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Alzheimer's Disease & Dementia-From Pathophysiology To Clinic

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ABSTRACT

Dementia is a syndrome that occurs due to the difficulty of a patient in doing his cognitive and instrumental activities of daily life with the same performance as before, bringing him losses. This syndrome is caused by numerous primary and secondary etiologies. The most common primary cause of dementia is Alzheimer's disease (AD), which reaches almost 50% of dementia cases. The DA it consists of biological fragments of the amyloid precursor protein that are deposited in the brain 10 years or more, before the first symptoms appear. The period before the onset of symptoms is called the preclinical stage. The transition between the silence of symptoms and their appearance, usually due to memory loss for recent events, is known as the prodromal phase. Continuing the pathophysiological process, the stage of mild dementia takes place, when the patient has one more cognitive component associated with memory loss; follows the moderate, severe, profound and terminal phase of dementia.

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DEFINITION & GENERALITIES

Major cognitive disorder

This criterion was developed by DSM-5, for cases that do not characterize neurodegenerative disease[40]. A - Evidence of significant cognitive decline from a previous level of performance in one or more cognitive components - complex attention, executive function, learning and memory, language, perceptual-motor or social cognition. A.1 - Complaint by the individual, informant or clinician with significant decline in executive function. A.2 - Substantial impairment in cognitive performance, preferably documented by standardized cognitive assessment or in its absence by another quantitative assessment. B - Cognitive deficits interfere in daily activities - at least they require assistance with complex instrumental activities of daily life, such as paying bills or handling medications. C - Cognitive deficits do not occur exclusively in the context of delirium. D - Cognitive deficits are no longer explained by another mental disorder such as schizophrenia or major depression.

Dementia is a syndrome characterized by recent memory loss and, at least, one more cognitive component that causes impairment in activities of daily living, for a minimum period of 6 months. Dementia can start before age 65, called pre-senile, or after age 65, celled senile. In general, most of the pre-senile dementias present with a greater intensity of symptoms (BRITO-MARQUES, 2006)[1,2].

AD can be divided into typical and atypical. Typical forms are presented in two ways regarding evolution: (1) The typical form by progressive anterograde amnesia (PAA), with damage to the neurons of the hippocampus, especially the CA1, CA3 and the dentate gyrus regions. It compromises the brain's neural networks of attention and the formation of memory, where the patient does not learn and becomes progressively restless; and (2) the typical form of forgetfulness declines memory, but maintains lucidity and, progressively, other cognitive components dependent on memory loss appear. A typical form of AAP is always decreasing the degree of memory, which can be noticed by a decline in the mini-mental state examination (MSE) between 1 to 3 points per year, while a typical form of forgetfulness, keeping the MSE result almost unchanged by year. However, a group of patients of the latter form, with apolipoprotein-E (APO-E) ε4 allele, starting at a given point in the course of the disease, begins to decline progressively the same as another form (BRITO-MARQUES, 2001)[3].

Atypical forms of AD are not common and memory loss is not the center of the clinical picture. We will mention some forms: 1) variant of progressive aphasic - speech is not fluent, rich in neologisms and jargon, there are anomies and paraphasias; 2) logopenic progressive aphasia - its clinical characteristic is the loss of repetition of sentences, search for words in spontaneous and confrontational speech, phonological errors in spontaneous speech and naming; 3) visospatial variant - patient gets lost in familiar places, has difficulty dressing, prosopagnosia, acinetopsia, does not recognize objects, visual hallucinations; 4) frontal variant - behavioral disorder with progressive apathy, loss of spontaneity, loss of empathy, alien hand phenomenon; 5) temporal encephalopathy - anxiety disorder accompanied by unexplained fear, followed by loss of memory and, finally, behavior change; 6) senile dementia type tangles - shows behavioral disorder, loss of old memory, delusions; 7) senility with high schooling - lack of cognitive flexibility, slowness in thinking, important occasional memory loss (BRITO-MARQUES, 2018)[4].

EPIDEMIOLOGY

Primary care for the elderly in health posts still needs a more directed policy to serve this group of patients who depend on a diagnosis with difficult access to third-party hospitals and, consequently, a trip to the State Pharmacy to receive their medication. In most cases, memory loss is the most common complaint, since the acquisition of new information is limited to data of personal interest already acquired. The retention capacity of the new one decreases significantly,

from the third and, mainly, from the fourth decade. So, do not incorporate new technology, no thoughts and no mental strategies, being less apt to learn new aspects of a world seething that every day becomes more distant. The present gradually becomes part of the past, and the elderly come back to remember episodes making them a pleasurable gift or not, declining their functional capacity. This physiological change is compensated for a long time in people who have a good intellectual level to learn new data in their time, stimulating their cognition to suit their personal interest (BRITO-MARQUES, 2006)[2].

The cases of dementia reached 11 million in 1980, 31 million in 2000 and 35 million in 2010 worldwide, and if nothing is done to control it, the expectation for 2030 will be 65 million and, for 2050, 115 million. The main reason for this explosion of prevalence in dementia is the aging of the population (ADI, 2009)[5]. In 2006, 500 million people (8% of the world population) were over 65; for 2030, 13% of the total population is expected to be over 65 years of age. In developing countries, such as Brazil, there is a rapid and dramatic expansion of the elderly, with an increase of 141% when compared to only 51% of developed countries. And the fastest growth is reserved for those 85 years of age or older; for this population group, an increase in the range of 151% is expected between 2005 and 2030 (NIA, 2007)[6].

To obtain accurate estimates of the prevalence of memory impairment associated with age, dementia and AD, a population-based study was carried out in Turegano, a rural community of 1,011 inhabitants in the province of Segovia, Spain. The study was divided into two phases: a door-to-door survey of the entire population aged 40 or over (503 people), followed by a clinical examination of suspected cases for positive and differential diagnosis of dementia and cognitive impairment. The prevalence of age-associated memory was 3 to 6% in individuals aged 40 and over and 7.1% in individuals aged 65 and over, while dementia was found in 2-6% and 5-2%, respectively. The prevalence rates of both clinical conditions increased with age. The most prevalent clinical category of dementia was Alzheimer's, which represented 1-8% and 3-8% of these two age groups. The corresponding values for vascular dementia were 0.4% and 0.90% and for secondary dementia 0.44% and 0.5%. The memory impairment associated with age is an age-dependent disorder, with high prevalence among the elderly; some of these patients may represent an early stage of AD, suggesting that the prevalence of this disorder may be higher than previously estimated (CORIA et al., 1993)[7].

A study carried out in Europe, indicated that Europeans are well aware of the potentially devastating consequences of AD, but few are familiar with the symptoms of the initial phase. Most members of the general population accept that early intervention and therapy are essential to delay the effects of the disease. Caregivers often delayed consulting a doctor about a loved one's behavior, in part because of uncertainty about the early signs of AD. They also expressed doubts about the doctors' ability to make the diagnosis. They experience profound effects of AD in all areas of their lives - emotional, physical, social and financial. People with AD responded to their diagnosis in three ways: a fatalistic attitude, a belief that their problems are linked to old age or lack of acceptance. Respondents from three populations were critical of the level of government investment and support for AD (RIMMER et al., 2005)[8].

CLASSIFICATION OF DEMENTIA

Dementias can be divided into different categories: by cause - degenerative and non-degenerative; location - cortical and subcortical; age of onset - early before age 65 and late after age 65; treatment - treatable and non-treatable; and evolution - rapidly or slowly progressive. Among dementias, AD is the most common cause, reaching the diagnosis of certainty with 50% of all cases of dementia. After 31 years of studying dementias, the pathological diagnosis was confirmed in 102 cases followed up since the clinical diagnosis. The distribution of etiologies were:

49% Alzheimer's disease, 17% cerebrovascular disease, 8% Infection, 5% Parkinson's disease, 4% Brain tumor, 3% Pick's disease, 3% amyotrophic lateral sclerosis, 2% Lewy disease, 2% Nonspecific, and 9% Collection of basal cortical degeneration, Machado-Joseph disease, Huntington's disease, Steiner's bodies, Epilepsy, Progressive Supranuclear Palsy, Meningeal carcinomatosis, Adrenoleukodystrophy (Figure.1).

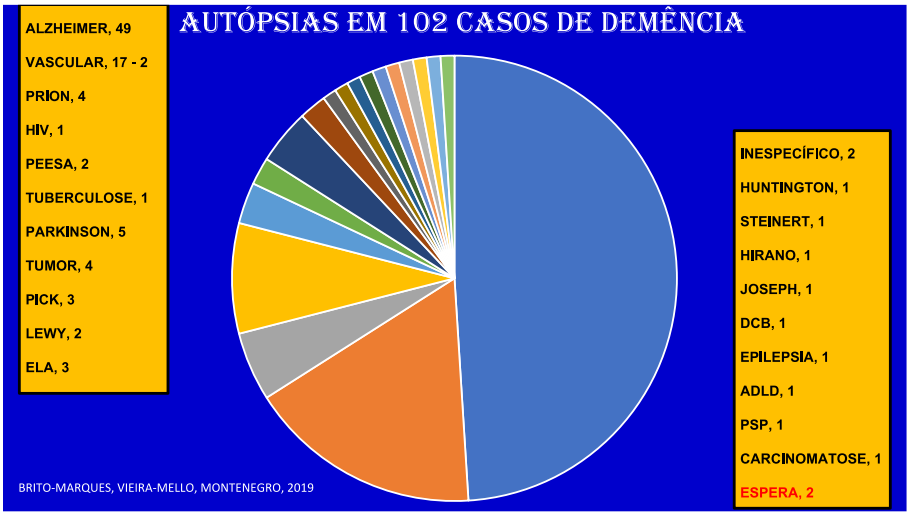

Figure1. Autopsies in 102 cases of dementia

RISK FACTORS

Risk factors for AD are quite large, since a chronic oxidative stress with hippocampal volume loss by a genetic determination autosomal dominant. The most common risk factors are age - aging, genetic - first degree relative and predisposition, head trauma - loss of consciousness, and depression - after 50 years.

Aging

Aging is considered the greatest risk factor for AD: the older you are, the greater the risk of developing it. Studies show that the incidence of dementia doubles approximately every 5-6 years, between the ages of 65 and 90 years (ZIEGLER-GRAHAM, 2008)[9]. The incidence of all causes of dementia is very high in people aged 90 and older, 41% per year, and continues to increase exponentially with age in both sexes. Projections for the number of people with dementia should be incorporated into this continuing increase in dementia after age 90. These data predict the growing burden of dementia on public health in an increasingly aging and underserved population (CORRADA et al., 2010)[10].

Genetic aspects

The so-called familial genetic form corresponds to 3 to 5% of AD cases and the rest are sporadic forms. Early onset Alzheimer's disease (EOAD) begins before age 50, sometimes as early that arises in the decade of 20 years and has a strong genetic connotation. Three chromosomes are part of EOAD. Chromosome-14 and 1, are responsible for mutations of presenilins-14 and 1, and chromosome-21, for the amyloid precursor protein; are autosomal dominant forms of AD In contrast, late-onset Alzheimer's disease (LOAD) has an increased risk relationship with first-degree relatives who also had the same disease, although it is not an established genetic cause. On chromosome-19 there is the gene that transcribes apolipoprotein-E (APO-E), which is presented by the ε2, ε3 and ε4 allele; the ε4 allele is considered a risk factor and the ε2 allele as a protective factor for LOAD. When the patient has the heterozygous form, ε3/ε4, his risk of developing DAIT increases up to 5 times, when he has the homozygous form, ε4 / ε4, the risk can reach up to 15 times (SCHU et al., 2012)[11].

Head trauma

Head trauma (HT) is the third leading cause of dementia in people over 60 years old, especially in athletes and soldiers. One study showed that a severe head injury resulted in the deposition of beta-amyloid protein (βA) in the cortex of 30% of patients who survived for less than two weeks. Multiple cortical areas were examined from 152 patients (age range 8 weeks to 81 years) after severe traumatic brain injury with a survival time between four hours and 25 years. This series was compared with a group of 44 neurologically normal controls (age range 51 to 80 years Increasing age appeared to accentuate the extent of βA deposition and potential correlations with other pathological changes associated with HT were also investigated. The data in this study support that the increase in βA expression is part of an acute phase of HT in response to neuronal damage in the human brain, this increase in βA may lead to its progressive deposition to Alzheimer's pathology, and HT may be an important etiological factor in Alzheimer's disease (ROBERTS et al., 1994)[12].

Depression

Depression has been identified as a risk factor for AD. People with a history of depression are 2.5 times more likely to develop AD than people who have never had depression, this association being independent of the incidence of vascular risk factor and stroke. Those who have late-onset depression, after 60, but not depressive symptoms, are especially vulnerable to AD, with a 4-fold increased risk, regardless of the volume of the amygdala or the hippocampus (GEERLINGS et al., 2008)[13]. Patients with a family history of depression or who started early in adulthood, should generally not be considered as a risk factor for AD. It is not uncommon, in patients with mild AD, to be reported in the history, that before the memory loss had one or more episodes of depression, treatment was done, improved, but then the progressive memory loss appeared.

CRITERIA FOR DIAGNOSIS OF DEMENTIA OF ANY ETIOLOGY

In dementia there should be no deficit in any of the 5 senses, nor motor. 1. Dementia is diagnosed when there are cognitive or behavioral symptoms that: 1.1. They interfere with tasks, work or daily activities. 1.2. They represent a decline from previous levels of functioning and performance. 1.3. They cannot be explained by delirium, confusion or psychiatric illness. 2. Cognitive impairment is diagnosed by combining: 2.1. Anamnesis with the patient, and an informant who has knowledge of the history. 2.2. Objective cognitive assessment with the mini-mental state examination; Comprehensive cognitive assessment should only be performed when necessary.3. The cognitive or behavioral components affect at least two of the following components: 3.1. Memory, with inability to learn and recall recent information; repetitions of questions or subjects, forgetting events, where they kept their belongings. 3.2. Executive dysfunctions (plan, alternate and execute); affect understanding, judgment, taking care of finances and making decisions. 3.3. Visospatial difficulties due to agnosia for objects and face, optical apraxia, difficulty in handling utensils, dressing. 3.4. Language dysfunction (expression, comprehension, reading and writing), difficulty in finding or understanding words, and anomie. 3.5. Personality or behavior altered by mood (lability and fluctuations), agitation, apathy, disinterest, social isolation, loss of empathy, disinhibition, obsessive, compulsive or socially unacceptable behaviors (McKhann et al., 2011)[14].

CRITERIA FOR DIAGNOSIS OF ALZHEIMER'S DISEASE

The definition of AD criteria has been going on for more than 2 decades. In the beginning, AD was considered only a pathological disease. From 2007, AD started to be considered a pathophysiological continuum between the presymptomatic, prodromal and dementia phase (Dubois et al. 2007; Dubois et al. 2010)[15,16]. These criteria described by Bruno Dubois and team for AD are one of the most complete carried out in recent years, they correspond to a sci-

entific research very well elaborated and executed, however it is not a static model, it serves as a diagnostic guide lived together with the experience examiner. Other criteria were also published for AD (McKhann et al., 2011; KNOPMAN et al, 2018)[14,17].

Alzheimer's disease

AD is a diagnostic label that is restricted to the clinical disorder that begins with the first specific symptoms of the disease and encompasses both pre-dementia and dementia. AD refers to the entire spectrum of the clinical phase of the disease and is not restricted to dementia syndrome. The diagnosis is now established in vivo and is based on a double clinical-biological entity that requires evidence of specific memory changes and in vivo markers of AD. The pathology includes, in the CSF, a reduction in the levels of amyloid protein, and an increase in total tau protein and tau phosphorylated protein; the retention of specific amyloid tracers in the PET-scan exam; atrophy of the medial temporal lobe at MRI; and / or temporal / parietal hypometabolism on PET-scan with fluorodeoxyglucose. The clinical phenotype can be typical or atypical. In addition, two different clinical stages can still be significant: a prodromal phase and a dementia phase.

Prodrome of Alzheimer's disease or “pre-dementia phase in AD”

This term refers to the early symptomatic phase of AD in which (1) clinical symptom, including episodic memory loss of the hippocampal type, characterized by deficit of free recall in non-normalized tests with clue, but are not severe enough to affect activities that are instrumental in daily life and do not justify a diagnosis of dementia; and (2) evidence of CSF or image biomarkers supports the presence of pathological changes in AD. This phase is now included in the new definition of AD. The term prodromal AD may disappear in the future if AD is considered to encompass the stages of pre-dementia and dementia.

Dementia in Alzheimer's disease

This term refers to the AD phase during which cognitive symptoms are severe enough to interfere with social functioning and instrumental activities of daily living, a threshold considered as a determinant of dementia associated with changes in episodic memory and at least one other cognitive component. It may also be significant to identify the dementia threshold for clinical trials or socioeconomic assessments.

Typical Alzheimer's disease

This term refers to the most common clinical phenotype of AD, characterized by an early and progressive episodic memory deficit, which remains dominant in the more advanced stages of the disease, being followed or associated with other cognitive changes, such as executive functions, language, praxis and complex visospatial deficits, and neuropsychiatric disorders. The diagnosis is further supported by one or more life-positive biomarkers of Alzheimer's disease.

Atypical Alzheimer's disease

This term refers to the less common and well-characterized clinical phenotypes of the disease that occur with Alzheimer's disease. These clinical syndromes include progressive non-fluent primary aphasia, logopenic aphasia, frontal variant of AD and posterior cortical atrophy. In the presence of one of these clinical representations, the diagnosis of AD is supported by living evidence of amyloid protein deposited in the brain using PET-scan or CSF, with changes in the concentration of βA protein, tau-protein and tau-phosphorylated.

Mixed Alzheimer's disease

This term refers to patients who fully meet the diagnostic criteria for typical AD and, in addition, present clinical and biological brain imaging evidence of other disorders such as cerebrovascular disease or Lewy body disease.

Preclinical states of Alzheimer's disease

These terms refer to the asymptomatic phase since the oldest pathogenic events of AD brain lesions, and the first appearance of specific cognitive symptoms. A preclinical or asymptomatic phase was recognized post-mortem by evidence

of histological changes typical of Alzheimer's pathology in individuals considered to be cognitively normal in life. Currently, two preclinical stages can be isolated in life: (1) Asymptomatic risk stage for AD - this stage can be identified in vivo by evidence of amyloid in the brain, with retention of specific markers on amyloid PET-scan or CSF examination with changes in β-amyloid protein concentrations, phosphorylated tau and tau. In the absence of knowledge about the value of these biological changes to predict disease development, the asymptomatic phase of AD is still referred to as a “risk stage for AD”. (2) Pre-symptomatic stage of AD - this stage applies to individuals who will develop AD. This can only be determined in families that are rarely affected by autosomal dominant monogenic mutations (monogenic Alzheimer's disease).

Alzheimer's pathology

This term refers to the underlying neurobiological changes responsible for AD that encompass the earliest pathogenic events in the brain and that include specific neuronal brain injuries, neuritic plaques, senile and neurofibrillary tangles, synaptic loss and vascular amyloid deposits within the cerebral cortex. This term can be applied regardless of the existence of a clinical manifestation.

Mild cognitive impairment

This term applies to individuals with measurable mild cognitive impairment (CCL) in the absence of a significant effect on instrumental activities of daily living. This diagnostic label is applied if there is no disease to which the CCL can be assigned. It continues to be an exclusion term for individuals who are suspected of having it, but do not meet the new research criteria proposed for AD, as they deviate from the clinical-biological phenotype of prodromal AD because they have memory symptoms that they are not characteristic of AD, or because they are negative biomarkers.

COGNITIVE EVALUATION

Assessing a patient with possible AD is more than a cognitive task. It is a disease in which the patient does not recognize himself in a mirror, he loses the notion of extrapersonal space and his peripheral self when mentioning how he, in this way, is facing a disease without a soul. The evaluation presents two moments of investigation using: (1) subjective instruments, and (2) objective instruments. The subjective instruments are the most important, which acquire patterns of clinical behavior proportional to the experience of the examiner. The objective instruments work as a complementary exam, which must have a direct connection with the data obtained in the subjective investigation (BRITO-MARQUES, 1999)[18].

The first subjective instrument is the medical history that can reach the possibility of 60% of the clinical diagnosis, especially when it comes to neurodegenerative diseases. The story requires both specialized medical training and a humanistic perception of the patient and his family, in knowing that the other is also part of you as a distorted mirror image. The patient is vulnerable, even if he is not aware of his suffering, therefore, the doctor must welcome him at his best. The development of this humanistic sense gives the doctor a closer relationship with his patient, consolidating the cornerstone of medicine - the doctor-patient relationship.

The second subjective instrument is the knowledge of neurophysiology of the cerebral cortex applied to the clinic. Emphasize, at least, how the five neural networks of the cerebral cortex work as a prerequisite for the early diagnosis of AD. Neural networks are at association levels using tertiary and quaternary brain areas, through attention, memory, language, visospatial and executive. (1) Dominant spatial attention network in the right cerebral hemisphere, with the posterior parietal cortex, frontal field of the eyes and the cingulate gyrus as epicenters; (2) Dominant language network in the left cerebral hemisphere, with epicenters in the areas of Wernicke and Broca; (3) Memory and emotion network with epicenters in the entorhinal, hippocampal and tonsillar complex regions; (4) Net-

work that holds executive functions with epicenters in the lateral prefrontal cortex, orbitofrontal and posterior parietal cortex; (5) Object and face identification network with epicenters in the lateral temporal cortex and in the temporal pole (mesulam, 2000)[19].

The third subjective instrument is the quality of the patient's education. In developing countries like Brazil, the level of education may not serve as a parameter. The patient's school and professional life, as well as his emotional family situation are factors of great impact in the diagnosis process. In a cross-sectional study, people between 60 and 90 years were studied, whose illiterates differed from individuals with 5 years of schooling (BRITO-MARQUES, CABRAL-FILHO, 2003; BRITO-MARQUES, CABRAL-FILHO, 2004)[20,21].

The first objective instrument is the mini-mental state examination (MSE). It is a clinical screening test that initiates a cognitive assessment by directing the examiner to the most altered cognitive components. This test was first described by Folstein et al. (1975)[22], to differentiate psychiatric and neurological patients with schooling from 8 years old. In Brazil, the MSE was adapted in 1994 by Bertolucci et al.[23], Studying patients between 15 and 65 years of age or older, showing the great impact that had on education. In 1999, Brito-Marques, changed the MSE to the mini-mental state exam according to schooling (MSEAS). He studied patients between 60 and 92 years of age, living in a community (BRITO-MARQUES, 1999)[24,25].

The MSE is a screening tool, the score ranges from 0 to 30, divided into temporal and spatial orientation, immediate memory, evocation, language and praxis. The cutoff point is variable, between 24 to 26 points, in the State of Pernambuco 24 is accepted. The MSE when used for diagnostic purposes, has several limitations, especially with individuals with high education. These elderly individuals may have MSE above 26 points and, even so, be in the prodrome or mild dementia stage. Returning to the neural networks, it can be observed in the conversation with these patients, with MSE above 26 points, a greater difficulty in understanding, an easy smile and not fixing new information, which are incompatible data that the high score (BRITO-MARQUES, CABRAL-FILHO, 2005)[26,27].

Assessment of mood in Alzheimer's dementia

Humor is the fuel that provides conditions for the balance of brain functioning. It is from this balance, more or less, that cognition feeds a behavior such as: pleasant or unpleasant. The assessment of mood must be carried out in all patients over 60 years of age who are experiencing some difficulty in their family or professional life, directly affecting the cognitive. The elderly go beyond a stage of life when they feel vulnerable more easily than in previous times. Monitoring the mood of the elderly patient along with the evolution of a cognitive decline may show more clarity in the cognitive diagnosis. The geriatric depression scale is a useful tool for assessing patients with dementia and mood disorders. The scale has 30 items with YES and NO responses (YESAVAGE et al. 1983)[28]. The Brazilian version of the geriatric depression scale was reduced to 15 items (PARADELA et al. 2005)[29].

Functional assessment

The functional fragmentation of the elderly is less influenced than that of cognition when they have little schooling, vice versa. In people with little schooling, the automation of functional tasks is organized in motor programs, formed on a daily basis during the life of each person and, when elderly, the losses of little cognition increase and give way to functionality.

In practice, a fast and reliable instrument is needed to detect the presence of intellectual disability and the degree. A short Mental State Questionnaire, containing 10 items, easily administered by any clinician in the office or in a hospital, was designed, tested, standardized and validated. It was found that educational level and race had to be taken into account when scoring individual performance. Based on the large population of the community, performance

standards have been established for: 1) intact mental functioning, 2) borderline or mild organic impairment, 3) defined but moderate organic impairment, and 4) severe organic impairment. There was a high level of agreement between the clinical diagnosis of organic brain syndrome and the scores in the Pfeiffer Functional Activity Questionnaire (FAQ), which indicated moderate or severe organic impairment. Up to five points, the Pfeiffer questionnaire is acceptable as normal (PFEIFFER, 1975)[30].

COMPLEMENTARY EXAMS

Alzheimer's disease cannot be diagnosed by any additional exam. However, specific blood rates must be performed to rule out other morbid conditions. For example, examining vitamin B12, homocysteine, folic acid and CBC can lead to another diagnosis. The blood rate of altered homocysteine should be corrected as a factor associated with the evolution of AD and other dementias, such as vascular dementia. The blood rate of VDRL and FTA-abs can show syphilis, which can facilitate the diagnosis of dementia. The altered rate of thyroid hormones may be relevant in the diagnosis of dementia. The low rate of chronic sodium may justify the altered level of consciousness and, consequently, dysfunction of the content of consciousness.

The glycemia rate, even in non-diabetic individuals, is important in the rare cases of insulinoma, evolving with fluctuating hypoglycemia, deterioration of cognition and dementia. Type III diabetes is one of the causes of AD, although this biological marker does not yet exist in Brazil. Blood tests showing abnormal levels of creatinine and / or urea, such as liver function rates, can direct the diagnosis in another direction. The tests for dyslipidemia, total cholesterol, fractions and triglycerides are not of great relevance for the diagnosis of AD. However, there is a clinical form of AD that evolves slowly with changes in cholesterol, which is why, for a long time, it was believed that cognitive changes are caused by increased levels of cholesterol in the blood. Routine is thyroid, renal, hepatic function; blood count, ionogram, blood glucose, VDRL and vitamin-B12.

Neuroimaging exam

Neuroimaging is used in the diagnosis of dementia, especially Alzheimer's disease (AD). Computed tomography (CT) can be used to exclude other causes of dementia than AD. The finding of cortical or subcortical atrophy on CT or magnetic resonance imaging (MRI) itself does not indicate AD. Atrophy of the hippocampus on CT / MRI provides a useful early marker, although a longitudinal and neuropathological study is needed. CT and MRI-based measurements of hippocampal atrophy are promising in providing useful diagnostic information to discriminate patients with probable AD from normal elderly. The use of a standardized imaging protocol, including some assessment of hippocampal atrophy, can reduce costs, as patients with suspected AD should undergo a cross-sectional imaging study to exclude other (treatable) causes of dementia.

The combination of an assessment of hippocampal atrophy with measurements of cerebral blood flow by single-photon emission computed tomography is not justified clinically or economically. MRI examination of the skull may show specific changes in atrophy between the cerebral cortex and the hippocampus. The cerebral cortex shows atrophy expected for age, while the hippocampus shows atrophy in an advanced degree for age, according to an MTA scale. Scheltens showed that in MRI of the skull, in coronal section, it shows 4 degrees of atrophy; up to 75 years old, the 2 degree atrophy score will be accepted as normal. Score 0: no atrophy. Score 1: only widening of the choroidal fissure. Score 2: widening of the choroidal fissure and temporal horn of the lateral ventricle. Score 3: moderate loss of hippocampal volume (reduced height). Score 4: severe loss of hippocampal volume (SCHELTENS, 1999)[31].

Examination of the cerebrospinal fluid

CSF testing is generally used for patients with cancer, suspected neuroinfection, positive VDRL and FTA-abs in the blood, but should be

used in patients under 55 years of age, including those with MCI. In the NINCDS-ADRDA guidelines, the CSF examination was recommended as a non-Alzheimer's dementia exclusion process, due to inflammatory vasculitis, demyelinating disease or secondary demyelination, etc. In the last decade, the MCI's request to observe the concentration of biomarkers, including their concentration by age group, has been growing. The biological markers in CSF for AD include (βA-42), phosphorylated tau protein (tau-181 and tau- 231) and total tau protein (tau-t).

In AD, βA-42 protein levels are inversely related to the number of amyloid plaques, total tau protein levels represent the intensity of neuronal degeneration and are increased, and levels of tau phosphorylated protein indicate the intensity of neurofibrillary degeneration, which are increased. Therefore, the concentration of Aβ-42 in the CSF is low, and that of the protein tau-t and tau-f high, compared with controls. CSF Aβ-42 protein levels are about 50% lower in AD patients than in controls of the same age group. The levels of tau protein do not correlate with the MSE score. The tau protein is increased in most patients at an early stage of AD, and can be used as a support in their diagnosis. The concentrations of different epithets of the tau-f protein can also be high, the most specific for DA (GALASKO, 1997; SKILLABACK et al., 2015)[32,33].

TREATMENT IN ALZHEIMER'S DEMENTIA

To date, AD has no cure, but it has treatment. Non-pharmacological treatment emerges as a promising attempt for the prodromal phase of AD, when there is still no anticholinesterase response. For the mild to moderate dementia phase, donepezil, rivastigmine and galantamine are used, and in the moderately-severe to severe phase, NMDA receptor inhibitors are associated. In the next 5 years, we will have a new treatment, anti-beta-amyloid, to be used in the prodromal and mild phase of Alzheimer's dementia.

Non-pharmacological treatment

Accumulated evidence has shown that nutritional factors influence the risk of developing AD and its rate of clinical progression. Loss of episodic memory and insight are clinical manifestations of the prodromal phase of AD, not yet noticed in objective assessments. This is the first time that a randomized, double-blind clinical trial using Souvenaid has shown that a nutritional intervention can help conserve the ability of patients with prodromal AD to perform everyday tasks, such as paying bills or finding their way back. This is important because patients with prodromal AD currently do not have available and approved pharmacological options. The study found no significant benefit in broad cognitive function. The cognitive decline during the study period was less than originally expected when it was designed ten years ago, so the differences found between the two groups were too small to be statistically significant due to the size of their samples (SOININEM et al., 2017)[34].

Pharmacological treatment

Donepezil is a highly specific, reversible cholinesterase inhibitor. Piperidine-based molecule without hepatotoxic effect with linear pharmacokinetics and long life, which can be administered once daily at a dose of 5 mg / day or 10 mg / day. The dose can be increased for patients in the moderate to severe phase up to 23 mg \ day, as long as they have used a dose of 10 mg per day for at least 3 months without intolerance. The dosage of donepezil is 5 mg daily, orally, for 45 days; followed by the 10mg dose, always at the same time after a meal. If after dinner, the patient favors himself with mild drowsiness. Side effects are nausea, diarrhea, abdominal discomfort, headache, insomnia, fatigue and nightmares, disappearing with drug suspension or dose reduction (WANG et al., 2010)[35].

Rivastigmine is a selective and pseudo-reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. The oral dosage should be started at 1.5 mg 12 \ 12 hours and increase to 3.0 mg 12 \ 12 hours, 4.5 mg 12 \ 12 hours and 6.0 mg 12 \ 12 hours, right after breakfast and dinner. The dose increase should be done every

15 or 30 days, depending on the possible side effects. Patients have side effects in 20% of cases, as the titration of the drug increases, such as: nausea, vomiting, dizziness, diarrhea, headache and weight loss, isolated or associated. Adhesive, transdermal rivastigmine, with a dose of 9 mg \ 24 hours and, after 30 days, 18 mg \ 24 hours, without gastric effects. This presentation helps treatment due to the fact that 73% of AD patients need help to take their medication, 22% manage to take it without help, and 5% do not take it; besides the certainty that the patient is using it. The transdermal dosage starts with 5 in the first month; 10, in the second, and 15, in the third onwards, always reevaluating the possibility of the presence of side effects (SPIEGEL, 2002)[36].

Galantamine is a competitive, selective cholinesterase inhibitor that also acts on cholinergic nicotinic neurotransmitters by modulating nicotinic receptors. Oral galantamine-ER begins to be taken at a dose of 8 mg in the first month, 16 mg in the second month, and 24 mg in the third month onwards, always after one of the three main meals; the therapeutic dose is between 16 and 24 mg. Side effects include nausea, vomiting, anorexia, weight loss and diarrhea. Studies with galantamine have shown their most specific action in mixed dementias, those that have vascular pathology associated with Alzheimer's pathology, improving executive and memory alterations (COREY-BLOOM, 2003)[37].

The N-methyl-D-aspartate (NMDA) receptor is a glutamate receptor indicated for pathological changes in AD. Blocking this receptor can protect neurons against excitotoxic effects, which lead to cell death. Memantine is a non-competitive NMDA receptor antagonist, with mild to moderate affinity. It blocks the selection of excitotoxic effects associated with abnormal glutamate transmission, while allowing physiological transmission related to normal cell function to occur.Memantine has been approved by the FDA for the treatment of AD in the moderately severe to severe phase. It should be administered in slowly progressive doses with 5 mg per day, for a week and increase 5 mg every week, until reaching the therapeutic dose of 10 mg for 12 \ 12 hours or 20 mg / day. Its immediate, most common side effects are: dizziness, headache, constipation and confusion (REISBERG et al., 2003)[38].

Antidepressant treatment

Every patient with AD who presents depressive symptoms should start pharmacological treatment. Serotonin reuptake inhibitors are important in memory formation at a very early biochemical stage. The starting dose of the drug depends on the personality profile brought by the patient, especially if he is aware of his pathology. In a more advanced, moderate to severe phase, the patient should use trazodone as the first option, for cases of self-destruction, which starts as subtle as a tic, scratching the same place or touching the hair, until forming wounds and infected alopecia.

Antipsychotic treatment

In the moderate phase, the first signs of distortion of thought begin. The personality profile has great relevance at this stage. Diplomacy can help balance episodes. Pharmacological treatment is necessary in some cases, especially in males. The choice is based on the experience of each doctor, but in decreasing order: olanzapine, quetiapine and risperidone are the most used. Start with a low dose and find out if there is a stress factor triggering the crisis. This factor can have an emotional or physical basis. The emotional is linked to life history, basically fear, especially at night. The physical may be dental caries, fecaloma, joint pain, muscle strain, etc (ROPACKI, JESTE, 2005)[39].

(1) confusion between lived situations, despite having existed, time, place or people are exchanged, generating a confusion of ideas that, unsuspecting caregivers can increase, but coherent ideas can be partially rescued with diplomatic help, giving the person his reason or subtly, to divert the focus of attention from the conversation and change the environment; (2) Illu-

sions begin with visual doubts, later accompanied by hallucinations. The phenomenon of prosopagnosia is one of the moments of greatest emotional conflict for the spouse and relatives and, seeing what does not exist, opens the door to the next phase. This phase is followed by Capgras syndrome, or the double. In this phase, there is a functional disconnection of the corpus callosum between the language and the visospatial areas, especially when the patient is in front of the mirror. The mirrors of the house must be removed.

(3) Delusions are related to the past life that works for the patient as a present. He does not recognize his spouse, his children or his home, and lives as if they were all other people named by him, the spouse can be the father or the mother, the daughter the sister, etc. Thus, the person declines to childhood. There were opportunities to experience this fact at the Karolinska Institute, Stockholm, when people lived in custom kits for their young adult days; smiling, welcoming people as if they were in their own home.

The 10 most common psychotic symptoms in patients with dementia in Alzheimer's disease, which occur at least 2 or 3 times a week, are: 1) people are stealing from him; 2) his spouse is cheating on him; 3) unwelcome guests are living in his home; 4) his spouse or other relatives are not who they claim to be; 5) his home is not him; 6) His family members plan to leave him; 7) The TV characters are present in his home and interact with him; 8) Talk to people who are not present; 9) See people or animals that other people don't see; 10) He says he feels things walking on his skin.

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