Practice of physical exercises as a non-pharmacological strategy in the treatment of alzheimer's disease treatment

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ABSTRACT

Studies show that the life expectancy of the world population is increasing and consequently the elderly population. With aging is observed a loss of cognitive skills that can occur pathologically such as Alzheimer's disease (AD). AD is a neurodegenerative disease characterized by the accumulation of extraneuronal amyloid plaques and intraneuronal neurofibrillar entanglements located in regions of the temporal lobe, which result in progressive cognitive decline. Physical activity programs can reduce the risk of AD development. Thus, this study aimed to portray the pathophysiological aspects of AD, and the practice of physical exercise as a non-pharmacological method in its prevention. The research was carried out from a bibliographic review of specialized literature, being consulted scientific articles located in the databases Medline, Scielo, Lilacs, Google Academic and the portal of CAPES Journals published until 2019 and additionally consultation of academic books to complement the research. Physical exercises can prevent and delay the disease, in addition to physical benefits such as improved psychological state, behavior disorders, improved ability to perform daily life activities, reduced risk of falls and the social relationship of the patient.

Keywords: Alzheimer, Old man, Physical exercise, Cognition.

1 INTRODUCTION

According to Martelli (2013), memory, defined by the organism's capacity to change its behavior due to previous experiences, is of paramount importance in our lives because of its capacity to retain the knowledge that has been acquired throughout life, as well as in the past and present. The

findings in the literature are vast, citing that memory declines to the detriment of aging and researchers are challenged to explain this phenomenon during the process (HAMDAN, 2008).

The number of elderly people in the world is increasing due to the improvement in their life expectancy, but parallel to this phenomenon there is an increase in the prevalence of AD (FERNANDES and ANDRADE, 2017). AD is considered to be the main cause of cognitive decline in adults, especially the elderly, which could be associated with both a pathological condition and a fall in memory (FORLENZA, 2005; PAULA et al., 2009). According to Paula et al. (2009), age is the main risk factor for AD prevalence, rising from 0.7% for ages 60-64 to 40% in groups aged 90-95.

In the world, approximately 35.6 million people are affected by AD, and in Brazil of the 1.2 million cases, most of them still undiagnosed (ABRAZ, 2019). Almeida et al. (2014), describe AD as a neurodegenerative, progressive and still irreversible disease that gradually affects the cognition of people and subsequently the good functioning of the whole body. They also mention that this pathology acts in 5% of the cases of dementia in the USA and Great Britain, corresponding to the fourth cause of death in the elderly of these countries.

Hamdan (2008), says that in 1950 there were more than 214 million elderly people in the world over 60 years of age, estimating that this number will reach 1 billion by 2025. IBGE data (2018), showed that in 2000 people over 65 represented 5% of the population and in 2010 this percentage represented 7.4%. Corroborating this projection Trentini and Gonçalves (2009), cite that in 2050 the prospect is that this number will reach 18% of the Brazilian population.

The description of this pathology was initially performed by the German neuroscientist Alois Alzheimer, who in 1907 described the case of a 51-year-old patient who presented with a decline in memory and several cognitive deficits and behavioral disorders (GUERRA et al., 2009).

AD develops as a function of the formation of senile plaques that result from abnormal metabolism of amyloid precursor protein (APP) that ends up forming aggregates of beta amyloid peptides and neurofibrillar entanglements, which are formed from the collapse of the neuronal cytoskeleton, due to hyperphosphorylation of the TAU protein (FORLENZA, 2005; PAULA et al., 2009; HOGLUND e BLENNOW, 2007).

The person has a high impairment of recent memory and with the development of the disease mental disorders appear as well as a difficulty in appointment and attention deficit, which ends up harming people with AD in their daily life, family coexistence and socialization (COELHO et al., 2009).

AD is characterized by stages in which its severity is evident and its treatment is usually directed to the control of the disease. In the beginning the person is confused and forgotten, not finding the right words to communicate, is sloppy with his appearance, without initiative and autonomy in

some daily activities. After this phase, the person may not recognize their family members, becoming incapable of more complex judgments and thoughts, needing help at times such as changing clothes, bathing, eating, medication and hygiene activities. In the advanced phase of the illness, weight loss and total dependence on others occur, where the person becomes incapable of performing any day-to-day activity with loss of the ability to concentrate and understand things (ABRAZ, 2019).

Researchers agree that a physical exercise program can decrease or mitigate the risk of AD development and its aggressive effects. Studies show that elderly people who participate in these programs can reduce cognition impairment by 40% and AD development by 50%. Corroborating with this data, Nobrega *et al*., (1999); Lima, (2008) and Matsudo, (2006), show that the positive effects of a physical exercise program can promote in AD patients an improvement in cognitive function, behavioral aspects, motor function and social aspect. Besides promoting neurophysiological benefits (COTMAN and BERCHTOLD, 2002; ANNUNCIATO, 1995)

Considering that AD is a chronic-degenerative disease that mainly affects elderly people, where its main syndrome is characterized by a progressive decline in cognition, the present study presented as an objective a review of the literature addressing the brain alterations of people with this pathology and the possible effects of a physical exercise program, as a non-pharmacological adjunct method, in improving the quality of life of these people.

2 METHODES AND MATERIALS

This review study was conducted through a bibliographic survey using the databases of Medline, Scielo, Lilacs, Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), libraries and the Google Academic data search of national and international scientific articles using as search means: *Alzheimer's disease*, *Neurofibrillary tangles*, *Cognition*, *Physical Exercises*, Elderly. Some specific academic books, related to the area, were also used to complement the information on AD and cognitive improvement with the regular practice of physical exercises.

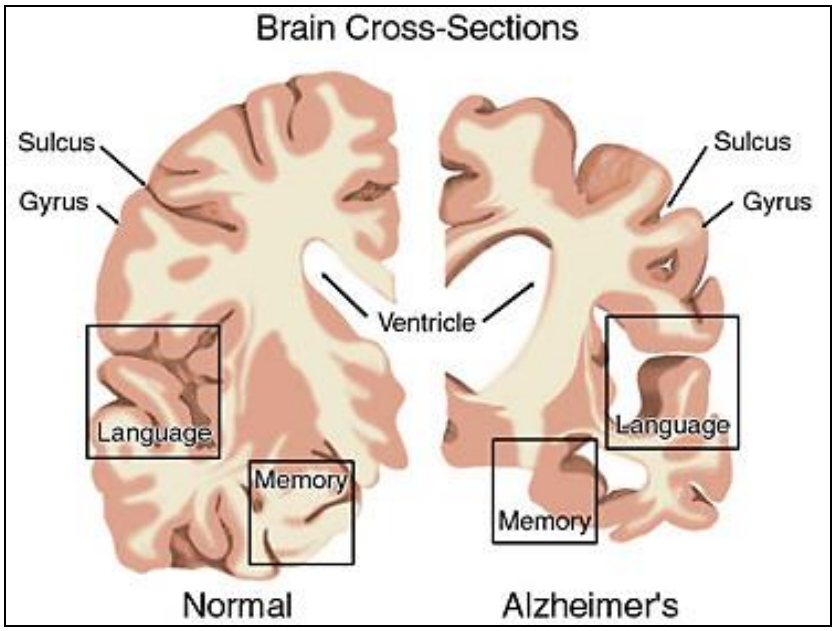
The articles selected and included in the research were composed of clinical trials, original articles, reviews and systematic reviews. As an eligibility criterion, we used studies that presented data regarding cognitive disorders caused by AD as well as brain alterations, such as senile plaques and neurofibrillar entanglements formed from the collapse of the neuronal cytoskeleton and the reports collected from the regular practice of physical exercises for patients with this pathology.

3 MORPHOCEREBRAL CHANGES IN ALZHEIMER'S DISEASE

The pathophysiology of AD is characterized by synapses degeneration and death of neurons, which occur as a result of the reduction of acetylcholine, choline acetylcholitransferase, changes in sensitivity and quantity of nicotidic and muscaridic receptors (ALMEIDA, 1998; INOUYE, 2008).

Regarding the macroscopic structures of a brain with AD, Hamdan (2008) cites two consequences, bulb atrophy and olfactory tract and the shrinking of the hippocampus. By performing a macroscopic examination of the brain demonstrated in figure 1 Chai (2007), he observed a variable degree of cortical atrophy, an increase in ventricular volume and a widening of the most pronounced brain grooves in the frontal, temporal and parietal lobes.

Figure 1. Cross-section of a normal person's brain and an Alzheimer's carrier showing cortical atrophy and enlargement of the grooves.



Source: Arte cor Doença – Alzheimer, 2019

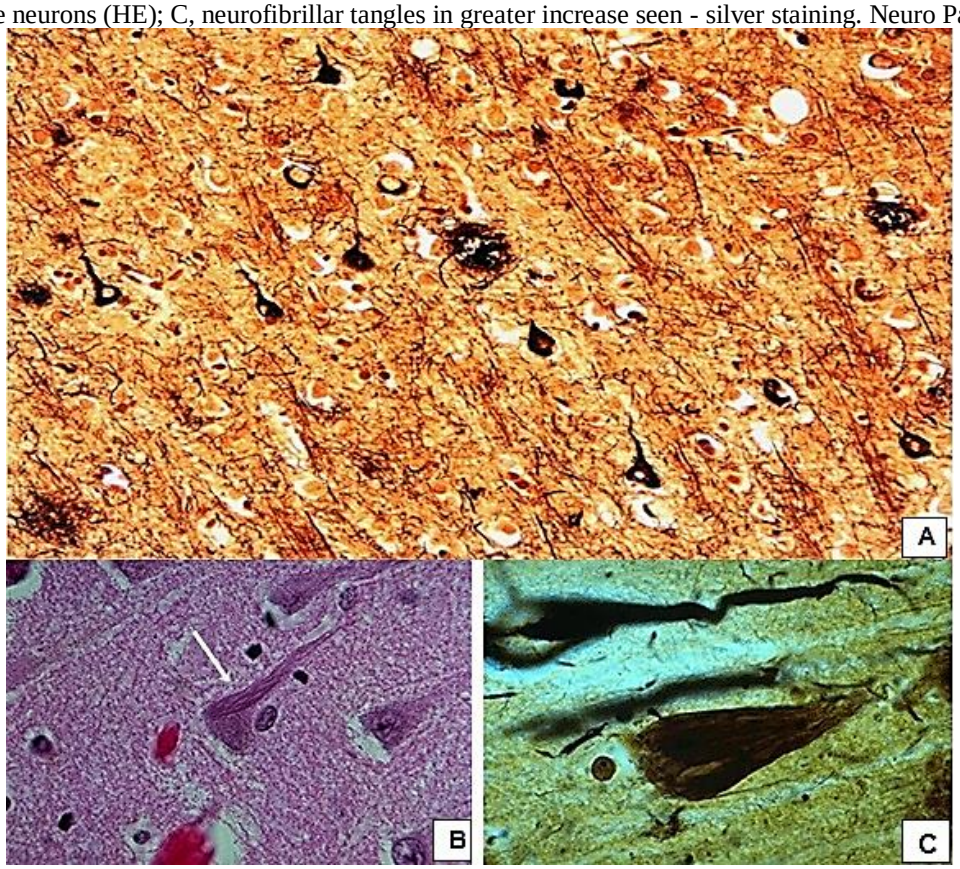
When AD manifests early, below 65 years of age, a more pronounced cortical atrophy occurs in relation to central atrophy, unlike cases with a late onset, above 65 years of age (PENDLEBURY and SALOMON, 1996). Regarding histological and neuropathological aspects, AD presents a great loss in synapses and neuronal death, well observed in regions with cognitive functions (TRENTINI and GONÇALVES, 2009). Almeida (1997), complete suggesting that neuronal death occurs after rupture of the cell cytoskeleton.

As the disease progresses, typical lesions appear as a result of the appearance of senile plaques containing extracellular deposits of beta-amyloid and entangled neurofibrillar protein composed of hyperphosphorilated Tau protein (CHAI, 2007; SERENIKI and VITAL, 2008, COELHO *et al*., 2009).

These situations could be described from the 60s with the use of electron microscopy (FRIDMAN *et al*., 2004).

As shown in figure 2A the neurofibrillar entanglements correspond to intraneuronal structures composed of pairs of filaments with helical characteristics that have several elements of the neuronal cytoskeleton (SERENIKI and VITAL, 2008; HAMDAN, 2008). These bundles of filaments in the cytoplasm surround the cell nucleus, whereas in pyramidal neurons these filaments end up forming the neurofibrillar entanglements in an elongated form, as seen in Figures 2B and 2C (KUMAR *et al*., 2005).

Figure 2. Neurofibrillar entanglements in the AD. In A, upper temporal cortex section showing the neurofibrillar entanglements (Bielschowsky silver x 300) David et al., 2003. On B, a neurofibrillar tangle (arrowhead) and long filaments present inside the neurons (HE); C, neurofibrillar tangles in greater increase seen - silver staining. Neuro Pathology.



AD acts differently in people than in other dementias, mainly due to disorders of the patients' behavior towards it, perhaps because each person has his/her own genetic characteristics (DOURADO 2006).

For a definitive diagnosis of AD, a histopathological analysis of the post-mortem brain tissue should be done (HARTMANN *et al*., 2004; GALLUCCI NETO *et al*., 2005; SILVA *et al*., 2010). According to Nitrini (2005), imaging examinations such as Nuclear Magnetic Resonance,

Computerized Axial Tomography, Single Photon Emission Tomography, Positron Emission Tomography among others can also be used.

Although in recent years important advances in methodology and technology have allowed the opening of a new area of research in AD, with the use of molecular biology, its early diagnosis, according to Martelli (2013), still represents a great challenge for the medical community and the greatest challenge of the 21st century will be to care for the elderly population, which could exceed 32 million, where most of them have low socioeconomic and educational levels with a high degree of chronic-degenerative diseases.

4 PHYSICAL ACTIVITY IN PEOPLE WITH ALZHEIMER'S DISEASE

The practice of physical activity is extremely important and has been increasing since our origin in the early days of mankind, where man depended on his physical abilities to survive, thus becoming extremely active (PITANGA, 2002).

There is a gap in the recommendations, intensity, type of exercise, frequency and duration of exercise related to the elderly population (COELHO et al., 2009). Brito et al. (2011) and Hernandes et al. (2011), they conclude by saying that despite much evidence regarding the benefits that physical exercise provides, few studies have been conducted relating it to patients with AD.

However, regular physical exercise has been pointed out as a non-drug strategy with excellent benefits for physiological systems that present some kind of deterioration through aging and accelerated with AD (BRITO et al., 2011; HERNANDEZ et al., 2011). Studies show that regular, low-intensity exercise can have a positive mental and psychological impact on people, who feel healthier and consequently make fewer visits to doctors and still reduce the risks of possible hospitalizations (HEPA, 2006).

Matsudo et al. (2008), cite that many studies relate the benefits that physical activity can bring to the aging process such as anthropometric, motor, metabolic, cognitive and psychosocial effects as well as therapeutic effect. Specifically related to cognitive and psychosocial aspects, Matsudo et al. (2008) say there has been an improvement in self-esteem, body image, mood and insomnia, in preventing or delaying the decline in cognitive functions, decrease in stress and depression, drop in drug consumption, and improvement in socialization.

In a study conducted by Larson et al. (2006), with 1740 people over 65 years of age and without incidence of dementia, the frequency with which they practiced physical exercise and cognitive function, physical, depression, health conditions and lifestyle were verified, with reassessment every two years. After a six-year follow-up, 107 volunteers were identified with AD, with an incidence of dementia of 13 per 1000 in the year among people who exercised three times a

week or more and among the group of people who exercised less than three times a week the incidence was 19 per 1000 people in the year, reaching the conclusion that the people who exercised more had lower rates of dementia.

According to Vital et al. (2010), The cognitive drop is characterized by hypoperfusion in AD, where one of the possible causes would be a functional alteration of nitric oxide, which consequently can cause alterations in hemodynamic functions and neurotransmitters, where physical exercises could act as a resource to improve cerebral perfusion and increase production of nitric oxide, anti-inflammatory activity as well as production of acetylcholine but these effects would depend on the cardiovascular condition of the patient, where an evaluation to verify these conditions is necessary.

According to Scherder *et al.* (2007), It is in the intermediate phase of AD that motor changes are most evident and it is in this period that the elderly have the highest rates of falls, due to the deficit of attention, agility and balance.

Numerous studies confirm the hypothesis that a physical exercise program can provide important positive changes in the cognitive function of patients with AD. Following this line, Hernandez et al. (2010), observed that patients with AD who attended a program of systematic physical exercises, showed improvement in cognitive functions, balance and risk of falls, compared to those who did not participate. Studies on the type, intensity and volume of training are not well clarified, however Schmitz (2011), cites that physical exercises in general, can promote the elderly with dementia, an improvement in functional capacity, develop physical abilities, improve the lipid profile, prevent adjacent diseases, decrease muscle stiffness, recover joint mobility, stabilize blood pressure, activate blood circulation and improve VO2, thus reducing depression.

Physical exercise has been shown to be an important neuroprotective agent in the face of neurodegenerative aspects of the central nervous system, improving brain circulation and favoring the synthesis of neurotrophic factor, stimulating neogenesis, it can also increase mitochondrial cytochrome oxidase activity, which acts in the transport of electrons and energy production and has protective function against AD (COTMAN and BERCHTOLD 2002). Through these Annunciato (1995) benefits, he complements by saying that exercise still reinforces the neuronal structure facilitating synaptic transmission, increasing resistance to the brain aggressions that the disease can cause, reinforcing the premise that exercise can benefit brain physiology.

After a 12-week training program with 16 patients aged over 70 years with AD, which combined resistance training, joint mobility and coordination, Sosa et al. (2008) observed a significant improvement in overall functional capacity, with increased muscle strength, flexibility, agility and coordination, where consequently there was a reduction in fall risks and improved ability to perform daily activities.

Stein (2010), made an association between weight training and exercise level with sleep and quality of life in AD patients and observed an improvement in both situations. In studies conducted by Castilho (2006), Nobrega (1999), Arcoverde (2008), Rolland (2008) and Matsudo (2006), it was observed that physical exercises are a positive factor in the quality of life of patients with AD and their benefits include improved balance and gait, motor coordination, muscle strength and flexibility, cardiorespiratory capacity, improved behavior and sleep disorders, symptoms of depression, anxiety, aggressiveness, self-esteem, contributes to learning, memory and attention and even less dependence to perform daily activities.

A line of studies says that the hormone irisin, produced in the muscles during physical exercises, would work as a chemical messenger, which when reaching the Central Nervous System, could act directly on the brain, so it was named - irisin in homage to the Greek Goddess Iris, Goddess messenger. Irisine plays an important role in the synapses of the brain, helping to fight the forgetfulness that is very common in patients with AD (ABRAZ, 2019).

ABRAZ (2019) performed tests on mice with AD that received doses or produced the hormone irisin when exercising and observed that the brains affected by AD have low levels of this hormone, that replacement of the levels of irisin in the brain, including exercise, was able to reverse the memory loss of these mice affected by AD and that irisin can still regulate the positive effects of exercise on the memory of these animals.

Patients with AD have low levels of irisin in the brain, the same deficiency observed in mice used in studies, in this sense, Wrann et al. (2013) observed that through stimulation of the PGC1-alpha-FNDC5-Irisin pathway by exercise there was an increase in both expression and secretion of the brain-derived neurotrophic factor, which can increase nerve cell survival, neurogenesis and synaptogenesis, and also stimulate both differentiation and neural and synaptic plasticity, factors directly related to learning, cognition and memory.

According to Martelli (2013), research related to AD is relatively recent in Brazil and needs to evolve and develop with agility, thus allowing public health strategies appropriate to the needs of the population, as it will have to face an increased demand for diagnoses and therapies for chronic diseases, mainly cardiovascular and neurodegenerative, such as AD, where regular exercise programs are included.

5 CONCLUSION

The aging process requires attention from both family members and society, and this attention needs to be doubled when talking about elderly people with AD. Thus, this research aimed to report the phases of development of this pathology that has as an end result an involution process that leads to

addiction, collections, in many cases hurt and conflicts, which can be minimized through a pharmacological treatment associated to physical exercises that can delay or reduce the aggressive effects of the disease.

Physical exercises are of paramount importance for the whole of society, but when we talk about patients with neurodegenerative diseases such as AD, their effectiveness is proven in improving the quality of life and well-being of these patients. It is important to emphasize that physical exercises do not replace pharmacological treatments, but they enter, as adjuvants in the treatment, where their application at no time should be proposed with drug interruption. Thus, exercise programs can be very efficient in both prevention and delay of AD, because these performed in a systematic way are directly associated with the reduction of risks in the development of AD. For people where the disease has already developed, physical exercise can act as a tool to help improve cognitive, behavioral, functional, motor and social function. Finally, new studies should be conducted to enable a possible training protocol for these individuals.

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