DEMENTIA NEUROPATHOLOGIES: DESCRIPTION AND CHARACTERIZATION
NEUROPATOLOGÍAS DE DEMENCIA: DESCRIPCIÓN Y CARACTERIZACIÓN

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ABSTRACT
Neuropathology is the branch of neurology that studies diseases of the nervous system and their links with the entire physiology of the organism, including diseases of the nervous system and its reflexes. Neurological pathologies have high economic and social costs. Dementia is a syndrome that progresses with progressive and global memory decline associated with a deficit of functions with an intensity that brings important limitations in the individual's daily social or occupational performance. The number of new annual cases of dementia makes this syndrome more expensive than cancer and heart disease combined. The prevalence of dementia is increasing at an alarming rate as the world population in general is aging, and by 2050 it is estimated that 131 million people will have dementia. In view of the importance of studying neurological pathologies, especially dementias, the present study carried out a literature review on the main dementias, bringing data related to their pathogenesis, occurrence and molecular characterization.

KEYWORDS: Alzheimer dementia. Vascular dementia. Frontotemporal dementia Lewy dementia.

RESUMO
A neuropatologia é o ramo da neurologia que estuda doenças do sistema nervoso e suas ligações com toda a fisiologia do organismo, incluindo doenças do sistema nervoso e seus reflexos. Patologias neurológicas têm altos custos econômicos e sociais. A demência é uma síndrome que progride com declínio progressivo e global da memória associado a um déficit de funções com uma intensidade que traz importantes limitações no desempenho social ou ocupacional diário do indivíduo. O número de novos casos anuais de demência torna essa síndrome mais cara do que o câncer e doenças cardíacas combinadas. A prevalência de demência está aumentando a uma taxa alarmante à medida que a população mundial em geral está envelhecendo, e até 2050 estima-se que 131 milhões de pessoas terão demência. Tendo em vista a importância de estudar patologias neurológicas, especialmente demências, o presente estudo realizou uma revisão bibliográfica sobre as principais demências, trazendo dados relacionados à sua patogênese, ocorrência e caracterização molecular.


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1. INTRODUCTION

Neuropathology is the branch of neurology that studies diseases of the nervous system. The term "duck" derives from the Greek páthos, which means "everything that affects the body and soul, especially with evil, such as disease". The term "logia" also has its etymological origin from Greek, and one can translate lógos as word, speech, language, study, theory, bringing to the term a sense of study (Duchowyny, 2016).

In classical antiquity scholars of the human body had a cardiocentric view, where the heart was considered the only vital organ, and the brain, a secondary viscera and not essential to life. However, in the 12th century it was found that decapitated bodies died an immediate death, because they lacked a central orientation, which was then attributed to the brain. Many years later, in the 19th century, the idea of Atria mortis emerged, which considers brain, heart and lung three noble organs in parallel, and understands as cause of death the failure of any of them. Only in the last century, in 1959, did the debate around the clinical, electrophysiological and ethical aspects of brain death (then called irreversible coma) arise, which brought the first idea of neurodeath. About a decade later, in 1968, the "irreversible coma" was defined as a cause of death by the Ad Hoc Committee of Harvard University School of Medicine, in the United States, which listed brain death as a criterion, requiring the absence of electrical activity confirmed by electroencephalogram (Nogueira; Pereira, 2006).

Ventura (2010) describes the 21st century, as the century of the brain, in which the great achievements of humanity are/will be directed to the understanding of human neural functions. Neuroscience comprises the study of the nervous system and its connections to the entire physiology of the organism, including behavior. This science also studies diseases of the nervous system and their reflection in all the functions of the individual, seeking methods of diagnosis, prevention and treatment, as well as the discovery of causes and mechanisms.

However, to understand neurological pathologies, it is of paramount importance to understand the anatomy and physiology of the nervous system, which is composed of three closely connected parts: central nervous system (CNS), peripheral nervous system (PNS), and autonomic nervous system (ANS) (O'neill; Nestor, 2010).

The CNS consists of the two cerebral hemispheres, brainstem, cerebellum, and spinal cord, and communicates with the rest of the body through the PNS. The PNS, in turn, is composed of nerves, which are bundles of nerve fibers surrounded by connective tissue, and ganglia, which are clusters of neurons. The nerves can be spinal, totaling 31 pairs that connect to the spinal cord, being responsible for the innervation of the trunk, limbs, and some specific regions of the head; or cranial, composed of 12 pairs, which connect to the brain and innervate the structures of the head and neck. Finally, the ANS regulates the body's life support systems without consciousness, controlling the muscles of the heart, digestive system and lungs, certain glands, and homeostasis, while the ANS itself is controlled by nerve centers in the spinal cord and brainstem, and is tuned in the higher areas of the brain, such as the mesencephalon and cortex (O'neill; Nestor, 2010).
The deepening of research in neuropathology allows the recognition, study and treatment of neurological and mental diseases. These diseases are extremely costly, both in terms of their economic costs related to treatment and to the development, production and marketing of drugs and diagnostic equipment, and in terms of social costs. In addition to the suffering and disability of the individual, these diseases also represent direct costs in medical resources and indirect costs in lost productivity (Ventura, 2010).

The DALY (Disability Adjusted Life Years) index, which computes the years of health-related life lost to disease, either through premature death or disability, shows that mental diseases, for example, represent 13% of the DALY index, among all disease categories (Ventura, 2010).

In the list of neuropathologies that take hold in childhood, in descending order according to occurrence, the following are prevalent: epilepsy, followed by cerebral palsy and autism. And brain tumors are the second leading cause of cancer death in children up to 15 years of age. As for diseases affecting adults, brain trauma and spinal cord injuries occur mainly before the age of 30, while multiple sclerosis usually manifests itself after that age. As for neuropathologies in people over 60, dementia, stroke, and Parkinson's disease are the most prevalent. Strokes are responsible for a large part of the causes of death and disability in the elderly population. Mental diseases, in turn, affect up to 22% of the adult American population each year, causing alterations in thought, mood and/or behavior, leading to suffering and/or functional impairment of the individual (NIH, 2002).

In addition, according to information compiled by Raz et al. (2015), in 2010, there were approximately 35.6 million people living with dementia, and this number is expected to triple by 2050. According to the authors, because of the high volume of annual diagnoses of new cases of dementia worldwide, the burden of medical costs exceeds that of cancer and heart disease combined.

According to Arvanitakis et al. (2019), worldwide, 47 million people are living with dementia, and by 2050, the number is expected to increase to 131 million. The prevalence of dementia is increasing at an alarming rate, as the world population in general is aging. In the United States alone, for example, the nonagenarian and centenarian population are expected to grow from 2 million to 10 million by the year 2050. This creates a major public health challenge due to increasing age-related health issues, particularly the debilitating effects of neurodegenerative diseases. Dementia is believed to affect 11% of the US population over the age of 65 overall, and the incidence of dementia doubles approximately every five years to numbers as high as 40 to 60% of the population after age 90 (Miller et al., 2017). Due to the heterogeneity of clinical presentation and complexity of neuropathology of dementias, their classifications remain controversial (Raz et al., 2015).

In Brazil specifically, epidemiological studies show a prevalence of dementia close to 10% in individuals over 65 years of age. Among the diseases, Alzheimer’s accounts for slightly more than half of the cases; followed by vascular dementia, frontotemporal dementia, and dementia with Lewy bodies. However, dementia is commonly associated with more than one neuropathology, usually Alzheimer's disease with cerebrovascular pathology (Teixeira-Jr; Salgado, 2006; Arvanitakis et al., 2019).
In view of the importance of the study of neurological pathologies, especially dementias, in view of the high growth of patients with diagnosis, the present study aimed to perform a literature review about the main dementias, bringing data related to their pathogenesis, occurrence and molecular characterization. Therefore, since this is a literature review article, which addresses and describes neurological pathologies from the evidence obtained in scientific publications, it aims here to offer, in a simplified and assertive way, some guidelines on the subject. The reasoning was based on assertions and evidence published in scientific journals specialized in the subject. An electronic search was carried out in the base of the Virtual Health Library, where publications were gathered from the search terms (both in Portuguese and English) “neuropathology”, “neurological pathology”, “dementia”, “Alzheimer”, “vascular dementia” and “lewy dementia”.

Establishing fixed criteria for the selection of the publications identified by the above methods, were publications that fit the initially proposed topic.

2. LITERATURE REVIEW

Dementia is a syndrome that is associated with progressive and global decline in memory associated with function deficits of an intensity that brings important limitations in the individual’s daily social or occupational performance. Emotional and behavioral disturbances are also observed in dementias, which may include symptoms such as mood swings, delusions, hallucinations, apathy, irritability, disinhibition, anxiety, catastrophic reactions, verbal and physical aggressiveness, stereotyped behavior, incessant pacing, insomnia, changes in appetite, and sexual behavior (Araújo; Nicoli, 2002).

The main dementias that affect the world population are Alzheimer’s disease (AD), vascular disease (DV), frontotemporal dementia (FTD), and Lewy body dementia (LBD). Diagnosis initially requires noting cognitive deterioration or decline from the patient’s previous condition (Araújo; Nicoli, 2002). Although each of these dementing conditions has its own unique pathological signature, a common etiology shared among all of these conditions is cerebrovascular dysfunction at some point during the disease process (Raz et al., 2015). Laboratory and imaging tests must be performed to determine the etiology, and a characteristic neuropsychological profile is important (Araújo; Nicoli, 2002).

To further complicate diagnosis and treatment, pathologies associated with dementia are widespread in the elderly brain even in the absence of dementia. Almost 50% of the non-demented elderly who participated in a post-mortem study conducted by performing autopsies and CNS evaluation had brain lesions associated with dementia pathologies (Miller et al., 2017).

3. RESULTS

3.1 Alzheimer’s Disease (AD)

AD is the leading cause of dementia, accounting for over 50% of cases in individuals over the age of 65. It is estimated that by 2015 approximately 2/3 of dementia cases will be diagnosed as AD,
which will account for about 13.8 million cases of dementia. This progressive disease is clinically characterized by cognitive and behavioral changes, with preservation of motor and sensory functioning until the most advanced stages of the disease (Caramelli; Barbosa, 2002; Miller et al., 2017).

In AD, the patient presents maladaptive cognitive responses due to their extensive brain impairment. Cognitive impairment is responsible for the loss of autonomy and decision-making capacity, in addition to affecting the occupational and social functioning of each individual (Araújo and Nicoli, 2010).

The first symptoms presented by the patient course with episodic memory loss and spatial disorientation, cognitive aspects largely dependent on the hippocampal formation. This symptomatology attributed to AD is due to the degeneration of the hippocampal formation, with subsequent impairment of associative cortical areas and relative preservation of the primary cortices. Thus, the distribution of the pathological process causes the clinical picture of AD to be characterized by these alterations (Caramelli; Barbosa, 2002).

The symptoms usually begin insidiously, with slowly progressive worsening, although periods of relative clinical stability can occur. The first symptom of AD is usually the decline in episodic memory, which can be followed by language alterations, mainly anomia, disturbances in executive functions and visual and spatial abilities. Senile patients also present with relative frequency psychotic symptoms, with delusional ideas and hallucinations. In patients in the pre-senile range (before age 65), on the other hand, where this dementia is less prevalent, signs of psychosis are rarely reported, and language disorders may be the predominant manifestation of AD (Miller et al., 2017).

This dementia can be divided into three stages: initial, lasting two to three years; intermediate, lasting two to ten years; and terminal, eight to twelve years. In the initial stage there are vague and diffuse symptoms, with episodic memory loss and difficulty in grasping new knowledge. In the intermediate phase the patient already presents loss of the ability to speak or understand, to name objects and express ideas, and to execute coordinated voluntary movements. Postural, muscle tone, gait, and balance alterations can also occur. In the terminal stages all brain functions are affected, with changes in the sleep-wake cycle, behavioral changes, irritability, aggressiveness, psychotic symptoms, inability to walk, talk, and perform personal care, which places AD among the irreversible progressive conditions (Araújo and Nicoli, 2010).

The clinical diagnosis of AD is based on the observation of a compatible clinical picture and the exclusion of other causes of dementia through laboratory tests and structural neuroimaging. Imaging tests when analyzed in isolation allow a probable diagnosis of AD to be made. Computed tomography and magnetic resonance imaging allow the observation of diffuse distribution or with predominance in posterior regions, of atrophy of the hippocampal formation and cerebral cortex. Definitive diagnosis can only be closed by anatomopathological examination. Therefore, the diagnosis of the patient should be made from the clinical evaluation associated with complementary exams, which has a diagnostic accuracy of approximately 80% (Caramelli; Barbosa, 2002).
Although diagnostic classification systems have been developed for these pathologies that variously correlate with cognitive and behavioral function, there is no consensus on whether these microscopically observed pathologies are causal or effects of other underlying processes (Miller et al., 2017).

Tau protein is one of the proteins whose main function is to stabilize microtubules by aggregating tubulin (microtubule associated proteins - MAP). AD is characterized by stereotyped progressive neurodegeneration and accumulation of two misfolded proteins in brain regions important for cognition and memory. It is believed that in AD, hyperphosphorylated Tau proteins form intracellular neurofibrillary tangles initially in projection neurons of the cortex and hippocampus. Similarly, amyloid beta (Aβ) forms in extracellular plaques in cortical and deep brain structures, and microvascular lesions can occur throughout the brain. Despite enormous efforts, no anti-tau or anti-amyloid therapy has been successful (Miller et al., 2017).

3.2 Vascular disease (DV)

DV is the second most frequent cause of dementia in Western countries, accounting for about 10% of cases, with a prevalence of 1.2% to 4.2% in the senile population. Moreover, the association DV with AD occurs in about 15% of dementia cases (Caramelli; Barbosa, 2002).

The term vascular disease is related to the dementia pictures caused by cerebrovascular diseases that act as triggering factors for the evolution of dementias. DV is defined by significant neuronal and dendro-synaptic changes, resulting in executive dysfunction and related cognitive deficits. Diffuse white matter changes from cerebrovascular diseases, involving myelin loss and axonal abnormalities, in addition to global cerebral atrophy and focal brain degeneration, including medial temporal lobe atrophy, are also features of DV similar to AD (Kalaria, 2018).

The essential feature of dementia of vascular etiology are cognitive deficits with likely interference with complex attention, such as speed of information processing and executive ability, which are attributed to a disruption of cortico-subcortical circuits. Personality and mood changes, abulia, depression and emotional oscillation can also be observed (Gonçalves et al., 2020).

Aging is the most significant risk variable for the occurrence of a cerebrovascular event and is directly related to hypertension, arrhythmias, myocardial infarction, peripheral vascular disease, lipid changes, diabetes mellitus, autoimmune and infectious vasculitides, and smoking (Gonçalves et al., 2020).

Thus, DVs are associated with a wide range of factors, being mainly associated with the effects of large thromboembolic lesions, such as thromboembolic lesions, but also occur due to lacunar states in single lesions of cerebral sites, dementias associated with extensive white matter lesions, amyloid angioplasty, and dementia due to hemorrhagic strokes (Araújo and Nicoli, 2010).

According to Gonçalves et al. (2020), there is currently a DV epidemic in Brazil. The authors bring data that show the country as the ninth in prevalence of dementia, having a higher proportion of DV than in other locations. Some of the possibilities raised are risk factors associated with DV, which
may have a higher occurrence in Brazil, and they can be genetic, metabolic, toxic, related to high blood pressure, cardiac events, menopause, age, sedentary lifestyle, use of general anesthesia, inflammation, stress, infection, depression. In addition, studies have shown greater neuropsychiatric in patients with high education, demonstrating lower risk to DV, indicating education as a form of prevention.

Accurate diagnosis of DV is based on clinical, neuropsychological and neuroimaging measures. Factors that define the subtypes of DV include the nature and extent of vascular pathologies, the degree of involvement of extra- and intracranial vessels, and the anatomical location of tissue changes, as well as the time after the initial vascular event. Combined atherosclerotic and cardioembolic diseases appear as the most common subtypes of vascular brain injury. In recent years, cerebral small vessel disease has gained prominence as an important cause of DV (Kalaria, 2018).

Although it is a very similar disease to AD, the presentation and abnormalities present in the tissues differ. DV can be sudden, however it more often presents with a gradual course, with focal neurological symptoms related to the infarct areas. As well as cognitive deficits may occur after acute focal neurological deficits, or may follow a sequential course, with distinct episodes of impairment and disability (Gonçalves et al., 2020).

3.3 Frontotemporal Dementia (FTD)

Frontotemporal dementias (FTDs) are a heterogeneous group of neurodegenerative disorders characterized clinically by personality changes, language impairment, and occasionally extrapyramidal movement disorders. The symptoms can be variable. While some patients show primarily frontal lobe signs, with personality changes, others show primarily temporal lobe dysfunction, causing language impairment. Patients may present with features indistinguishable from Alzheimer's disease or may present with movement abnormalities similar to those seen in Parkinson's disease (Mott et al., 2005).

This pathology was first described in 1892 by Arnold Pick, who described cases of cognitive deterioration, notably of language, associated with brain atrophy focal or circumscribed to the temporal and frontal lobes. About 20 years later, Alois Alzheimer evaluated the histopathological picture of these patients, describing them with the absence of senile plaques and neurofibrillary tangles, and the presence of neuronal inclusions (Pick's bodies) and swollen cells. Only a century later, in the 1990s, were the clinical and neuropathological criteria for the diagnosis of DFT proposed, recognizing that only 25% of individuals exhibit the typical findings of Pick's bodies and Pick cells as originally described. The most commonly observed pattern is the microvacuolar type (60%), characterized by neuronal loss and microvacuolar degeneration. In the remaining patients (15%), there is concomitance of pathological findings of microvacuolar degeneration with those of motor neuron disease. In clinical terms, it was postulated that, in addition to DFT, semantic dementia and progressive non-fluent aphasia would be clinical manifestations of the spectrum of frontotemporal lobar degeneration. Thus, the dementia picture changed from "Pick's disease" to "frontotemporal dementia" (Teixeira-Jr; Salgado, 2006).

Historically, the diagnosis and classification of DFTs, especially with regard to establishing a consensus on neuropathological diagnosis, has been challenging. However, it is known that about 40%
of patients have a family history of dementia, suggesting an important role of genetic factors in the development of DFT. DFTs lead individuals to death after a course of the disease ranging from five to 10 years (Mott et al., 2005), and manifest mainly in the pre-senile period, between 45 and 65 years of age, occurring in the same proportion in men and women (Teixeira-Jr; Salgado, 2006).

DFT is the third most common neurodegenerative dementia, behind AD and Lewy body dementia. Although this group of neurodegenerative dementias is not uncommon, a simplified classification system has not yet been well defined (Mott et al., 2005). The diagnosis of DFT is usually proposed to classify approximately 15% to 20% of dementia syndromes. According to pathological criteria, it is estimated that 3% to 10% of cases diagnosed post-mortem correspond to DFTs, and this number is higher (20%) in cases of presenile degenerative dementia (de Paula et al., 2009).

Studies related to the comparative biochemistry of tau aggregates in neurodegenerative diseases, such as DFTs and Alzheimer's, provide important insight into the pathogenesis of these diseases. The tau protein plays an important role in the pathogenesis of these disorders. Conformational abnormalities are present in up to 50% of sporadic DFT cases. From a neuropathological point of view, DFTs can be classified into Tau negative and Tau positive, the latter also classified among the tauopathies (Mott et al., 2005).

The tau protein plays a key role in the pathogenesis of DFTs and other neurodegenerative diseases. One of the major markers of degeneration in DFTs is the inclusion and aggregation of tau protein filaments in neurons and glial cells, preferentially from the substantia nigra, which appears posterior to the collapse of the neuronal cytoskeleton. Tau protein, associated with microtubules, participates in several essential functions, such as polymerization, stabilization and modulation of microtubule dynamics (de Paula et al., 2009).

The human tau protein gene is located on the long arm of chromosome 17 (17q21) and has 16 exons. In the human brain, tau is a soluble protein, presenting in six isoforms derived from alternative mRNA splicing. Alternative splicing of exons 2, 3 and 10 results in the presence of six different isoforms that contain, respectively, none, one or two insertions in the amino-terminal segment. Alternative splicing of exon 10 produces either 4R or 3R isoforms of tau, depending, respectively, on the presence or absence of the amino acid sequence encoded by it. The expression of tau isoforms is regulated during development. In the adult brain all tau isoforms are expressed. The ratio between the 3R and 4R isoforms of tau is usually 1:1, since alterations in this ratio are related to certain mechanisms of neurodegeneration. In humans with tauopathies, tau protein is present in the form of insoluble, hyperphosphorylated abnormal filaments (de Paula et al., 2009).

3.4 Dementia with Lewy bodies (or corpuscles) (DCL)

DCL is a clinicopathological syndrome considered to be part of a larger spectrum of diseases exhibiting diverse clinical presentations, including Parkinson's disease, primary autonomic and REM sleep failure, and behavioral disorder. The central feature of this dementia is the loss of abilities related to visual, attention and executive perceptions, fluctuating cognition, recurrent visual hallucinations, and
extrapyramidal motor symptoms, which occur as a result of a combination of cortical and subcortical damage (McKeith, 2007). Attention, executive functions, and visuospatial abilities are the most compromised cognitive domains in the early stages, with relative preservation of memory. This is perhaps the most relevant for differential diagnosis with AD (Caramelli; Barbosa, 2002).

CDL is clinically characterized by a dementia picture in which occur: fluctuation of cognitive deficits in a matter of minutes or hours, very detailed, vivid and recurrent visual hallucinations and parkinsonian symptoms, usually of the rigid-kinetic type, of symmetrical distribution. Two of these manifestations are required for a probable diagnosis of CLP (Caramelli; Barbosa, 2002).

DCL is a dementia with insidious onset, usually occurring in patients over 60 years of age, and with a slightly higher prevalence in males. Despite having certain clinical and/or pathological similarities with AD and Parkinson's disease, CDL is increasingly considered a distinct nosological entity with its own unique characteristics (Couto, 2013), accounting for up to 20% of all cases of dementia in the elderly that reach post-mortem examination. At autopsy, it is neuropathologically indistinguishable from the late-onset dementia of Parkinson's disease (McKeith, 2007).

Even Lewy bodies were first described by Foster and Lewy in 1912 in the brain stem of parkinsonism patients, but it wasn't until 1961 that Okazaki discussed the possibility of Lewys bodies being associated with dementia. DCL was first described in 1960. Until the mid-1980s it was considered a rare entity, as few cases had been reported until then. However, the development of anti-ubiquitin and, more recently, alpha-synuclein immunohistochemistry techniques have made it easier to visualize cortical Lewys bodies, which has led to the disease being recognized and valued as an important cause of dementia and as such, more diagnosed (Couto, 2013).

Lewys bodies are intracytoplasmic localized, eosinophilic, spherical structures with a complex biochemical composition. Histologically they can be classified into classical and cortical. Classical Lewys bodies have a dense center surrounded by a clear halo of radiating filaments, usually seen in neurons of the substantia nigra and locus cereleus. Cortical Lewys bodies are ill-defined structures, with a more rounded or elongated shape, and rarely show the radiating filaments surrounding the center. Lewys bodies are composed of proteins that have been shown to have a cytoprotective effect, namely ubiquitin and alpha-beta-crystallin, neurofilament proteins, and the presynaptic protein alpha-synuclein. The latter is suspected to be primarily involved in the formation of Lewy bodies, aggregating to form intracellular inclusions. These inclusions occur in oligodendrocytes and are part of degenerative diseases such as DCL atrophy and Parkinson's disease. Lewys bodies, in addition to representing neurons that have undergone degeneration, possibly exert a regional neurotoxic effect (Couto, 2013).

Substantial advances in clinical criteria and neuroimaging technology over the past 30 years have allowed major advances in the detection and differential diagnosis of these disorders. Alpha-synuclein aggregation is a neuropathological feature of many neurodegenerative diseases, including Parkinson's disease, Parkinson's disease with dementia, and DLB, collectively termed α-synucleinopathies. However, while the variety of different imaging modalities in clinical use allows for a robust diagnosis of α-synucleinopathies compared to healthy individuals, there is no clear diagnostic
imaging marker that provides a reliable differential diagnosis between the different Lewy forms, or that could facilitate the tracking of disease progression. Vernon et al. (2010).

Based on this, Vernon et al. (2010) raises the need for neuroimaging biomarkers for Lewy bodies positive for α-synuclein, to be used for both early detection of the disease and its progression.

The techniques used to identify Lewys bodies are hematoxylin-eosin for Lewys bodies located in the basal ganglia and ubiquitin and alpha-synuclein immunohistochemical techniques to localize cortical Lewys bodies. The latter technique is only effective in cases where AD can be ruled out, since ubiquitin is also found in the neurofibrillary spindles, sometimes leading to confusion. The use of alpha-synuclein immunohistochemistry techniques is proposed, which are more sensitive to detect DCL in any circumstance (Couto, 2013).

In addition to differential diagnosis with AD, conditions such as delirium and vascular dementia, which can course with fluctuations, should be excluded. Patients with SLD usually present with frequent episodes of falls or syncope. The response of parkinsonian symptoms (rigidity and akinesia) to levodopa is usually poor in CDL, unlike what occurs in idiopathic Parkinson's disease. Another important aspect is hypersensitivity to the use of neuroleptics, which aggravate parkinsonism symptoms, often without improvement of psychotic symptoms (Caramelli; Barbosa, 2002).

4. DISCUSSION

The dementia pathologies are an extremely important problem that occurs worldwide. The aging of the population is one of the main factors leading to an increase in the prevalence of dementias, which occur mostly in the senile population.

However, there is a cascade of pathophysiological events that act directly at the molecular level, which lead to neurotransmitter deficits, consequently causing the pathology of dementia. Most dementias have an insidious onset and a course of progressive deterioration, with impairment in fixation memory. During the course of the disease there is a progressive deterioration in the performance of functional activities and daily living. As time goes by, the picture becomes progressive and irreversible, and neurological signs and symptoms, body deterioration, and other associated pathologies may appear. The differential diagnosis of dementias is based on clinical history, laboratory and imaging tests, neuropathological examination, differentiation of the characteristic profile to neuropsychological evaluation.

Yet, the identification of biological and environmental factors critical to the etiology and progression of neurodegenerative processes is a fundamental piece for the development of preventive and therapeutic strategies in the aging brain.

In the research conducted, it was evident that most types of dementia involve an underlying small vessel disease or cerebrovascular dysfunction at some point during disease progression. However, the causality dilemma still exists in identifying the circular cause and consequences between vascular dysfunction and the clinical signatures of different dementias, which is an important exploratory topic for future research.
Dementias still need to be well studied and known by society, since even though there are studies in several areas of these pathologies, most of them are not entirely complete. In broad bibliographic research conducted by Araújo and Nicoli (2010), the authors report a limitation of information regarding the number of publications, free and open access, socializing more comprehensive and exhaustive explanations of these worrying pathologies, highly incident in contemporary society with a growing elderly population.

The study of the neuropathogenesis of dementias is of extreme importance, since it directly influences the early diagnosis, treatment, and quality of life of patients. Regarding the study of proteins related to different dementias, it is known that excessive phosphorylation of tau isoforms leads to pathological aggregation within neurons and glia. Neurodegenerative diseases characterized by tau aggregation, such as DFTs and Alzheimer's differ in the relative composition of the six isoforms. However, although the current classification system is useful and reproducible, further revisions are likely to be needed in the future, particularly with regard to neuropathological subtypes that lack clearly discernible tau pathology.

Research by Raz et al., 2017 brings forth the need to create basic science animal models to address the neurobiological mechanisms underlying ASD and related dementias and develop new biomarkers for clinical trials. The author presents the priority goals recognized in the field: animal models to understand the mechanistic link between cerebrovascular dysfunction and cognitive decline and investigate the neuropathological time course of neuronal and white matter damage; models of small vessel disease mimicking human dementias related to AD; biomarkers capable of detecting preclinical dementia are needed, as early detection is key to future therapeutic interventions; establishing pathological boundaries between normal aging and AD-related dementias using better diagnostic criteria.

Miller, 2017, in his cohort study on aging, dementia, and traumatic brain injury, brings the related debate to genome-wide mapped gene expression analyses to identify molecular pathways affected by aging and dementia. The author reports that aging brains show greater variability in this transcriptional patterning compared to younger brains. By comparing brains of people who died with a clinical diagnosis of AD with brains of people who died without dementia, several studies have identified dysfunction of biological pathways and processes, including synaptic transmission, energy metabolism, inflammation, cytoskeletal dynamics, signal transduction, transcription factors, and cell proliferation. Many of these same pathways show disrupted gene expression in older individuals compared to younger individuals not diagnosed with dementia.

5. CONCLUSION

AD is the dementia form with the highest prevalence in society, followed by DV, DFT, and DCL. The causes of dementia can be diagnosed by medical history, physical and cognitive examination, laboratory tests, and brain imaging. Management should include non-pharmacological and pharmacological approaches, although the effectiveness of available treatments remains limited.
Control of risk factors and detection of the disorder in early stages could be important in trying to ameliorate losses, decreasing the number of cases.

6. **BIBLIOGRAPHIC REFERENCES**


