that mitochondrial dysfunction play in synaptic degeneration and loss of dendritic arbores in AD [111, 112]. In the suprachiasmatic nucleus of the hypothalamus a substantial number of neurons made evident the marked decrease of the spine density at the secondary and tertiary dendritic branches, which affects reasonably the neuronal interactions in AD. A substantial body of evidence plead also in favor of the important role that mitochondria and Golgi complex play in the morphological and the quantitative stability of the dendritic spines in neuronal networks [105, 109–112], whereas experimental studies underline the spinal vulnerability to nonfibrillar Aβ peptide [110].

The hypothalamus play a central role in autonomic functions, including the generation and control of the circadian rhythms, the thermoregulation, the homeostasis of proteins [25], the maintenance of energy supply and the feeding behavior [113–115]. The pathological alterations of hypothalamic nuclei in AD would induce the autonomic instability, which would be particularly prominent at the advanced stages of the disease, aggravating the clinical condition of the patients exceedingly [116–118], a fact which is also observed in experimental models of AD [119] as well as in the behavioral variant of frontotemporal dementia [120].

In conclusion, the serious autonomic dysfunction in advanced stages of AD composes the tragic epilogue of the disease which is related with the involvement of the hypothalamus during the continuous pathological process of the disease.

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Chapter 9

Updated Information on Some Cognitive Disorders

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Additional information is available at the end of the chapter

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Abstract

Dementia is a neurodegenerative disorder characterized by a progressive decline in cognitive and daily living activities. The present review aimed to highlight the most relevant and updated information available in the medical literature on mild cognitive impairment, Parkinson's dementia, Alzheimer's disease, vascular dementia, normal pressure hydrocephalus, and Wernicke-Korsakoff and to deliver some personal observations about cognitive disorders and dementia.

Keywords: dementia syndrome, Alzheimer's disease, frontotemporal dementia, vascular dementia, normal pressure hydrocephalus, Wernicke-Korsakoff, alcohol-related dementia, Parkinson's dementia, mild cognitive disorder

1. Introduction

Disorders of cognition have been identified since the beginning of the humankind, and since then, different types of clinical presentation have been reported. The same happened with the clinical manifestations of dementia.

Dementia is a neurodegenerative disorder characterized by a progressive decline in cognitive and functional abilities. This neurodegenerative process has multiple causes, clinical manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes [1–3].

In 2015, it was estimated that there were 46.8 million people with dementia worldwide, of whom 58.0% were living in low- and middle-income countries, and that there were annually 9 million new global cases of dementia.

The estimated prevalence of dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, and 6.4% at North America. Currently, the number of patients with dementia is projected to increase to 131.5 million by 2050 [4].

Apart from some neuropsychological test that we will describe at the end of this chapter, there are some radiological investigations that can help in increasing the certainty of dementia diagnosis. A positron emission tomography (PET) scan and a special form of MRI can more

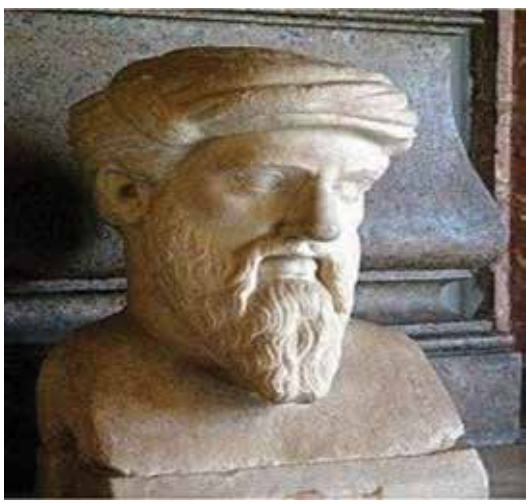

Figure 1. Pythagoras of Samos (c 570 BC–c 495 BC).

Figure 2. Alois Alzheimer 1864–1915 from Bavaria.

definitively confirm the diagnosis of various types of dementia and raise the accuracy of the diagnosis to 90%. A PET scan administered and reviewed by an expert delivers the most accurate and suggestive results while diagnosing dementia. The most accurate form of PET scanning for types of dementia is called stereotactic surface projection, which involves an advanced statistical analysis of the data.

We did a bibliographic investigation, and then the PubMed, Embase, and Web of Science were searched. In this chapter, we comment about some types of dementia and cognitive impairment according to the available publications in the medical literature, and we also delivered some comments based on our clinical observation from working with affected patients in Mthatha (one of the rural areas of South Africa) over the past21 years.

The first man who made allusions to dementia at the seventh-century BC was the Greek philosopher Pythagoras (**Figure 1**) followed by Solon, Aristotle, Plato, Cicero, Galen, Celsus, Roger Bacon, and others. That related cognitive dysfunction with the aging on the brain is not well described until 1906, when Alois Alzheimer (**Figure 2**) found at postmortem brains of affected younger people, with dementia symptoms the microscopic plaques and tangles now known as hallmarks of the disease.

2. Novel information on mild cognitive impairment

The concept of MCI is described in the nineteenth century when loss of recent memories was documented as the first sign of dementia [5]. Some degree of cognitive disturbance was thought to be part of normal aging, and then various names were used to define it such as (1) age-associated memory impairment, (2) age-associated cognitive decline, and (3) benign senescent forgetfulness [6, 7].

In 1980, with the arrival of new neuropsychological test to measure subjective and objective cognition, an intermediate phase between normal aging and dementia became more widely accepted [8]. At that time, it was defined as the presence of subtle deficits in cognition with some impairment in executive function. Following an expert international conference, all previous definitions and the way of diagnosis and management of MCI were better performed [9, 10].

Historically, the term MCI has been in the literature for almost four decades, with the initial use coming from investigators at the New York University who referred to stage 3 on the Global Deterioration Scale as being MCI [11].

In 1999, some authors at the Mayo Clinic reported subjects in their community aging study presenting a memory problem beyond what was expected for age and who demonstrated a MCI (by neuropsychological test) yet did not meet criteria for dementia [12].

The prevalence of MCI is estimated around 3–19% in the elderly people. However, in a community setting, 44% of people with MCI returned to normal after 1 year [13].

Conversion rates to dementia vary according to the setting, with 11–33% conversion over 2 years [14].

In 2015, other authors demonstrate that females with MCI have greater longitudinal rates of cognitive and functional progression than males [15].

Gauthier et al. [9] also defined MCI as a syndrome of cognitive decline, which is greater than would be expected for an individual's age and level of education but does not impede the individual's ability to perform daily activities of normal life.

Most of our patients presenting MCI had behavioral changes, depression, anxiety, and apathy, and most of them were full aware on their condition and personal frustrations, and their daily skills and activities necessary for independent daily living within the home and their communities such as dressing, grooming, ambulating, feeding, bathing, continence, transferring, and toileting were not affected. However, some authors have report that MCI patients may have difficulties in performing instrumental activities such as cooking, shopping, cleaning, laundry, driving, self-medication, and making call telephonically, among others, comparing to age-matched normal cognitively people [16, 17].

The Mayo Clinic criteria previously cited have been focused on a memory disorder and were delivered to clarify the earliest symptomatic stages of AD. However, soon later, it was well established that not all intermittent cognitive states were due to incipient AD and not all patients have just a memory impairment. To solve this dilemma, the Key Symposium was held in Stockholm, Sweden, in 2003, and in 2004, broad scope and other goal were delivered [18, 19].

Including a broad classification scheme beyond memory, the recognition of MCI could result from multiple causes and not just AD.

The Key Symposium characterization has been very useful in our practice and allowed us to distinguish the amnestic form of MCI from the nonamnestic ones, among other benefits.

Recently, Su et al. demonstrated that CA1 atrophy and subiculum thinning is significantly greater in AD and MCI patients than their control group, but similar between MCI and AD, as have been reported in previous investigations. It is proved that CA1 and subiculum changes at the hippocampus occur early on these pathologies [20].

Numerous international studies have been completed involving several thousand subjects, and these studies tend to estimate the overall prevalence of MCI in the range of 12–18% in persons above the age of 60 years. Lifestyle modifications and other nonpharmacologic therapies have been investigated by Petersen who found that aerobic exercise may be effective at reducing the rate of progression from MCI to dementia. Criticism has been raised regarding the boundaries of the condition of MCI with respect to differentiating it from changes of cognitive aging and also differentiating it from dementia [21].

Biomarkers provide a path toward the early detection of people at high risk for cognitive disorder and thereby its early prevention and/or management. *Nevertheless, these advances, whether for PD or AD, came with some risks and limitations that should to reconcile the potentially negative aspects of early diagnosis, the risk-benefit ratios of various treatments, and accessibility of biomarker testing and clinical resources, counseling, and ways of therapies once available* [22].

MCI is well represented in our series PD, and in our opinion, Parkinson's disease-cognitive rating scale seems to be more selective in detecting MCI and PDD than Montreal Cognitive Assessment.

Plasma α-synuclein level was not associated with the presence or type of cognitive impairment, but the *ApoEe4* allele carrier status was significantly associated with executive dysfunction in PD, and both depression and diabetes mellitus are well known as risk factors for cognitive impairment [5].

The biomarkers of cognitive disorder in patients with diabetes can be grouped according to the following three aspects:

1. Functional or metabolic changes by neuroimaging tools
2. Serum molecules or relevant complications
3. Genetic types

In diabetic patients with cognitive disorder such as specific factors related to associated depression, inflammation, poor glucose metabolism, insulin resistance, micro/macrovascular complications, neurotrophic molecules, adipokines, and Tau protein presented remarkable changes. In diabetic patients, some neuroimaging studies provide more information on functional, structural, and metabolic changes during the cognitive decline progression [23].

Publications from several authors suggest that greater degrees of atherosclerosis of the carotid artery are associated with the progression from MCI to dementia [24, 25].

In another study, the authors demonstrated that alterations in the intima media thickness (IMT) of the common carotid artery and the number of plaque (confirmed by ultrasound) are associated with an increased risk of MCI and dementia. In MCI, the IMT was more frequently observed, whereas in patients with dementia, the most common finding was increased numbers of carotid plaques. These researchers suggest that their findings may aid in identifying elderly people at higher risk for the progression of MCI when morphological impairment of cerebrovascular structures has been identified. In other words, the presence of atherosclerotic changes and modifications in blood factors such as p-selectin glycoprotein ligand, platelet-leukocyte aggregates, and platelet-monocyte aggregation can be used to predict MCI and dementia [26].

Some authors introduced a novel methodology to get an accurate classification of patients with AD or MCI from cognitively unimpaired (CU) people for clinical diagnosis and adequate intervention, respectively. These researchers focused on differentiating AD or MCI from CU based on the multifeature kernel supervised within-class-similar discriminative dictionary learning algorithm confirmed that methodology had superior performance in face recognition. They also included structural MRI, fluorodeoxyglucose PET, and florbetapir-PET data from the Alzheimer's Disease Neuroimaging Initiative database for classification of AD versus CU, MCI versus CU, as well as AD versus MCI, successfully [27].

Tai Chi is a type of mind-body exercise that combines physical and cognitive-stimulating activity that provides good benefits on general cognition and instrumental activities of daily living in patients with MCI [28].

Mueller et al. [29] have documented spoken language as a noninvasive, multidimensional, and informative biological sample for the early diagnosis of AD, primary progressive aphasia, and other cognitive disorders. They also confirmed that connected language analysis is one of

the most promising state-of-the-art diagnostic tools for MCI. Their results provide evidence that features of connected language are associated with very early, subclinical memory loss in late-middle age. This study helped toward a better comprehension of early language dysfunction associated with a cognitive decline.

Recently, Shang et al. [30] investigated differences in plasma fatty acids, adiponectin, reptin, plasma markers of inflammation, serum amyloid A, plasma lipids, and low-density lipoprotein in patients with AD, MCI, vascular dementia, and ischemic stroke in comparison to normal controls. They found different levels in almost all patients, indicating that these diseases have diverse pathological mechanisms.

The evaluation of inner retinal layers as a biomarker of MCI has brought more novel information about the possibility to predict cognitive decline, which can be used as prognostic information for patients who need to take financial and family decisions, advanced directives, afford care/residence decisions, etc. This reliable prognostic information and planification of the future will serve as significant societal benefit, taking into account the high societal cost of cognitive disorder care all over the world [31].

The level of relationship between cognition and functional outcomes in the MCI population is affected mainly by cognitive domains and a little bit by age and educational level. Early identification of subtle functional disturbance in MCI and comprehension of its cognitive and noncognitive correlates are determinant in the diagnostic process because of its prediction for dementia progression [32].

A recent meta-analysis investigation showed that hearing impairment is associated with a higher risk of MCI and dementia in elderly people [33].

Recently, a group of Korean researches have confirmed that a dietary pattern based on seafood and vegetables in older Korean adults can reduce MCI remarkably [34].

Recent study made by Correa-Jaraba and colleagues confirmed that the event-related potential technique is useful for evaluating changes in brain electrical activity and increased amplitude of the P3a component is a novel neurocognitive marker for differentiating amnestic MCI [35].

On the other hand, it seems to be that telerehabilitation by videoconference can improve cognitive function in patients with MCI, but this procedure needs more investigation to confirm its feasibility [36].

Three months ago, some investigators documented the association between the presence of hallucinations, delusions, anxiety, depression, and abnormal motor behavior, with the risk of developing incident dementia*, independent of other known risk factors, including MCI in the future, a simple, low-cost strategy for screening population groups at dementia risk, particularly in environments with limited access to specialized services and very sophisticated resources* [37–40].

3. Some comments about Alzheimer's disease

Alzheimer's disease is a progressive nonreversible neurodegenerative disorder, characterized by cognitive decline including learning capacity, emotional and behavioral alterations, motor

skills impairment, including dysfunction of the autonomic nervous system and desynchronization of circadian rhythms. According to Picard et al. [41], early-onset Alzheimer's disease (EOAD) and behavioral variant frontotemporal dementia (bvFTD) are the most common types of presenile neurodegenerative dementia (i.e., age at onset around 65 years old). Compared to the typical episodic memory dysfunction of late-onset AD, EOAD patients show a constellation of multidomain deficits at presentation, which can include not only memory, but also language, executive, visuospatial abnormalities, and behavioral disturbances like bvFTD cases [42].

Volumetric and cortical thickness studies have shown a prevalent involvement of posterior parietal regions in EOAD and of anterior fronto-insular-striatal areas in bvFTD [43, 44]. Some studies reported a greater white matter (WM) involvement in bvFTD compared to EOAD [45–50]. Filippi et al. and Zhou et al. [51, 52] found a divergent pattern of altered functional connectivity in the default mode network (DMN) and salience network comparing EOAD and bvFTD patients.

Some specialists from Alzheimer's Association consider that AD is the underlying cause of all types of dementia, and it is characterized by β-amyloid plaques, neurofibrillary tangles, and neurodegeneration in areas of the brain associated with cognition, such as the cortex and hippocampus. AD is also characterized by disturbances of the daily activities involving memory, speech and language, reasoning, planning, and other cognitive abilities [53].

The Framingham Study, which followed up 2611 cognitively intact participants (1550 women and 1061 men) on many for 20 years, indicated that risk factor for AD in 65-year-old woman was almost twice that of men [1] because it seems to be that life expectancy is longer in ladies. Other epidemiologic investigations also confirmed that neurodegeneration develops more rapidly in females who are often diagnosed earlier than males [54, 55]. And they are often diagnosed earlier in the course of illness than men. In many cases, inflammation is another risk factor for AD that dysregulated neuroinflammatory reaction is another possible AD etiology, which is more pronounced in females [56, 57].

Some research suggests the important of sex differences in microglia development and in response to fluctuating gonadal steroids during the life and there are more microglia in female than males [58]. Females have been shown to have more microglia than males [1].

Apart from the previous statements, some authors suggest that particular aspects of music perception such as pitch pattern analysis may open a channel on the processing of information streams in major dementia syndromes. Therefore, the potential selectivity of musical deficits for particular dementia syndromes and particular dimensions of processing warrants further systematic investigation [59].

Between classical thiamine deficiency and Alzheimer's disease (AD), many similarities exist and in both are associated reductions in brain glucose metabolism with cognitive deficits. Vitamin B1-dependent enzymes are critical components of glucose metabolism that are reduced in the brains of AD patients and by thiamine deficiency, and their decline could account for the reduction in glucose metabolism [59]. Nevertheless, many other conditions not related with AD can cause dementia as well, and it should be taken into account in the process of diagnosis and management. As the reader can see below, apart from AD, other types of dementia and their etiology are also listed.

In the past decade, we applied the term "mild cognitive impairment (MCI) due to AD" to refer to the symptomatic predementia phase of AD; in other words, patients with cognitive decline whose primary underlying pathophysiologic was AD but no evidence of a remarkable impairment in social or occupational activities; currently, we separate those patients in two groups.

Typically, amnestic MCI is the type of prodromal stage of dementia due to AD, but other phenotypes can also mimic to this kind of dementia, such as posterior cortical atrophy (also known as the visual variant), logopenic aphasia, or a frontal lobe-dysexecutive presentation of AD. Therefore, as a general agreement, not all MCI is early AD. The Key Symposium characterization of MCI helps to differentiate between the amnestic form of MCI and the nonamnestic one. These clinical syndromes appeared to be aligned with causes in a differential fashion and may have variable outcomes [60]. The Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria are useful in prediction of amnestic MCI progression to AD, including medial temporal lobe atrophy and hypometabolism in MRI and FDG-PET, respectively [10, 61, 62].

Recently, some researchers reported that plasma total tau and pTau181 levels were higher in AD dementia patients than those in cognitively unimpaired. Plasma pTau181 was more strongly associated with both Aβ and tau PET. Plasma pTau181 was a more sensitive and specific predictor of elevated brain Aβ than total tau and better than the combination of age and apolipoprotein E, and they concluded that plasma pTau181 may have utility as a biomarker of AD pathophysiology and as a noninvasive screener for elevated brain Aβ [63].

Few weeks ago, some authors have found that [^{18}F]AV-1451 uptake showed the strongest regional correlation with hypometabolism. Correlations between [^{18}F]AV-1451 uptake and both hypometabolism and cortical thickness were stronger in participants with greater cortical tau severity. In addition, age, tau asymmetry, and clinical diagnosis influenced the strength of the correlation between [^{18}F]AV-1451 uptake and cortical thickness. Therefore, all these findings support a close relationship between tau and hypometabolism in Alzheimer's disease but show that correlations between neuroimaging modalities vary across participants [64].

Some investigations have confirmed that people with MCI and a positive amyloid PET scan are more liable to progress rapidly and, again, ADNI data confirmed this. Nevertheless, it is well known that carriers of the apolipoprotein E4 (*APOE4*) genotype are more susceptible to progress rapidly; however, in clinical practice, *APOE* testing did not contribute remarkable to the diagnostic assessment [65].

The study done by Hansson and colleagues relieved more information with regard to these data and corroborates the suspicion that those individuals, particularly with amnestic MCI presenting low CSF levels of $A\beta_{42}$ and elevated total tau and phosphorylated tau, are at the higher risk for progressing faster than those patients with the same clinical phenotype but normal biomarkers on the CSF [66, 67].

All people presenting a mild cognitive impairment in our series did not present an early Alzheimer's disease later.

The criteria for MCI due to AD developed by the National Institute on Aging and the Alzheimer's Association essentially adopted the Key Symposium criteria and explained more explicit some of the diagnostic features. These criteria also considered biomarkers for underlying AD's pathophysiology trying to define the underlying cause and, hence, predict outcome.

Now, the pathological criteria for AD require the presence of Aβ deposition in plaques and tau deposition in neurofibrillary tangles. The absence of biomarkers of Aβ deposition strongly suggests that AD is not the cause of MCI.

The definitive absence of evidence of either Aβ deposition strongly suggests that the MCI syndrome is not due to AD. This marker analyses the lower $A\beta_{42}$ levels on CSF [68] and the evidence of Aβ deposition, using a variety of specific ligands in PET scan [69] and the increased accumulation of tau or phosphorylated tau in the CSF is another biomarker [68].

AD and atrophy in entorhinal cortex (ERC), the hippocampus, and its subfields Cornu Ammonis 1(CA1) and subiculum are simultaneous, and these abnormalities can predict conversion from MCI to clinical AD. It has been documented that in the early stages of AD, some changes at the stratum radiatum, lacunosum, and molecular involving ERC and CA1 can be observed [70].

Lewy body dementia and other types of cognitive disorder are not included in this revision due to limitation of space.

4. Some information about Parkinson's disease

Parkinson's disease (PD) is an idiopathic type of parkinsonism, which progresses gradually in spite of the medical or surgical treatment implemented and it is characterized by bradykinesia, tremor at rest, gait disturbance, postural problems, rigidity, dysarthria, dysfunction of the judgment, reasoning, memory, depression, anxiety, insomnia, and cognitive decline due to loss of midbrain dopaminergic neurons in the pars compacta of the substantia nigra and consequent loss of dopamine input to the caudate nucleus and putamen (striatum), and it is more prevalent in men, whereas rigidity, difficulties pertaining to daytime sleepiness, dribbling saliva, interest in sex, and problems having sex are more common among men with PD [71].

Dementia affected almost 50% of our patients with PD within the first decade after diagnosis is made, but the intensity of their manifestations varied considerably among them. Prospective investigations reveal patient differences in the progression of cognitive deficits and in risk factors for developing PD dementia (PDD) [72].

Identifying patients at risk of dementia and those at the earliest stages of cognitive involvement is important for three important reasons:

1. As new disease-modifying treatments in Parkinson's are emerging, early intervention to slow or prevent Parkinson's dementia is becoming a realistic prospect.
2. Earlier detection of cognitive involvement offers the hope of prognostic information.
3. Finding the earliest features of cognitive involvement may provide insights into underlying mechanisms of disease progression, ultimately leading to identification of novel therapeutic targets [73].

The concept of MCI is introduced in the 1980s, and it is characterized mild cognitive deficits that did not qualify to a diagnosis of dementia in patients with AD, and more recently, it was also introduced for patients with PD [5].

As far as we remember, the concept of "mild cognitive impairment" as a transitional or pre-dementia state in Parkinson's disease was delivered before 2014, and we also believe that PD-MCI is a transitory stage between normal cognition and dementia.

A recent study showed a strong correlation between the extent of neurofibrillary tangles and alpha synuclein [74]. It seems to be that the insula lobe is one of the vulnerable regions by alpha-synuclein deposition.

The treatment of cognitive symptoms has shown some good results with the introduction of cholinesterase inhibitors (ChEIs) that is more effective in PDD, compared to AD, because of their early, prominent CNS cholinergic disturbance [75].

Rivastigmine has been approved by the United States and European Union for the treatment of PDD with promissory results, while levodopa and other dopaminergic medications are still effective for tremor and parkinsonian motor symptoms of PDD. For the treatment of psychotic manifestations, atypical antipsychotics (e.g., quetiapine, clozapine) have been used in PDD. There is current evidence-based medicine favoring clozapine in PDD [76].

Novel information about imagenological assessment of PDD is positron emission tomography (PET) scan using C-labeled radiotracer Pittsburgh compound B that has been widely applied for the in vivo assessment of amyloid-β (Aβ) deposition in patients with AD, with successful results [77, 78].

Progressive supranuclear palsy is included in the classification of Parkinsonism and is also a form of dementia that is characterized by vertical gaze palsy, falling backward, hypokinesia, rigidity, irritability, dysphagia, dysarthria, apathy, depression, and cognitive decline, which is sometimes misdiagnosed as PD. Based on clinical observations from our series of patients with Parkinsonism, neuropsychologically assessed at the early to moderate stages, cognitive decline was a common problem found and some of those patients developed dementia with reduction of quality of life and functional disability. However, an important number of patients presenting mild cognitive impairment (MCI) did not develop dementia up to date. Because we have not resting-state functional MRI (rs-fMRI) facilities in our setting, we could not document the expected structural and functional connectivity alterations of the brain. Recently, some author confirmed that the temporal connectivity alterations found in patients with PD and PD-MCI could be related to the presence of cognitive impairment in PD [79].

5. Updated information on idiopathic normal pressure hydrocephalus

Idiopathic normal pressure hydrocephalus (iNPH) is an important geriatric disease, a treatable cognitive disorder, which can be reliably diagnosed with an organized approach, and its prevalence is expected to increase gradually. This type of hydrocephalus is characterized by late-onset, surgically treated progressive neurodegenerative disease caused by inadequate cerebrospinal fluid (CSF) dynamics and ventriculomegaly, while other types (including low-pressure hydrocephalus) are usually secondary to head injury, subarachnoid hemorrhage,

infections, and other disorders that cause an accumulation of the cerebrospinal fluids (CSF) in the ventricular system of the brain mainly associated to its impaired drainage [80]. Approximately 700,000 persons may have iNPH in the United States. Neuroimaging with either CT or MRI is required for the diagnosis of iNPH [81].

The iNPH, the most common form of hydrocephalus in adult's population, affects the brain parenchymal on the cerebral hemisphere causing cognitive dysfunction, lack of balance, urinary urgency with or without incontinence, problem-solving disabilities, dysarthria, and apraxia of gait apart from spasticity, hyperreflexia, and other upper motor neuron signs.

Gait apraxia is typically the first and worst disturbance in patients with iNPH. The overall prevalence of iNPH ranges from 0.02% to up to 5.9%, depending upon age and specific population studied [82, 83]. Another author reported a prevalence about 0.51–2.9% in the elderly population [84]. Some authors found that the male-to-female ratio for those with idiopathic NPH (iNPH) is 1.39:1 ($P < 0.0001$), and the corresponding incidence rate ratio between males and females with iNPH is 1.838 ($P < 0.0001$), indicating that iNPH is almost twice as likely to occur in older males than older females [85].

In patients presenting Huntington disease with an associated inability to walk or rapid progression of their symptoms, a diagnosis of iNPH should be considered, and they are going to improve the cognitive disorder, gait, and chorea after the lumbar puncture and surgical treatment [86].

Mild apathy is the more common neuropsychiatric symptom in patients with iNPH, and the frontal lobe pathology is the main cause of increased correlation between neuropsychiatric symptoms and cognitive impairment [87].

MCI is quite common presentation in patients with iNPH, and their neuropathological findings are generally consistent with white matter damage, regardless of the underlying, yet unknown, pathophysiological mechanisms [88–92].

Diffusion tensor imaging (DTI) is a useful MRI technique that can reflect the structural integrity and interstitial space of the white matter by detecting the directionality of extracellular water diffusion [fractional anisotropy (FA)] and of free water diffusion [mean diffusivity (MD)] and has been applied to evaluate white matter damage in iNPH [93–96]. Some authors have confirmed that after shunt surgery in patients presenting iNPH, the fractional anisotropy (FA) in the corona radiata decreases, and the regions involved were located between the enlarged lateral ventricles and Sylvian fissures. The plasticity of the brain for mechanical pressure from the CSF system is also confirmed by their findings [97]. An interesting exception found in iNPH is the increased FA within the corticospinal tract [98–102].

Treatment outcome can be predicted by quantitative image biomarker from diffusion MRI, which also serves to distinguish between reversible and irreversible changes in iNPH [103].

Alzheimer's disease can be differentiated from iNPH by cerebral retention of Pittsburgh compound B (PIB: *N*-methyl-[^{11}C]2-(4-methylaminophenyl)-6-hydroxyben-zothiazole) in positron emission tomography (PET) because in iNPH it was limited to the high-convexity parasagittal regions, whereas in AD it spreads over the frontal and temporoparietal lobes. Therefore, the

PIB-PET is very useful in the differential diagnosis between iNPH and AD. Kondo et al. have demonstrated that 3 of 10 (30%) patients with iNPH without any clinical signs of AD had obvious cortical retention in PIB-PET, indicating that iNPH is one of the PIB-positive diseases [104].

In 2016, several studies on iNPH were published in the medical literature [105]. Below, interested readers can find a summary from the most relevant conclusions.

There is no standardization of care or differentiation between various types of hydrocephalus among the confirmed cases of hydrocephalus in the Middle East.

The most common complication seen in postshunting surgery is subdural hematoma, and it shows reduced and even worsening of gait in iNPH.

Remarkable improvements in gait and clinical outcome are seen in patients presenting iNPH after shunting surgical procedures.

After 6 months of shunt surgery in patients presenting iNPH, the best test for identifying clinical improvements is the European-iNPH scale.

Some authors have demonstrated that the vascular brain expansion (during cardiac cycle) is quickly compensated by CSF volume flush, toward the spinal compartment due to a decreased spinal canal compliance, a decreased vascular brain expansion, or an increase of subarachnoid space resistance to CSF flow.

Based on the knowledge that venous drainage helps to control intracranial pressure, some authors have highlighted the potential role of the right side of the heart and the jugular vein valves in the physiopathology of the intracranial pressure.

In iNPH, the main goal of shunt therapy is to improve the patient's mobility and a mean improvement of 0.4 mph has been confirmed.

Dr. Hakim described the iNPH for the first time in 1964, but its physiopathology was not satisfactorily elucidated as yet. Although changes seen on the brain parenchymal after shunt surgery have not been documented, it seems to be that a number of patients with cerebral atrophy could be presenting a reversible subarachnoid augmentation.

At the present moment, reliable biomarkers for selection of iNPH patients for shunt therapy and T-tau or Aβ-42 for predicting shunt responsiveness are not available and need to be identified. Nevertheless, some potential microRNA biomarkers in the CSF are useful to differentiate iNPH patients from other presenting overlapping symptoms of other disorders such as AD, PD, and progressive supranuclear palsy.

A possible genetic component involved in the pathogenesis of iNPH may be present.

In iNPH patients, the endoscopy third ventriculostomy is also a choice of treatment although some authors have found that it is not effective in treatment of iNPH [106, 107].

Ventriculoatrial shunt (VAS) is another choice of treatment of iNPH, and some authors recommend it as a first choice because it is more physiological, no cardiopulmonary complications have been reported, and less shunt malfunction in the follow-up is found.

The CSF tap test shows good results for diagnosis of iNPH, but its accuracy is not certain, even for bedridden patients, indicated.

The relationship between radiological markers and mortality rate in iNPH is unknown. However, in AD and VaD, the radiological findings are related with high mortality.

A possible comorbidity between FTD and iNPH is suspected because the prevalence of the C9ORF72 is greater than expected.

The genetic and pathophysiological mechanism in AD and iNPH are completely independent.

Sometimes, the best selection of iNPH patients for VPS can be very difficult, but the CSF tap test by removing 30–50 ml of CSF can be used as prognostic test for shunt surgery outcome, but its negative predictive value is not certain. The most common interval between the LP and the formal follow-up examination is between 2 and 4 hours, and nauseous vomiting and headache are less frequent in iNPH patients than the other ones. Shunt surgery is not contraindicated in patients under antithrombotic therapy, and neurotoxic proteins in CSF can be removed from the brain and also improve learning, retention, and delayed recall of verbal memory. The vast majority of patients improve some memory functions [108].

After shunt surgery, some patients do not get the proper regular follow-up by their attending neurosurgeons apart from the first checkout surgical wound and are seen again when the shunt mechanism has failure (i.e., overdrainage due to shunt setting that is too low); patients develop some complication or neurological manifestations (headache that worsens with sitting and standing and improves when lying down) and pain or discomfort from the shunt components, including abdominal pain that requires surgical approach or risk of shunt infection. Longitudinal care can be provided by neurologists if they are well trained. Some adjustable shunts can be affected by strong external magnetic fields [81].

Apart from iNPH patients with depression, the associated presence of delirium, hallucinations, visual or auditory agnosia, impaired naming, anosognosia, failure to recognize close relatives, families, and friends suggest a comorbidity with other types of dementia or neurological disorder [109].

Obviously, in patients presenting dilatation of the ventricular system with an associated cognitive decline only or even only urinary incontinence, the attending doctor should search for another neurological disorder before considering iNPH mainly in those patients without gait disturbances. In cases presenting delirium and ventriculomegaly, the underlying cause of the delirium should be found, treatment initiated, and the patient must recover and return to a stable baseline before looking for iNPH [81]. Currently, the iNPH is the only type of dementia that has an effective treatment for slowing its progression or for curative purposes.

6. Frontotemporal dementia

Frontotemporal dementia (FTD) is a common neurodegenerative disease associated with progressive atrophy of the frontal and temporal lobes, leading to changes in personality,

behavior, and/or speech and language disorder. FTD is less common than the before-mentioned dementias. Among these clinical presentations, Pick's disease is the most common type of presentation due to damage on the frontal and temporal lobes characterized by behavior and personality (apathy) disorders, which usually precede memory loss and dysarthria.

Sometimes, clinical manifestations such as behavioral and personality changes, psychomotor slowness, and decline in executive functions can be seen in both iNPH and behavioral FTD (BvFTD) at the same time and indistinctly [110], and other neuropsychiatric symptoms are frequently detected in both diseases [111, 112] including mania, aggression, disturbances of impulse control, obsessive-compulsive disorder, and psychosis, including paranoia and hallucinations [113–115]. It is well known that personality changes, impulsive behavior, apathy, decreased social interest, and executive dysfunctions, including impairment in solving problems and inhibitory control, are typical manifestations of BvFTD [116]. Almost one-half of patients with frontotemporal lobe degeneration (FTLD) have a familial component, and some authors have found mutations in microtubule-associated protein tau, progranulin, and expanded hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 (C9ORF72) as a common cause of the problem [117]. The expansion of C9ORF72 as a major genetic cause of FTLD has been confirmed by others [118]. On the other hand, Majounie et al. [119] reported that the C9ORF72 repeat expansion is the highest in Finland and is present in about 48% of familial FTLD.

Amyotrophic lateral sclerosis (ALS) is the most common motor presentation associated with the *C9ORF72* expansion, but extrapyramidal symptoms have also been documented [120–122]. Fifty percent of patients with ALS exhibit frontal executive deficits during the course of their disease representing the comorbidity of FTD-ALS and associated delusional disorder.

To distinguish BvFTD from iNPH can be a very difficult task considering that both have similar clinical manifestations. Extrapyramidal clinical manifestations of parkinsonism are predominant in patients with BvFTD [117]. Apart from disorder of gait, other remarkable symptoms of iNPH are balance disturbances and psychomotor slowing [123]. Deficits in executive functions are core cognitive changes in both iNPH and BvFTD [116, 123].

Some authors have confirmed in large studies that the prevalence on FTD is 15 to 22/100,000 individuals [124, 125]. *The most prevalent age is among 60–69 years old with roughly 13% having onset when younger than age 50. Heavy genetic loading for FTD is the main cause of younger onset, with up to half of cases being familial and up to 40% autosomal dominant in nature* [99]. *Survival partially depends on the variant of FTD and ranges from 2 to 3 years after symptom onset when motor neuron symptoms are prominent and up to 12 years for the semantic dementia variant* [126].

A new of variant of FTD named phenocopy frontotemporal dementia (phFTD) has been described by Meijboom et al. recently [127]. It is an uncommon and poorly understood clinical syndrome characterized by similar clinical manifestations of BvFTD without abnormalities on MRI of the brain and without associated cognitive disorder. In contrast to phFTD, functional connectivity and white matter (WM) microstructural abnormalities have been observed in bvFTD. Some authors concluded that phFTD and bvFTD may belong to the same disease spectrum.

Canu et al. [128] reported some multiparametric MRI findings useful to differentiate early onset of AD (EOAD) from BvFTD based on the cortical thinning of the precuneus, posterior cingulate, superior and inferior parietal lobe, supramarginal, postcentral, and lingual gyri, and lateral occipital cortex bilaterally, and the left rostral and caudal middle frontal gyri seen in EOAD. Compared with the control group, the authors found a widespread pattern of cortical thinning involving all cerebral lobes, and compared to EOAD, BvFTD patients showed cortical thinning on the lateral orbitofrontal gyrus and temporal pole bilaterally, right entorhinal cortex, and right medial orbitofrontal gyrus. A severe cortical involvement is suggestive of EOAD, while a prominent white matter damage might be indicative of bvFTD.

7. Wernicke-Korsakoff syndrome and alcohol-related dementia

Wernicke encephalopathy and Korsakoff syndrome [Wernicke-Korsakoff syndrome (WKS)] and alcohol-related dementia (ARD) are preventable, life-threatening neuropsychiatric syndromes resulting from thiamine deficiency mainly in patients with chronic alcoholism, anorexia nervosa or patients who have undergone bariatric surgery for obesity, chronic hepatic disease, immunodeficiency syndromes, nutritional deficiencies of any cause, metastatic carcinomas, hyperthyroidism, prolonged parenteral nutrition, hyperemesis gravidarum, long-term dialysis and diuretic therapy, among other causes, and clinically, patients' complaints about short-term memory, confusional states, and neuropsychiatry manifestations.

In most of our patients, WKS is an acute nutritional disorder characterized by the clinical triad of ophthalmoplegia, cerebellar disorder, and altered mental state secondary to neuronal loss and hemorrhagic lesions in the periaqueductal gray matter of the midbrain, the anterior thalamus, and hypothalamus.

Altered mental state includes abulia, inattentiveness, and progressive memory disturbance with progressive deterioration of level of consciousness until comatose state if no treatment is received.

Before ophthalmoplegia is established, the eye movement abnormalities begin with limitations of abduction or horizontal gaze, and gait ataxia progresses to inability to stand.

All patients presenting thiamine deficiency improve their symptoms rapidly when thiamine is replaced in a timely fashion. Sometimes, patients do not improve completely, and nystagmus, broad-based gait, and cognitive dysfunction including a selective amnestic disorder (Korsakoff syndrome) remain present.

Some authors said that during the acute symptomatic stage of Wernicke encephalopathy, there is an impairment of the glucose and oxidative cellular energy metabolism, leading to an imbalance of the ionic gradients across the cell membrane causing cytotoxic edema (intracellular water shift and cell injury) and vasogenic edema because of breakdown of the blood-brain barrier permeability with intravascular fluids penetrating into cerebral parenchymal [102]. Currently, it is well known that the MRI findings of cytotoxic or vasogenic edema are a remarkable information to detect WE in clinical settings and the presence of bilateral

symmetrical signal hyperintensities in the periventricular region of the third ventricle, periaqueductal area, and hypothalamus confirms clinical impressions of WE [129, 130].

Dry beriberi happens when thiamine (vitamin B1) deficiency affects the central and peripheral nervous system, and wet beriberi happens when it damages the cardiovascular system. Ophthalmoplegia and nystagmus are present in 85% of patients with dry beriberi [131].

In developing countries, Wernicke syndrome is more likely to occur in nutritionally deficient alcoholics than in comparably deficient nonalcoholics, and thiamine deficiency in a nonalcoholic is more likely to produce wet beriberi with polyneuropathy than Wernicke syndrome [132]. However, several of Korsakoff's original patients had not been heavy drinkers [133].

Neuropathological report and MRI studies have confirmed that excessive and prolonged use of alcohol may lead to structural and functional damage that is permanent in nature [134].

Chronic and excessive drinking of alcohol can affect mentation in a different way, the commonest affected mechanism are systems of neurotransmitter by inhibition of excitatory glutamate receptors and by inhibition of γ-aminobutyric acid receptors [135]. In conclusion, alcohol intoxication has some mechanism to produce nervous system damage, including glutamate excitotoxicity and oxidative stress, which is increased by thiamine deficiency, hyperhomocysteinemia, and folate deficiency. Homocysteine functions as an agonist at glutamate NMDA receptors, increasing NMDA receptor transmission and the potential for excitotoxicity [136–138].

By neuropsychological investigations, Goldstein and Shelly [139] documented brain pathology in about 78% of patients with chronic alcoholism. However, there is debate about the relative contributions of the direct toxic effect of alcohol (ARD), and the impact of thiamine deficiency, to lasting damage [140]. The two main syndromes about alcohol-associated cognitive disorders are WKS and ARD. The last one has enjoyed little recognition as a discrete clinical entity because of lack of a distinct pathophysiological profile [141, 142].

Currently, it is well known that low-to-moderate ethanol consumption can reduce the risk of coronary syndrome and ischemic stroke due to the inhibitory effect of alcohol on platelet aggregation and the reduction of inflammatory markers and also by changing the lipid profile [143], while attempts to define a safe dose threshold for ethanol have been inconsistent. Parson and Nixon [144] reviewed 19 published studies addressing this issue and concluded that 5 or 6 "standard drinks" per day over extended periods resulted in "cognitive inefficiencies", that 7–9 drinks per day resulted in "mild cognitive deficits," and that 10 or more drinks per day caused impaired cognition of a degree encountered in frank alcoholics.

The neurotoxic effect of ethanol on memory and learning has been confirmed in animal studies [145, 146], and the abnormalities are found on the dentate granule cells, loss of hippocampal CA1 and CA3 pyramidal neurons, mossy fiber-CA3 synapses, pathological changes in neurons of cerebral cortex, hypothalamus, brainstem, loss of cholinergic neurons in the basal forebrain, and impaired pruning of redundant cortical synapses during early development [147–152].

Much of the debate surrounding ARD encompasses whether it is possible to have a dementia that is the direct result of ethanol neurotoxicity—a primary alcoholic dementia—or whether the clinical presentation of dementia represents another underlying pathology (that

is, thiamine deficiency) or multiple factors (for example, neurotoxicity in combination with nutritional deficiencies). Attempts to clarify this have been hindered by confounding factors that often accompany the lifestyles of alcohol abusers, such as head injury, psychiatric and other substance abuse comorbidities, and a higher rate of vascular risk factors [153].

According to neuroimaging and neuropathological findings, the main damage on the brain (in ethanol abuser) is prominent white matter loss (most remarkable in the prefrontal cortex, corpus callosum, and cerebellum) and neuronal loss in the hypothalamus, superior frontal association cortex, and cerebellum [154]. Nevertheless, the most susceptible region is the frontal lobe with documented evidence of markedly decreased neuron density, volume shrinkage, and abnormal glucose metabolism and perfusion [155]. Cholinergic neurotransmission in the basal forebrain, which plays a key role in attention, learning, and memory, also appears to be damaged by prolonged ethanol intake [156, 157].

Thiamine deficiency as a main cause for the development of ARD is another hypothesis, and ethanol abusers are at particularly high risk of thiamine deficiency due to poor dietary nutrition and also because of the direct effect of ethanol on thiamine metabolism [130].

Apart from deficient in thiamine, nicotinic acid, other B vitamins, and folate, alcoholics frequently develop neurological disorders associated with malnutrition, including cerebellar degeneration, amblyopia, polyneuropathy, and disorders affecting cognition. In pellagra, nicotinic acid deficiency results in skin, gastrointestinal, and mental abnormalities, which can progress to memory impairment, delusions, hallucinations, dementia, or delirium; hypertonus and startle myoclonus may be present. Symptoms usually improve following treatment with nicotinic acid or nicotinamide [158].

Some authors documented that ARD and WKS are different pathological process with overlapping clinical symptoms and both can be associated with ataxia and polyneuropathies [159].

One of the problems that we afford is the variety of available definitions for "standard drink" and its different meanings from country to country. While a standard drink in the United Kingdom contains 8 g of alcohol, a standard drink in Australia contains 10 g and in America and Japan contains 14 and 19.7 g, respectively [160], which affect the best comprehension of the information delivered in the medical literature.

As it was mentioned before, in the review made by Parson and Nixon in 1989, they found that consumption of five to six drinks per day (which, by US standards, equates to 70–84 g) over extended periods results in "cognitive inefficiencies," while consumption of 10 or more standard drinks a day manifests as moderate cognitive deficits equivalent to that found in individuals with diagnosed alcoholism [144], and studies conducted by Oslin and colleagues [161] suggested that consuming 35 standard drinks a week for men and 28 for women for 5-year history constitutes a sufficient level of neurotoxic burden to risk the development of ARD. However, other studies found that light to moderate ethanol intake *reduced* the likelihood of dementia [162–170].

Damage of the brain seen on MRI is the biggest in female's alcoholic patients compared with the male's ones. Therefore, it seems to be that females are more susceptible than males to adverse ethanol's effect, but their recovery after abstinence is better [171].

Because of the introduction of thiamine supplementation programs in some countries, as well as general dietary habits, there is no direct correlation between the prevalence of WE and per capita consumption of standard drinks, but all patients under suspicion of having WE should be treated immediately with parenteral thiamine [130]. Thiamine given orally does not work because it reaches poor concentration in plasma; therefore, a dosage of 200 mg IV three times a day (1 g may be required in the first 24 hours) for 5–7 days followed by oral thiamine in doses of 100 mg eight hourly for 1–2 weeks is strongly recommended. At this point, it is very important to highlight that other electrolyte deficiencies such as magnesium and niacin should also be corrected. Apart from parenteral thiamine, to eat food with a high content of vitamins such as peas, lentils, brown rice, pork, organ meats, milk, eggs, nuts, fruits, and vegetables is suggested. Alcohol interferes with thiamine uptake [172]. This treatment should be continued until no further improvement in signs and symptoms is evident [173].

Some patients with ARD and WKS have shown cognitive improvement following treatment with memantine, although these findings require replication [174, 175].

As we also mentioned before, ARD and WKS have some similarities. However, some neuropsychological studies have largely attempted to differentiate these syndromes by limiting individuals with more global cognitive impairment from WKS investigations and by excluding individuals with past symptoms of WKS from ARD studies, but the validity of this distinction is now being brought into question [140].

Ethanol concentration in blood raises blood levels of high-density lipoprotein cholesterol (HDL-C) in a dose-dependent fashion, and some studies suggest that this effect accounts for at least half of the protection against CAD [176]. Ethanol also increases insulin sensitivity [177], prevents platelet aggregation [178], increases fibrinolysis [179], opposes thrombin activity [180], and reduces inflammatory markers such as plasma C-reactive protein and fibrinogen levels [181].

While "dementia" in current neurological settings is typically used to describe a progressive disease of the brain, it perhaps more accurately encompasses a deterioration of intellectual or cognitive function that may or may not be progressive in nature [182]. Effect of ethanol on patients presenting ARD can be reversed if the diagnosis is made early enough (48–72 hours of the onset of symptoms) and adequately treated with parenteral thiamine [172]. Abovementioned foods are essential to replace the deficient vitamins/minerals, and faster recovery is usually seen in females than males as it was mentioned before as well. Support of family and friends is paramount in achieving abstinence [183]. The Wernicke's encephalopathy and WKS also may be reversed if diagnoses made at early stage (48–72 hours of the onset of symptoms) and adequately treated with parenteral thiamine [143]. In WE, if the administration of right doses of thiamine IV is not reached, then the mortality rate will be elevated up to 20% level [184] or patient will continue progressing up to Korsakoff syndrome or ARD.

In a prospective 12-week study done by Cheon et al. on patients with probable ARD, they found that memantine (a low-affinity NMDA receptor antagonist) improved global cognition, quality of life, and behavioral symptoms on their patients [174]. Another investigation reported that rivastigmine at the dose of 3–12 mg per day for 2 months improved clinical manifestations of ARD [185].

Because not all ARD patients recover from abstinence, around 20% of them need long-term admissions and the amount of ARD patients will increase gradually due to the growing proportion of aging population and rise in per capita ethanol consumption [174, 183].

Physicians should be aware of preventable vitamin deficiency-related neuropsychiatric syndromes and should consider new signs and symptoms in patients with known psychiatric disorders as potential harbingers of reversible WE and irreversible WKS [185, 186]. Indirectly, ethanol abuse can cause intoxication, brain injury, withdrawal, hypoglycemia, chronic liver disease, Marchiafava-Bignami disease, and cognitive disorders, and nutritional deficit causes WKS and pellagra.

Marchiafava-Bignami disease, a rare disorder nearly always diagnosed in alcoholics, causes mania, depression, paranoia, and dementia, plus seizures, paresis, and ataxia and often progresses to coma and death within a few months; symptoms are not readily explained by the prominent corpus callosum demyelination that is the pathological hallmark of this poorly understood disease [187]. For the other hand, low dosage decreases the risk for dementia and AD is included [156].

Results of neuroimaging studies have corroborated postmortem neuropathological studies and have expanded the understanding of the neuropsychological deficits resulting from thiamine deficiency, alcohol neurotoxicity, and their combined effect [188].

8. Brief information about how to diagnose dementia

First of all, it is very important to highlight the importance of clinical assessment on any type of dementia followed by imagenology and other investigations. The best assessment can be done by the well-skilled health-care professional knowing the clinical features of all dementia, duration, frequency, and rate of progression. This professional must guarantee an adequate comfortableness of the patients, while the process of diagnosis is finished. Therefore, the patient's fears regarding type of dementia and condition should be well managed including a full review of the patient's health care, family history and treatment history, proper evaluation for depression, toxic substance abuse and nutrition, and other conditions that can cause memory dysfunction such as infections, chronic anemia, vitamin deficiency, diabetes mellitus type 2, chronic kidney or liver disease, thyroid gland disease, cardiopulmonary disorders, and other risk factors for dementia including hearing loss. Currently, there is no single test that confirms Alzheimer's disease, although to achieve 90% accuracy is certain. Nevertheless, to identify the true underlying cause of the problem can be very difficult.

Findings from physical examination are crucial, and some laboratory tests such as CFS levels of total tau protein results are of relevant importance for identifying type of dementia and way of management. One of the most recent investigations has documented the results from evaluation of cerebrospinal fluid phosphorylated tau231 as a biomarker in the differential diagnosis of Alzheimer's disease and vascular dementia by assessing whether the use of sensitive and specific biomarkers such as phosphorylated tau proteins could contribute to an earlier and more accurate diagnosis of AD and VD, as well as to their differentiation, and the authors found that FS (p-tau231 and MMSE) has a strong potential to provide an early distinction between AD and VD [189, 190].

Obviously, according to the statement mentioned before, not every health professional is familiar with the complexities of dementia diagnosis. Therefore, to select the medical doctor with the necessary skill and experience to diagnose all different types of dementia is mandatory.

Below, we describe the most commonly used tests to diagnose dementia.

The MMSE is the most widely used cognitive screening test worldwide, and it is a very brief investigation of the patient's cognitive status used in diagnosing dementia types and serves to evaluate appearance and behavior, attitude, perception, orientation, judgment, cognition, abstraction, and insight. It can be administered quickly and repetitively. Patient is requested to identify the time, date, and place (including street, city, and state) where the test is taking place, be able to count backward, identify objects previously known by them, be able to repeat common phrases, perform basic skills involving math, language, and comprehension, and demonstrate basic motor skills. This examination provides information to distinguish organic from "functional" illnesses and also provides objective data regarding the patient's improving or deteriorating sensorium. It helps substantiate clinical decisions on competence, potential for danger, and hospitalization [191].

Some researchers have questioned the utility of brief cognitive tests such as the MMSE and the Montreal Cognitive Assessment in serial administration and suggested that brief cognitive tests may not accurately track changes in global cognition and other investigator also confirmed that there is limited utility in brief cognitive tests for tracking cognitive decline. Instead, they should be used for identifying participants who remain cognitively stable on follow-up. These results accentuate the importance of acknowledging the limitations of brief cognitive tests when assessing cognitive change [192]. Eleven versions of the MMSE were identified, and the Bertolucci et al. [193] version is the most cited in the medical literature [194].

The Mini-Cog is a brief, cognitive screening test that is frequently used to evaluate cognition in older adults in various settings; the mini-cog takes only a few minutes to administer and is used as an initial screening for different types of cognitive disorders. The patient is required to identify three objects in the office, then draw the face of a clock in its entirety from memory, and finally, recall the three items identified earlier.

There are currently few studies assessing the diagnostic test accuracy of the Mini-Cog in community settings. The limited number of studies and the methodological limitations that are present in the study done by Fage et al. *made it difficult to provide recommendations for or against the use of the Mini-Cog as a cognitive screening test in community settings. Additional well-designed studies comparing the Mini-Cog to other brief cognitive screening tests are required in order to determine the accuracy and utility of the Mini-Cog in community-based settings* [195]. The clock drawing test and the MMSE have been used in dementia screening over the past 30 years, and they were the tests of choice in almost all relevant investigations on cognitive disorders already done.

Montreal Cognitive Assessment (MoCA) is a cognitive screening instrument that was designed to address some of the limitations of the MMSE [196].

Based on the MoCA scores, the patients were further categorized as normal cognition (PD-NC) if their MoCA scores were 26–30 or mild cognitive impairment (PD-MCI) if their scores were 18–25 according to a Malaysian study [197].

Some authors discovered that the Parkinson's disease-cognitive rating scale (PDCRS) was better than MoCA in detecting MCI, while other test was more specific for executive dysfunction.

They failed to demonstrate the association between plasma α-synuclein levels and cognitive impairment in their PD patients. However, genotype *e3*/*e4* and being a carrier of e4 allele of the *ApoE* gene correlated with the presence of executive dysfunction in PD patients. Therefore, these findings can bring new perspectives to the understanding of the genetic influence on cognitive impairment and confirm a possible link between *ApoE* and cognitive impairment in PD [198].

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Conflict of interest

The authors declare that this chapter was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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This book contains selected peer-reviewed chapters that cover novel information on cognitive disorders and updated information on dementias written by international researchers.

In this project, we discuss the effect of metabolic disorders on the development of cognitive disorders in patients with type 1 diabetes mellitus. In another chapter, the authors highlight the usability of an assistive software application developed for patients with dementia. On the other hand, an extensive review of novel information on different types of dementia is made. This chapter covers the novel aspect of dementia without ignoring its foundation. Therefore, apart from classic issues that cannot be missed in any textbook about cognitive disorders, we introduce updated information on the commonest dementias.

The current situation of the prisoner population with dementia in a correctional setting is analyzed in another chapter, and specific recommendations to improve the health outcomes for prisoners are delivered. In more than one chapter, our authors wrote about a copious microtubule-associated protein (tau) as a biological fluid biomarker and tauopathies leading to cognitive disorder and cancer. Finally, the role of the hypothalamus in Alzheimer's disease is discussed.

We look forward with confidence and pride to the remarkable role that this book will play for a new vision and mission.

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