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THE AGE FACTOR AS A DETERMINING AGENT FOR MORTALITY RELATED TO ALZHEIMER'S DISEASE IN BRAZIL

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ABSTRACT

Alzheimer's disease is a neurodegenerative disease that affects synapses, considered the main cause of dementia in the world. This article presents, through an integrative review, the age mortality discrepancy for both sexes due to the disease in Brazil. The study aims to determine possible explanations for this difference in mortality between ages. In this review, searches were used in: TABNET-DATASUS, IBGE, Medline and PubMed; having, as a research parameter, articles and data relevant to the subject. The results are intended to determine pathogenesis related to the age group for this disease, concluding that it is an adversity in the process of being understood by Science.

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INTRODUCTION

With the advent of Alzheimer's disease (AD) by Alois Alzheimer, in 1906, there was a need to encourage research for a better understanding of this disease, which is the main cause of dementia in the world, affecting about 60-70% of people with dementia (LENG, F.; EDISON, P., 2021), being, due toTo this, a highlight for the performance of multiple clinical trials on its pathogenesis. Alzheimer's disease is a neurodegenerative disease characterized by progressively presenting synaptic collapses/losses in the regions mainly responsible for spatial memory. This occurs due to the fact that the brain areas in which these memories are located in the Temporal Lobe, as is the case of the Entorhinal Cortex and the Hippocampus, present a protein deregulation in their synapses, which, consequently, compromises both their function of storage, as well as synaptic communication with other brain structures also responsible for memories, resulting in a systemic brain atrophy, ending the individual in death (STONE *et al*., 2011). In this context, due to this systemic brain atrophy, AD tends to be a major mortality agent for the elderly population of both sexes when compared to the young and adult population, also of both sexes, together in the country. This can be explained by the increased susceptibility of oligodendrocytes in the production of the myelin sheath in the Central Nervous System (CNS) by age/genetic factors, such as the deposition of the Beta Amyloid peptide and the hyperphosphorylation of the TAU protein, which can compromise the integral functioning of these Glial cells by toxins (BARTZOKIS, G ., 2011). Therefore, in order to address the pathogenesis related to the Age Factor present in AD, the period of life is evidenced by determining an alarming variety of injuries that may contribute to the development and, if already present, to accelerate the disease, making it difficult in one possible future treatment, due to its high genetic tendency to mutate in multiple genes, thus aggravating the propensity of a definitive age etiology.

MATERIALS AND METHODS

This article is an integrative approach to several other scientific projects that have contributed to the enrichment of neuroscience. To carry out this work, they were selected through the scientific research platforms: Medline, PubMed, SciELO, Google Scholar, IBGE, TABNET-DATASUS and magazines/sites with a scientific approach; several other articles, highlighting those in English and Portuguese, in order to promote a better foundation on the topic addressed. Articles related to the following Keywords were selected: Alzheimer's disease, Mortality, Myelin Sheath, Oligodendrocytes, Synapses. The articles obtained had, as a selection criterion, data related to the theme:

´´The Age Factor as a determining agent for mortality related to Alzheimer´s disease in Brazil´´, discarding those that did not comply with the theme presented. There was no restriction regarding the date on which the particular article was published, thus selecting articles that were relevant to the subject from different times. Thus, in reference to the elaboration of the tables, searches were carried out on the websites of the national government TABNET-DATASUS and IBGE, in order to raise official data for data collection. To create the charts, several specificities were considered, including: age group, gender, Brazilian regions, period analyzed, type of death, cause of death and absolute population by region of the country. Two years of analysis were selected, that is, the year 2000 and the year 2020, for the possibility of a greater coverage of a sample space, which is the Brazilian population. In addition, there was no need to perform a proportion for the absolute population of the periods analyzed to match the populations, given the low rate of population increase that occurred in those years. Still on the periods addressed, these two years were selected to demonstrate, precisely, that, even with two decades of difference, it is prevalent among the elderly population. Regarding gender, only male and female were selected, with the division between these by age group and national regions. In view of this, a high diversity of ages was determined for the absolute population considered young and adult, choosing the age groups from less than 1 year old to 59 years old and, as for the absolute elderly population, from 60 years old to 80 years old or more. This range of ages for young people and adults was selected to be increased precisely to prove that, even with a larger absolute population of young people and adults, the mortality of the absolute population of elderly people due to AD is still higher. In addition, to calculate the Mortality Rate, the formula ´´Mortality Rate by Specific Reason´´ was used, which consists of the number of cases of the specific cause of death divided by the absolute population of the analyzed area, being , this result, multiplied by 100,000 for a larger sample space.

RESULTS

Thus, when analyzing the data from the charts and comparing such alarming values, there are several factors to explain the reason why this discrepancy in deaths occurs between the absolute elderly and young/adult populations, highlighting the degradation of the myelin sheath. In this context, the myelin sheath, which has the important functions of lining dendrites and accelerating/isolating electrical impulses from synapses to promote rapid information processing, can be degraded by the accumulation of toxins in its cellular composition by the following adversities : the deposition of the peptide beta-amyloid, hyperphosphorylation of the TAU protein and the amount of cholesterol dependent on association with iron.

Together, excess beta-amyloid can result in the formation of Amyloid Plaques (HARDY, J.; ALLSOP, D., 1991), which, in addition to being toxic to neurons, also has as a consequence the promotion of TAU protein hyperphosphorylation (ASHRAFIAN, H.; ZADEH, E. H.; KHAN, R. H., 2021), compromising the integrity of this synaptic lining and thus being one of the determining factors for the occurrence of death from AD. Firstly, in relation to the peptide, the APP gene is responsible, through its gene expression, for determining the synthesis of the Amyloid Precursor protein, which, during its proteolysis, results in the generation of a peptide called Beta Amyloid. Thus, the excess of these peptides can cause the formation of Amyloid Plaques (HARDY, J.; ALLSOP, D., 1991), which, due to the fact that they are neurotoxic and composed of portions of protein fibers, can be deposited in tissues nervous, preventing the exercise from accelerating and isolating the synaptic communication of the myelin sheaths, given the gradual exposure of accumulations of Amyloid Plaques (TURNER, P. R.; O´CONNOR, K.; TATE, W.P. *et al*., 2003). Secondly, now referring to the TAU protein, the deposition of these Amyloid Plaques contributes to the occurrence of hyperphosphorylation of the protein responsible for stabilizing nervous microtubules, the TAU protein.

This process occurs due to the fact that, when the Beta Amyloid peptide is formed in the extracellular environment, it triggers, within the microtubules, a signaling response of activation of kinases, which, when activated, transfer a phosphate group to the protein. TAU, causing it, now phosphorylated, to leave the microtubules, destabilizing them (ASHRAFIAN, H.; ZADEH, E. H.; KHAN, R. H., 2021). Finally, this destabilization may be related to an increase in the susceptibility of oligodendrocytes to a variation of neurotoxic properties, such as hypoperfusion, accumulation of free radicals and even excitotoxicity, thus affecting their metabolic demand, which may impact , negatively, in the synthesis of the myelin sheath (BARTZOKIS, G., 2011). Thirdly, in allusion to the amount of cholesterol associated with the levelsiron, the production of cerebral cholesterol occurs, in the CNS, mainly by oligodendrocytes, and 80% of the concentration of cerebral cholesterol is present in the composition of the outer membrane of the myelin sheath bilayers (MUSE, E. D.; JUREVICS, H.; TOEWS , A.D. *et al*., 2001). This fact is of extreme neuronal relevance, as cholesterol allows synaptogenesis to take place, which can be affected by the fact that this lipid structure is reduced in old age (BARTZOKIS, G., 2011). In addition, the level of intracellular iron is of paramount importance, since up to 70% of brain iron is associated with the myelin sheath (QUINTANA, C.; BELLEFQIH, S.; LAVAL, J. Y. *et al*., 2006), its deficiency may result in failure of iron-dependent enzymes to synthesize cholesterol in the outer membrane of myelin sheaths, resulting in loss of outer membrane integrity and, consequently,

Table 01. Mortality of cases of alzheimer among the young and adult population in brazil

Age range considered for the young and adult population: under 1 year old up to 59 years old **Sexes analyzed:** Female and Male **Period analyzed:** 2000 and 2020 **Deaths by Occurrence**				
Period analyzed: 2000				
Region	**Sex feminine**	**Sex masculine**	**Total**	**Mortality Rate (2000)**
South region	4	4	8	(8 / 25,110,349) x 100,000 = 3.18 deaths per 100,000 inhabitants
Southeast region	11	6	17	(17 / 72,430,194) x 100,000 = 2.34 deaths per 100,000 inhabitants
Midwest region	0	1	1	(1 / 11,638,658) x 100,000 = 0.85 deaths per 100,000 inhabitants
Northeast Region	2	2	4	(4 / 47,782,488) x 100,000 = 0.83 deaths per 100,000 inhabitants
North region	1	0	1	(1 / 12,911,170) x 100,000 = 9.77 deaths per 100,000 inhabitants
Brazil	18	13	31	(31 / 169,872,859) x 100,000 = 1.82 deaths per 100,000 inhabitants
Period analyzed: 2020				
Region	**Sex feminine**	**Sex masculine**	**Total**	**Mortality Rate (2020)**
South region	17	10	27	(27 / 30,192,315) x 100,000 = 8.94 deaths per 100,000 inhabitants
Southeast region	34	23	57	(57 / 89,012,240) x 100,000 = 6.40 deaths per 100,000 inhabitants
Midwest region	1	6	7	(7 / 16,504,303) x 100,000 = 4.24 deaths per 100,000 inhabitants
Northeast Region	11	10	21	(21 / 57,374,243) x 100,000 = 3.66 deaths per 100,000 inhabitants
North region	2	4	6	(6 / 18,672,591) x 100,000 = 3.21 deaths per 100,000 inhabitants
Brazil	65	53	118	(118 / 211,755,692) x 100,000 = 5.57 deaths per 100,000 inhabitants

Table 02. Mortality of cases of alzheimer among the elderly population in brazil

Age range considered for the elderly population: 60 to 80 years and over **Sexes analyzed:** Female and Male **Period analyzed:** 2000 and 2020 **Deaths by Occurrence**				
Period analyzed: 2000				
Region	**Sex feminine**	**Sex masculine**	**Total**	**Mortality Rate (2000)**
South region	205	142	347	(347 / 25,110,349) x 100,000 = 1.38 deaths per 100,000 inhabitants
Southeast region	619	399	1.018	(1,018 / 72,430,194) x 100,000 = 1.40 deaths per 100,000 inhabitants
Midwest region	32	15	47	(47 / 11,638,658) x 100,000 = 0.40 deaths per 100,000 inhabitants
Northeast Region	98	61	159	(159 / 47,782,488) x 100,000 = 0.33 deaths per 100,000 inhabitants
North region	7	6	13	(13 / 12,911,170) x 100,000 = 0.10 deaths per 100,000 inhabitants
Brazil	961	623	1.584	(1,584 / 169,872,859) x 100,000 = 0.93 deaths per 100,000 inhabitants
Period analyzed: 2020				
Region	**Sex Feminine**	**Sex Masculine**	**Total**	**Mortality Rate (2020)**
South region	2.971	1.566	4.537	(4,537 / 30,192,315) x 100,000 = 15.02 deaths per 100,000 inhabitants
Southeast region	7.898	4.177	12.075	(12,075 / 89,012,240) x 100,000 = 13.56 deaths per 100,000 inhabitants
Midwest region	968	711	1.679	(1,679 / 16,504,303) x 100,000 = 10.17 deaths per 100,000 inhabitants
Northeast Region	2.968	1.730	4.698	(4,698 / 57,374,243) x 100,000 = 8.18 deaths per 100,000 inhabitants
North region	466	279	745	(745 / 18,672,591) x 100,000 = 3.98 deaths per 100,000 inhabitants
Brazil	15.271	8.463	23.734	(23,734 / 211,755,692) x 100,000 = 11.20 deaths per 100,000 inhabitants

Source: Own elaboration based on databases from IBGE and TABNET-DATASUS (2023)

synaptic loss (CHEEPSUNTHORN, P.; PALMER, C.; MENZIES, S. *et al*., 2001). Thus, as could be explained, these factors contribute to the occurrence of age-related myelin degradation. This occurs because, unlike neurons, oligodendrocytes continue to divide and increase in numbers throughout the individual's life while carrying out their function of remyelination of damaged or lost sheaths in the CNS for the aforementioned reasons. However, these new myelin sheaths may be susceptible in relation to their structures, since, due to this constant remodeling, it tends to present a greater amount of interweaving and to be thinner, leaving it and the synaptic communication more susceptible to other possible stresses that may occur for these or other reasons (BARTZOKIS, G., 2011), thus ending in excessive brain atrophy, leading the patient to death.

DISCUSSION

Therefore, I conclude that the mechanisms of age and genetic factors presented in this article, the APP, the TAU protein and, mainly, the demyelination of the myelin sheath, may, due to the harm caused by advanced age to the structural composition of the myelin sheath, be determinant agents for the promotion of AD. These agents were extremely relevant for the current article, given the possibilities of presenting a high tendency to modify synaptic plasticity due to the fact that synaptogenesis is reduced in elderly patients and that the decrease in iron concentration in the intracellular environment is also reduced in patients with advanced age, resulting, in both cases, in a loss in the structural integrity of the myelin sheath and in the increased susceptibility of possible degradations to this important component neuronal, thus ending the patient in a progressive encephalic atrophy, leading him, for this reason, to death.

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