

ALZHEIMER AND PARKINSON DISEASES ASSOCIATES TO AGING

DOENÇAS DE PARKINSON E ALZHEIMER ASSOCIADAS AO ENVELHECIMENTO

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ABSTRACT: Aging is a natural process that leads to morphologic and physiologic alterations that may, in turn, lead to diseases, and the consequences of the neural system aging present clear relationship with the dementia etiology. The appearing of Alzheimer's disease (AD) is associated to genetic and aging factors, with inefficient treatments and neuropathology only detected after death. The Parkinsonism is also associated to genetic causes and aging, with treatment presenting results better than those of AD, and is divided into three basics types: idiopathic parkinsonism; drug-induced Parkinsonism and Parkinsonism-Plus syndrome. Descriptors were used to obtain several papers associated to aging, neural structure, AD and PK. Our results have demonstrated that association between dementias and aging are frequently cited in these papers; however, these associations are not quite clear in biochemical, physiologic and clinics terms, and otherwise, the treatment proposals are not clear. This vast material provided the possibility of classifying dementias as a risk factor for human health, considered as a public health problem that must be treated as early as possible, since literature data indicate a number of relations between aging and dementias here studied. Therefore, one concludes that, regardless difficulties found in knowing their etiologies, the dementia are associated to stochastic process to aging don't only to neural system, but too others organs and tissues.

KEYWORDS: Aging, Alzheimer disease, Parkinsonian disorders.

INTRODUCTON

General aspects on aging

The populational growth among elderly individuals has increased proportionally more than the general growth of the planet population in a forecast performed from 1990 to 2025 (HAYFLICK, 1996; SCHOUERI, 1998; PASCHOAL, 1999). This justifies the concern about healthy aging (senescence), in detriment of aging associated to pathological states (senility).

It is then reasonable thinking about preventive aspects in relation to aging, which is a time-dependent chronic-degenerative process of stochastic nature and with some genetic factors (ARKING, 1998), process through which more and more people will undergo, with the proposal of new techniques in the care of the elderly and the discovery of new drugs.

Aging is a non-uniform process significantly dependent on lifestyle. The organism ages as a whole, while the organs, tissues, cells and subcellular structures present differentiated aging processes (PEREIRA et al, 2004).

The aging of tissues is a result of the conversion of renewable cells into non-renewable ones, with the remarkable reduction on the cellular regeneration capacity (MCARDLE et al, 2003). However, the physiological aging includes a series

of alterations on the organic and mental functions exclusively due to the effects of aging on the organism, leading it to a decreased capacity of maintaining homeostasis and hence the several physiological functions progressively start to decline (STRAUB et al, 2001).

A decrease on weight and volume of organs is observed as result of cellular alterations in tissues, due to the replacement of dead cells by cicatrisation tissue, unequal and disharmonic atrophy, decrease on the tissue vascularization; reduction on the total water content in the organism at the expenses of the intracellular and interstitial water and increase on the body fat content (JUNQUEIRA; CARNEIRO, 2005).

Aging befalls from a certain growth and maturation organic programming, taking into consideration its universal character and variations from one individual to another, which could be considered in several dimensions that search to explain its phenomena (VIEIRA, 2004; PEREIRA, 2004).

A theory that has received considerable attention refers to the deliberate existence of a biological programming determining that each cell has a lifetime genetically established, where a normal cell presents the capacity of defining its own number of duplications, and when such capacity

depletes, the last clone of some lineage ages and dies (PEREIRA, 2004; HAYFLICK, 1990).

Other studies have demonstrated the influence of melatonin, a hormone produced in the pineal gland and the circadian rhythm, the daily light and dark rhythm on the aging process (FALCON, 1999).

DEMENTIAS

Alzheimer's disease

The Alzheimer's disease (AD), discovered by the German psychiatrist Alois Alzheimer in 1907 is the main cause of dementia (TEIXEIRA; CARAMELLI, 2006) and is associated to the reduction on the cognitive capacity (language, gnosis and praxis). Some researches admit that this disease follows the aging process naturally, with outcomes such as loss of memory, judgment and emotional stability (SMITH, 1999; CARAMELLI; BARBOSA, 2002). The disease appears in a deceitful way and progressively develops, leading to death with severe debility about 8 years after its appearance (VILELA; CARAMELLI, 2006).

There are two types of Alzheimer's disease, namely, the familiar and the sporadic types. The familiar type occurs to individuals at the pre-senile age, before 65 years of age and its origin is generally genetics. The sporadic type occurs even later and is the most common type. Both are undistinguishable in relation to the clinic and nosologic unit. In relation to the cognitive disturbance and the individuals' dependence levels, the disease is divided into three phases: light, moderate and severe (SMITH, 1999; BOTTINO et al., 2002).

The Alzheimer's disease is associated to the neural system activity deficiency, mainly the brain activities, indicating that a progressive neuronal disorder is underway (BOTTINO et al., 2002); this is the dementia characterized by mental deterioration and other neuropsychological alterations. The disease has no known etiology.

It affects mainly individuals older than 65 years of age and its prevalence doubles each five years resulting in a time-dependence exponential increase (CHARCHAT et al., 2001). Except for patients with trisomy of chromosome 21, what may lead to Alzheimer's disease at the age of 30 (TARIOT, 1994; OJOPI et al., 2004).

The clinical condition is characterized by psychomotor disorders, depression, psychosis, physical and verbal aggressiveness, non-cooperation in personal hygiene activities, memory deficits to remember recent facts and events defined in time

and space. The progress of the clinical condition leads to memory deficit reaching past facts and events, speech difficulties, convulsive crises, as well as the involvement of the hippocampus area and later involvement of the associative cortical areas (CARAMELLI; BARBOSA, 2002; RASKIND; PESKIND, 2002).

The senile plates are formed as a chain reaction, and contain the amyloid protein, a small-size protein derived from the cleavage of a larger peptide, the amyloid precursor protein (APP). The plate formed is a spherical structure containing neurons with axons and abnormal dendrites in the outer surface (TARIOT, 1994). Evidences suggest that the amyloid protein induces to structural changes in the tau protein in both cortex and hippocampus. The tau protein promotes the *in vitro* tubulin polymerization and the *in vivo* aggregation of microtubules found in PHF under the abnormally phosphorylated form, promoting ruptures in the cellular cytoskeleton that initially leads to dysfunction and later to the neuronal death (TARIOT, 1994; ALMEIDA, 1997).

Neurotransmitters are also affected by this disease, especially the production of acetylcholine from the choline acetyltransferase (ALMEIDA, 1998).

These alterations may be found in healthy elderly individuals; however, at lower intensities in relation to patients with Alzheimer's disease. In this disease, men and women are equally affected (SMITH, 1999).

The senile plates appear firstly at cerebral regions involved with memory and other cognitive functions. They consist of insoluble extracellular amyloid- β deposits, which is the product of the fragmentation of a transmembranal protein called amyloid precursor protein (APP). This fragmentation is mainly processed by three enzymes: α , β and γ secretase. The amyloid- β generated through the action of β and γ secretase generates multiple peptides, where the amyloid- β 40 (A β 40) and β 42 (A β 42) stand out (ALMEIDA, 1997; CLARK; KARLAWISH, 2003; HIGUCHI et al., 2004).

Mutations in genes of the amyloid precursor protein, of presenilin 1 (PSEN1) and presenilin 2 (PSEN2), promote increase on the total amyloid- β levels and it has been suggested that PS1 and PS2 are catalyzed by γ secretase (HIGUCHI et al., 2004).

However, if these plates are cause or consequence of the Alzheimer's disease is unknown, but there are evidences that the presence of amyloid- β is vital for the dementia development since in some cases, the amyloid- β seems to

increase the activity of some kinases that promote abnormal phosphorylation of the tau protein (ALMEIDA, 1997; CLARK; KARLAWISH, 2003; HIGUCHI et al., 2004).

The neurofibrillary tangles are predominantly formed by the accumulation of paired helical filaments (PHF), which are structures that develop irregularly through neurons impairing nervous messages to be transmitted, causing their degradation. The tau protein is one of its main components (ALMEIDA, 1997; HARTMANN et al., 2004), and the neurofibrillary tangles are considered vital for the development of the Alzheimer's disease and its seriousness.

The amyloid protein from neurofibrillary alterations has another origin. It is derived from the tau protein, basic protein for paired helical filaments (PHF), which accumulation is frequently observed in neurofibrillary tangles. The tau protein regulates the polymerization of microtubules (BLENNOW; HAMPEL, 2003; HUA; HE, 2003; SCHÖNKNECHT et al., 2003; GOEDERT, 2004; HIRAOKA et al., 2004).

It also promotes the polymerization of the tubulin and stabilization of axonal microtubules and during neurofibrillary formations, it is released in the cerebrospinal fluid (HIGUCHI et al., 2004; BLENNOW; HAMPEL, 2003; SCHÖNKNECHT et al., 2003).

In the AD, the tau protein is abnormally phosphorylated and less capable of polymerizing tubulin and otherwise, it aggregates as paired helical filaments, becoming highly insoluble. This aggregate is toxic to neurons. In fibrillar lesions, the tau protein is hyperphosphorylated into its aminoacids residues, some of which are exclusive of the Alzheimer's disease (ALMEIDA, 1997; HIGUCHI et al., 2004; GOEDERT, 2004; HIRAOKA et al., 2004). Thus, it is probable that abnormal hyperphosphorylations and phosphorylations of the tau protein reduce its capacity of linking to axonal microtubules, resulting in organization deficits of the axons cytoskeleton with consequent rupture of the cellular cytoskeleton, leading to neuronal dysfunction and death (HIGUCHI et al., 2004; GOEDERT, 2004).

The AD is a multifactorial etiology disease, with association of environmental and genetic factors (FRIDMAN et al., 2004).

The fact that patients with Down syndromes present clinical and neuropathological evidences of the Alzheimer's disease motivated investigations around chromosome 21, what led to the discover of the first gene associated to the Alzheimer's disease. This discovery was very relevant, since the gene

discovered revealed to be the responsible for the synthesis of the amyloid precursor protein (APP) (SMITH, 1999).

Further genetic investigations found other genes associated to the Alzheimer's disease such as that located at chromosome 14, which expresses the protein called as presenilin 1 (PSEN1). Its probable functions are associated to cell transportation and to APP rupture, producing amyloid- β and apoptosis; however, the apoptosis does not seem to be the main cause of neuronal death (SMITH, 1999; FRIDMAN et al., 2004).

In chromosome 1, the gene that expresses the presenilin 2 (PSEN2) was discovered, which probable function is also associated to cell transportation (SMITH, 1999; FRIDMAN et al., 2004).

Another gene associated to the Alzheimer's disease was found in chromosome 19, responsible for the apolipoprotein E production (Apo E). The Apo E is involved with the transportation of blood cholesterol, especially in the distribution for the regeneration of the central and peripheral nervous system. It also participates in the normal metabolism of neurons and glial cells; however, patients with Alzheimer's disease present high amounts of this compound in senile plates and neurofibrillary tangles. The Apo E presents polymorphism in alleles $\epsilon 4$ (Cys 112 \rightarrow Arg), $\epsilon 3$ (Cys 112), and $\epsilon 2$ (Arg 148 \rightarrow Cys), and among them, the one associated with the Alzheimer's disease is the $\epsilon 4$. It is known that its presence leads to higher risk for the Alzheimer's disease development, since this allele associates to senile plates to form a stable complex with amyloid- β (OJOPI et al., 2004; GOEDERT, 2004; FRIDMAN et al., 2004; LEWEZUK et al., 2004; FERNANDEZ; SCHEIBE, 2005).

The presence of $\epsilon 2$ and $\epsilon 3$ determines favorable characteristics for the Alzheimer's disease development, since these alleles facilitate the linking of the tau protein with microtubules, stabilizing the cytoskeleton (ALMEIDA, 1997).

Besides considering the genetic factor as one of the causes for the Alzheimer's disease, the toxicity to infectious agents, to aluminum, to oxygen free radicals, to neurotoxic aminoacids and the occurrence of damages to microtubules and associated proteins were also pointed as etiological agents (SMITH, 1999).

The processes most commonly employed to diagnose dementias are those from NINCDS-ADRDA (National Institute of Neurological Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders), besides the Mini-mental state examination [MEEM] (RASKIND;

PESKIND, 2002; ALMEIDA; CROCCO, 2000; BRIANI et al., 2002; ABREU et al., 2005). In these processes, the dementia diagnosis must be established by a clinical evaluation and confirmed by neuropsychological tests. Patients considered positive demented must present impairment in two or more neuropsychological functions, with limited capacity to perform their daily activities (CHARCHAT et al., 2001).

Once the dementia status is diagnosed, the patient must be submitted to specific selections with the objective of confirming the Alzheimer's disease etiological diagnosis. This, in turn, is based on laboratorial and neuro-imaging examinations that must demonstrate cerebral hippocampus and cortex atrophy, besides the verification of the characteristic neuropsychological profile (CAMELLI; BARBOSA, 2002; CLARK; KARLAWISH, 2003). These aspects are relevant for the differential diagnosis of several degenerative dementias, and the exclusion of any other type of dementia else than the Alzheimer's disease is required for an efficient treatment (CAMELLI; BARBOSA, 2002; BLENNOW; HAMPEL, 2003; DIAMANDIS et al., 2005).

Besides these methods, biochemical markers have been used for the diagnosis and monitoring of the evolution and treatment of this disease (CLARK; KARLAWISH, 2003; DIAMANDIS et al., 2005).

The Alzheimer's disease biomarkers may be divided into two groups: state markers, which reflect the process intensity, for example, the tau protein and the phase markers give an idea about the time when the neurodegenerative processes started such as the hippocampus atrophy measurement (BLENNOW; HAMPEL, 2003).

The cerebrospinal fluid is one of the preferential clinic samples for the analysis of biomarkers. However, urine and serum may also be used in researches using biomarkers (BLENNOW; HAMPEL, 2003; LEWEZUK et al., 2004; DIAMANDIS et al., 2005).

Two biomarkers have been currently used to diagnose the Alzheimer's disease, the tau protein (HARTMANN et al., 2004) and the amyloid- β 42, both used in the cerebrospinal fluid. Patients with Alzheimer's disease present tau protein concentrations significantly increased. The amyloid- β 42 presents opposite significance in relation to the tau protein (CLARK; KARLAWISH, 2003; BLENNOW; HAMPEL, 2003; LEWEZUK et al., 2004; BRIANI et al., 2002; DIAMANDIS et al., 2005). The analyses of these biomarkers are not highly specific and present no correlation with the

disease seriousness (CLARK; KARLAWISH, 2003; BRIANI et al., 2002; DIAMANDIS et al., 2005).

Diamandis et al. (2005) verified concentrations of a protease called human kalikrein 6. This protein seems to have amyloidogenic potential in the brain and seems to contribute for the Alzheimer's disease patogenicity. Its concentrations were found relatively increased in analyses of the cerebrospinal fluid and blood of patients with Alzheimer's disease.

Preliminary studies report the existence of several other biochemical markers such as levels of 8-hydroxiguanin in the cerebrospinal fluid, protoplasm and urine of patients, suggesting the presence of Alzheimer's disease (CLARK; KARLAWISH, 2003).

However, a definitive diagnosis of the Alzheimer's disease will only be possible through the anatomical-pathological post-mortem examination (CAMELLI; BARBOSA, 2002; CHARCHAT et al., 2001).

Parkinsonism

Parkinsonism (PK) is the second most common neurodegenerative disorder among elders, only behind the Alzheimer's disease (FAHN; SULZER, 2004; PANKRATZ; FOROUD, 2004). The yearly incidence rate is of 187 cases per 100.000 inhabitants (TEIVE, 1996), presenting an incidence rate of 14.9% among individuals with ages ranging from 65 to 74 years, and of 52.4% among individuals older than 85 years of age (LITVAN, 1998).

Parkinsonism, or kinetic-rigid syndromes, is characterized by movement alterations such as tremor, rigidity, bradykinesia (movement slowness), hypokinesia (reduction on the movement wideness), akinesia (absence of movement), posture alterations and "freezing" phenomena (periods in which patient stands still with feet literally stuck on the ground) (FAHN; SULZER, 2004; TEIVE, 1998; TEIVE et al., 2004). A cognitive compromising is frequently observed, and when associated to motor disorders, leads to incapacity comparable to that seen in the severe cerebral vascular disease (TEIVE, 1998).

Tremor is due to the inhibition of the gamma-motor neuronal activity. This inhibition leads to loss of sensibility of the gamma circuit, which results in a reduction on the motor movement fine control. This lack of control allows the appearance of involuntary movements generated by other levels of the central nervous system. This tremor is typical of rest, and decreases intensity

during the performance of a muscular activity (GILROY; HOLLIDAY, 1985).

The appearance of PK is associated to the dysfunction of the base nucleuses, among other situations, in function of the reduction on the dopamine concentrations due to the degenerescence of the nigrostriatal dopaminergic system, to the blockage of striatal dopaminergic receptors and to the dopaminergic depletion, or to the non inhibition of the subthalamic nucleus or the pallid globe medium (GUIMARÃES; ALEGRIA, 2004; SHIH et al., 2006).

There are evidences that oxidative damages to the complex I of the mitochondria of dopaminergic cells would reduce the ATP levels, causing the cellular death (MURRAY et al., 2003; FERRO et al., 2007).

There are studies showing genes presenting relationship with PK⁴⁰.

In relation to the etiology, the parkinsonism may be divided into 3 categories: primary parkinsonism or idiopathic Parkinson (IPD); secondary or drug-induced parkinsonism (DIP) and Parkinsonism-Plus syndrome (FAHN; SULZER, 2004; COSTA et al., 2003).

The IPD is one of the movement disturbances most found among old-aged individuals. Its cause remains unknown and it represents up to 70% of patients followed in specialized clinics worldwide (TEIVE, 1998; CARDOSO et al., 1998).

Its prevalence has been estimated to be between 85 and 100 cases per 100.000 people and it tends to increase with aging, being around 80% of total cases of parkinsonism observed. The disease occurs in all ethnic groups, presents distribution almost equalitarian in both genders and seems to present active neuronal development associated to the oxidative stress mechanism due to one or more different events (GUIMARÃES; ALEGRIA, 2004).

The beginning of manifestations is usually insidious and unilateral, with later generalization as a slow progression; however, generally maintaining asymmetric feature. Symptoms such as intense fatigue, loss of weight or depressive complaints are usual, and the initial diagnosis of Parkinson disease is frequently taken as depression, rheumatism or even neoplastic disease or stroke by mistake (FAHN; SULZER, 2004; GUIMARÃES; ALEGRIA, 2004).

In the secondary parkinsonism or DIP, a specific cause may be recognized. The main causes are: drugs (neuroleptic, benzamide), hexogen intoxications (manganese, cyanide, carbon monoxide, herbicides), encephalitis, expansive processes of CNS, cerebral multi-infarcts,

hydrocephalitis and metabolic and endocrine disturbances (COSTA et al., 2003).

De Melo Souza and Ragazzo (1989) found evidences of DIP through neurological examination in 27 patients, in a series of 28 individuals (25 women and 3 men), who had used flunarizine (Fz) for at least 20 days (average of 6 months) at daily dose of 10 mg for dizziness treatment. In this study, the age of patients ranged from 52 to 79 years, with average of 66.7 years.

In 2004, Fabiani et al. conducted a study involving 26 patients under chronic use of flunarizine (Fz) and cinnarizine (Cz). From this total, 9 patients (34%) presented DIP diagnosis. The average doses were 11.2 mg/day of flunarizine and 72.1 mg/day of cinnarizine.

The Parkinsonism-Plus syndrome refers to a group of degenerative diseases expressed as kinetic-rigid syndromes associated to other neurological disorders commonly not found in IPD (COSTA et al., 2003).

The Parkinsonism-Plus syndrome presents degeneration of the substantia nigra followed by an increase on the glial cells in the substantia nigra and decrease on the neuromelanin content, a pigment usually found in dopaminergic neurons (FAHN; SULZER, 2004; FABIANI et al., 2004).

The most common causes for the atypical parkinsonism or Parkinsonism-Plus syndrome are progressive supranuclear palsy (PSP), multisystemic atrophy (MSA) and the Lewy body dementia (GUIMARÃES; ALEGRIA, 2004).

The progressive supranuclear palsy (PSP) is, after the IPD, the most frequent cause for parkinsonism. PSP and IPD present several common clinic aspects: late beginning age, usually after the age of 40, a progressive course, bradykinesia and rigidity. Unlike IPD, most patients present, since the initial phases of the disease, postural instability and falls, and important and characteristic oculomotricity alterations or vertical eye supranuclear palsy. Axial rigidity, dysphagia and dementia are typical and most cases do not respond, or poorly respond to levodopa-based treatments. Histologically, the disease is characterized by the presence of neurofibrillary tangles at the base nucleuses and at the cerebral trunk associated to tau-positive astrocytes and to the loss of neurons and astrogliosis (LITVAN, 1999).

The multi-systemic atrophy is a sporadic degenerative disease of the central nervous system that causes parkinsonism manifestations, cerebella, anatomical and pyramidal combined dysfunctions at quite variable relative proportions.

The Lewy body dementia is the most

common cause of dementia among elderly individuals, followed by the Alzheimer's disease. However, the current accuracy of the clinical diagnosis is quite low, about 50% (LITVAN et al., 1998). Lewy bodies are found at the cerebral neocortex, limbic cortex, subcortical nucleuses and cerebral trunk.

There are no treatments for atypical parkinsonian syndromes previously mentioned, which efficiency could be comparable to levodopa in IPD. The lack of specific therapies corroborates the efficiency of levodopa, which in some cases, bring transitory benefits to the patient. Symptomatic support measurements, besides physiotherapy cares may also be performed (GUIMARÃES; ALEGRIA, 2004; PIERUCCINI-FARIA et al., 2006).

The main objective of this study was to use specific data from literature on dementias (Alzheimer and Parkinson), correlating aging and modified neural structures due to dementia and aging in order to generate hypotheses on prophylactic cares to be developed in order to avoid such diseases, since their cure either do not exist or are not satisfactorily efficient, thus justifying this study.

DEVELOPMENT

Searches in the following databases: MEDLINE, Scielo, PubMed, LILACS, CAPES Journals and Google were performed. This latter seemed to be quite efficient, since articles indexed in less known indexers may be found, using the term "pdf" after the keyboarding of descriptors. The descriptors used were: dementia, cortical structure, aging, Alzheimer, Parkinsonism.

Indexed articles mainly published between 2003 and 2007; older classic indexed articles, mainly classic articles on encephalic structure, aging and dementias, regardless their release date, were included in this review. Articles that do not approach the main ideas to be exposed in this work.

Articles and texts referring to several characteristics of dementias were found and divided into: (1) clinical cases; (2) etiology of dementias; (3) dementia-induced neuropathological alterations; (4) theories about aging; (5) cortical histology and structure.

The associations between aging and dementias here studied are frequently mentioned; however, an efficient biochemical and etiological correlation with senility is still lacking.

A justified concern in relation to the nosologic characteristics of dementias is observed in references studied and evidenced in the introduction

of this article, which sometimes are aimed at the molecular biology discoveries and sometimes to the lack of resources for treatments. Other references evidenced alterations on the behavior and neural system of patients without, however, concluding anything on a new clinical-scientific observation paradigm. However, it is worth emphasizing the scientific importance of publishing articles on the several conditions associated to dementias.

The neural system is the most complex structure ever known and, despite the scientific advancements, many questions are still unanswered and many more must be asked (AVERSI-FERREIRA; PENHA-SILVA, 2005) for the understanding of its functions, especially in relation to the aging process.

The cortex is the main structure of the neural system in relation to sensorial, motor and associative functions (SUPER et al., 1998). Since the beginning of the XX century, several questions on the origin, evolution and function of the cerebral cortex have been cleared; however, many more have not been answered yet (BROCCOLI, 1999).

The adult neocortex of mammals is composed of 6 horizontal Brodman layers (MARIN-PADILHA, 1992) stratified as columns, which are physiologically responsible for the motor command of several regions of the body and for the processing of information, also originated from several regions of the body (CAVINESS, 1975).

The horizontal stratification of the cerebral cortex is associated to the performance of normal functions of the brain.

The effective comprehension of the structure-function phenomenon has not yet been achieved by current sciences. Neurons morphologically similar present distinct functions, and associated or alone, form groups within the neocortex. The distinction between abstract and upper associative functions is not demonstrated by standard physiological procedures; however, this knowledge is based on animal behavior, which in turn, is based on subjective criteria.

Luria (1981) organizes neuropsychological functions through the definition of basic functional units, which geometry includes regions distinct from encephalic structures composed of different neurons; thus, the cerebral cortex depends on the subcortical afference for the precise performance of its functions.

Therefore, it is important emphasizing that alterations on such precise, diffuse and complex network will cause functional alterations that may be expressed as psychoses, neuroses, dementias, among others.

With the increase on the average population's life expectancy, the appearance of aging-associated diseases such as the Alzheimer's disease (VILELA; CARAMELLI, 2006) and Parkinsonism of etiologies not fully clear becomes more and more common.

Aging, or senescence, is not necessarily associated to chronic degenerative diseases that characterize senility (HAYFLICK, 1996b); however, the stochastic determinants of aging and chronic degenerative diseases may have a common origin.

The aging process and the biological processes associated to it may be the common point of diseases that occur to old-aged individuals.

The aging of the central nervous system (CNS) leads to the decrease of its volume (loss of neurons and other substances) and the nervous fibers lose their myelin – responsible for the nervous stimulus conduction velocity (STRAUB et al, 2001). Approximately 50.000 neurons/day are lost, mainly from the cerebral cortex, and a significant mental deterioration may occur with aging (KAPLAN; SADOCK, 1990), what may also reduce the ability of producing neuronal in the ventricular and subventricular zone, with reduced dendritical arborization and reduced mass and amount of neurons, causing destruction of the associative routes (BIZON; GALLAGHER, 2005).

The intellectual functions are also altered, for example: difficulty in the learning and memorization processes, what is probably associated with chemical, neurological and circulatory alterations, which affect the cortical function; reduced efficiency of the cell nutrition and oxygenation (ARKING, 1998) and learning difficulties associated to deficiencies in synapses and in the availability of some neurotransmitters (BRAVER; BARCH, 2002), leading to mental alterations similar to those of an incipient dementia, for example, the Alzheimer's disease (DAMASCENO, 1999) and to the progressive loss and decline of vision (REUTER-LORENZ; LUSTIG, 2005).

Immunohistochemical studies have demonstrated decrease on the number of cortical neurons and the volume of their nucleus in rats from both genders (TSUKAHARA et al., 2005), what indicate a reduction on the ability of generating neurons (BIZON; GALLAGHER, 2005).

In studies with hematoxylin and eosin in cerebella of 22-90-year-old humans, horizontal sections were analyzed and revealed that aging is associated to decreases on the amount of neurons

and increases on the content of gliocytes (KHUTORYAN, 2005).

Aging debilitates the nervous, endocrine and immunological systems (STRAUB et al, 2001).

As the CNS ages, there is a slight loss of the psychomotor capacities, especially those associated to coordination, mental agility and senses (vision and audition), leading elderly individuals to a less satisfactory performance when submitted to some long-duration or quick-execution test. A reduction on the velocity of reflexes and performance of gestures and an increase on the time of reaction due to the reduction on the motor response to a sensorial stimulus also occur (BRAVER; BARCH, 2002).

The normal cerebral aging, especially in relation to the cerebral cortex, may be followed by mental alterations, generating problems of differential diagnosis, especially the Alzheimer's disease (AD), which still does not have a known biological marker (DAMASCENO 1999).

There is an important correlation between alterations of the neural system associated to aging and alterations that generate or are generated by dementias; this is a point not cleared yet that needs to be detailed. Thus, there are two hypotheses to be considered: (1) the dementia is genetically programmed and generates modifications on the neural system; or (2) the modifications on the neural system result in dementias. However, both may occur at once.

In both cases, the aging factor is directly associated. In the first case, it is considered that the environment plays an important and effective role on the genetic factors; in the second case, the natural aging associated the stochastic factors is the cause of the problem. Currently, since the cure process does not present the desired result, avoiding dementia becomes vital. Thus, if the genetic factor is preponderant, the environment resources should be used in the attempt of preventing or attenuating the process, according to the classic and known concept that the genotype manifestation is partly dependent on the environment; however, if the phenomenon has a general metabolic cause, prevention may fully avoid these manifestations, using techniques that promote the "good aging". Thus, it is important considering dementias as a public health problem that requires attention since early childhood.

Aging generates known problems such as significant blood pressure alterations (JEDRZIEWSKI et al., 2005), increases on the fat localized deposits and cholesterol rates and alterations on the glycemic metabolism such as diabetes (ARKING, 1998; JEDRZIEWSKI et al.,

2005). In this context, one may consider that the high blood glucose rates lead to significant alterations on the structure of other biomolecules, as well as the oxidative metabolism, such as proteins (TARIOT, 1994), genic expressions and the DNA itself. Considering the Alzheimer's disease, which outcomes are associated to alterations on the amiloid- β and tau proteins (SMITH, 1999; TARIOT, 1994; ALMEIDA, 1997; CLARK; KARLAWISH, 2003; HIGUCHI et al., 2004; HARTMANN et al., 2004; BLENNOW; HAMPEL, 2003; HUA; HE, 2003; SCHÖNKNECHT et al., 2003; GOEDERT, 2004; HIRAOKA et al., 2004; LEWEZUK et al., 2004; DIAMANDIS et al., 2005; LITVAN, 1999), the metabolic hypothesis must be considered as cause of dementia.

In the case of Parkinsonism, protein alterations such as the formation of neurofibrillary tangles are mentioned; however, the main problem occurs in the dopamine metabolism. Such metabolic route is governed by genes; and then the metabolic hypothesis must be also considered.

Considering the factors that cause dementias only seems to be the problem that avoids finding its causes. It is clear that the aging process is associated to the appearance of dementias, and the focus should also be the organism that ages along with the neural system, and this is true, regardless

the several distinct times of tissue and physiological aging.

According to associations shown above on the structure of the neural system and its aging, one should consider that the neural system is quite labile and dependent on the circulatory system health and nutrition (ARKING, 1998).

Thus, the prevalence of dementias will only be reduced if general health cares associated to the constant exercise of intellectual and physical activities (CROWE et al., 2003; CARAMELLI, 2007) are encouraged since childhood.

However, it was observed that the lack of health preventive activities by the general population and the absence and/or inefficiency of public prevention programs might be the cause for the further development of dementias.

CONCLUSION

Aging-associated dementias may be caused by the total organs depletion, especially the neural structures, and the early prevention through cares with the general health in relation to problems from the glycemic metabolism is very important. The aging of the neural system generates biochemical and metabolic subsidies for the appearance of dementias with genetic or stochastic causes.

RESUMO: O envelhecimento é um processo natural e que traz consigo alterações morfofisiológicas que podem causar doenças, e as conseqüências do envelhecimento das estruturas neurais tem relação clara com as etiologias das demências. O aparecimento da doença de Alzheimer (DA) está associada a fatores genéticos e de envelhecimento, com tratamento pouco eficaz e neuropatologia que somente pode ser completamente detectada após a morte. O Parkinsonismo (PK) está, também, associado às causas genéticas e com o envelhecimento, possui tratamento com melhores resultados que a DA e é dividido em 3 tipos básicos: parkinsonismo idiopático; parkinsonismo induzido por drogas e a síndrome Parkinsonism-Plus. Foram utilizados descritores para a obtenção dos vários artigos associados ao envelhecimento, estrutura neural, DA e PK. Nossos resultados demonstraram que as associações entre as demências estudadas e o envelhecimento são muito citadas nos artigos, mas pouco desenvolvidas em termos bioquímicos, fisiológicos e clínicos, e quando o são, as propostas de tratamento não são claras. Esse extenso material proporcionou a possibilidade de enquadramento das demências estudadas como fator de risco para a saúde humana de um modo geral, tornando-as um problema de saúde pública, e que devem ser tratadas precocemente, pois os vários dados literários demonstram várias relações entre a senescência e as demências estudadas aqui. Concluimos, então, que, independente das dificuldades em se conhecer a etiologia das demências, estas estão associadas aos processos estocásticos para o ganho de idade não somente para o sistema neural, mas também para os outros órgãos e tecidos.

PALAVRAS-CHAVE: Envelhecimento. Doença de Alzheimer. Parkinsonismo

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