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Alzheimer's disease in Brazil: the influence of sex on the mortality profile

Abstract

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, and a leading cause of mortality in developed countries. It is essential that healthcare professionals know in more detail the mortality profile of this dementia so that they can offer a better quality of life to patients. The general objective of this study was to evaluate the AD mortality profile in Brazil, from 2010 to 2019, and the influence of sex and gender on this profile. This study is descriptive in nature with a quantitative approach, using secondary data, and during the presentation of this data, information reproduced by scientific articles on the topic will also be presented. The data were collected from the Mortality Information System (SIM), created by the Information Technology Department of the Unified Health System (DATASUS). The bibliographic survey was carried out in the Scielo and Pubmed databases. We conclude that females present more accelerated cognitive decline compared to males, and there is also a genotypic issue involved. In this way, we can affirm that sex and gender influence the clinical progression of AD, providing opportunities for measures to be taken early regarding these data, such as public health policies to combat AD.

Keywords: alzheimer´s disease, gender identity, mortality registries, prevalence, sex

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, and currently one of the leading causes of mortality in developed countries. It is a progressive and fatal neurodegenerative disorder, which is evidenced by cognitive and memory deterioration, with consequent progressive impairment of the patient's daily activities, and a range of neuropsychiatric symptoms and behavioral changes. The disease generally sets in insidiously. The etiology of Alzheimer's disease remains undefined, although considerable progress has been made in understanding its biochemical and genetic mechanisms.[1] The main mechanism of Alzheimer's disease pathogenesis is the accumulation of two substances, amyloid beta protein (Aβ) and tau protein, in certain regions of the brain, probably due to excessive protein production and defective removal.[2]

The question to be assessed is whether in the pathophysiological process of Alzheimer's Disease, the impairment caused by the accumulation of the proteins amyloid beta protein (Aβ) and tau protein, can occur with greater or lesser prevalence depending on gender or sex. Is there any predisposition among men and women, especially elderly people, for the manifestation of the neurodegenerative process in Alzheimer's dementia?

Material and methods

The collection of secondary quantitative data was carried out through the Mortality Information System (SIM), created by the Information Technology Department of the Unified Health System (DATASUS). Data were collected according to sex and respective year, in a time interval between 2010 and 2019. The search in the Mortality Information System was carried out in accordance with the International Classification of Diseases and Related Health Problems (ICD-10), using category G30, which corresponds to Alzheimer's disease (AD). There was also a bibliographical survey of articles that address Alzheimer's disease, its characteristics, risk and rotective factors, with the aim of comparing the quantitative data with the hypotheses raised by the articles, in order to verify whether the Brazilian profile of Mortality due to the pathology in that period coincides with the conclusions outlined in the academic articles analyzed. The search was carried out using the following descriptors: Alzheimer's disease, gender, mortality, elderly, prevalence. The inclusion criteria were working with scientific articles published in Portuguese or English, and that were correlated with deaths from Alzheimer's disease in Brazil and gender prevalence. Preference was given to publications from the last ten years.

Results

Initially, 54 scientific articles were selected, of which only 42 were used in this review. The clinical diagnosis of Alzheimer's disease is based on a syndromic assessment of dementia, however, the definitive diagnosis can only be obtained through necropsy or biopsy, with the identification of an appropriate number of plaques and neurofibrillary coils in specific regions of the brain, which is, however, not recommended in clinical practice. Although there are still no curative treatments for Alzheimer's disease, there are treatments available whose purpose is to provide the patient with a more dignified quality of life, seeking a long-term improvement in the neurological and behavioral changes associated with the disease.[3] Drug treatment currently includes esterase inhibitors and memantine (a glutamate antagonist), and monotherapy or a combination of both strategies can be used.

Alzheimer's disease has been increasingly present in the Brazilian medical scene. While 10,841 deaths from this pathology were recorded in Brazil in 2010, the value recorded in 2019 was 23,150 deaths, which represents an increase of 113.5% in the number of deaths in this period, demonstrating the growing presence of the disease. And, when analyzing mortality from Alzheimer's disease according to the sex of individuals, there is a relevant disparity between men and

women. Of a total of 164,976 deaths between 2010 and 2019, 106,485 were female (DATASUS, 2020)41, which corresponds to 64.54% of these deaths. The disparity between the sexes may be related to the greater longevity normally presented by females, since age is a well-established risk factor for AD. However, studies are looking for other additional factors that could explain such a difference. Table 1 shows the total number of male and female deaths from 2010 to 2019 (Table 1).

Table 1 Total deaths, deaths by sex, and percentage of deaths corresponding to females, from 2010 to 2019, due to Alzheimer's disease

Year	Total deaths	Male deaths	female deaths	% of female deaths
2010	10.841	3.888	6.953	64,14%
2011	11.957	4.314	7.643	63,92%
2012	13.142	4.675	8.466	64,42%
2013	14.015	4.973	9.041	64,50%
2014	15.718	5.495	10.219	65,01%
2015	17.306	6.03	11.273	65,14%
2016	18.409	6.574	11.835	64,29%
2017	19.844	6.968	12.873	64,87%
2018	20.594	7.287	13.305	64,60%
2019	23.15	8.269	14.877	64,26%

There is a growing amount of evidence that gender affects the etiology, clinical presentation, and treatment of several diseases, including Alzheimer's disease. The term gender (sex) refers to the biological and physiological differences between men and women, related to sex chromosomes (XX vs. XY) and gonadal hormones; factors that contribute to differences at cellular, organic, and systemic levels between men and women. The term gender, in contrast, refers to a combination of environmental, social and cultural influences on biological factors. An individual's gender has its roots in biology but is shaped by the individual's environment and sociocultural experience. Women are subject to risk factors for the development and progression of Alzheimer's disease related to sex and gender. Menopause and hormone replacement therapy are examples of sex-related factors, while inequality of access to education is an example of a gender-related factor. Such sex and gender differences should be better understood and measured when analyzing the epidemiology, clinical presentation and course of Alzheimer's disease, in order to expand the development of treatments and intervention measures.[4]

Between 2010 and 2019 there was a significant increase in the number of deaths from AD in females (Figure 1), and researchers have sought to find an explanation for this phenomenon. Probably life expectancy can confirm this disproportion between genders (Figure 1).

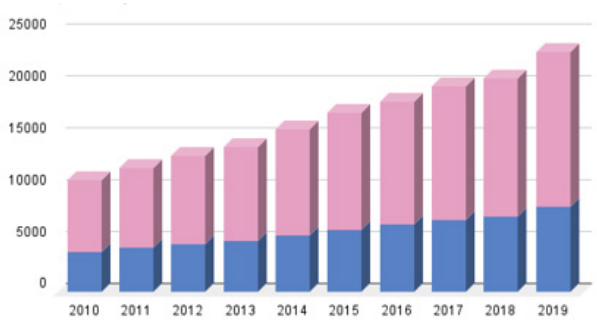

Figure 1 Mortality from Alzheimer's disease, from 2010 to 2019. Color pink represents the female gender, and the blue color represents the male gender.

Discussion

There are few scientific articles that address the incidence of Alzheimer's disease in the Brazilian population and also the impacts of this pathology on the national health system, the SUS (unified health system). Most of the articles analyzed in the bibliographic survey were, therefore, by foreign authors, analyzing the characteristics of Alzheimer's disease and its impact on populations from countries other than Brazil. An important factor that contributes to this difference between the sexes is the greater longevity shown by women. Advanced age is the strongest risk factor for the onset of AD, and there are more women living at an advanced age than men. In 2018, life expectancy at birth for females was 79.9 years, while life expectancy at birth for males was 72.8 years, according to IBGE. However, longevity alone does not explain the higher frequency of Alzheimer's disease cases among women and the greater risk of developing the disease.42. Depression can be a symptom of Alzheimer's disease in older individuals, but it is believed that depressive conditions throughout adulthood increase the risk of developing AD by up to 70%. Women have twice the risk of developing depression than men, a difference between the sexes that begins at puberty and intensifies during the menopause period.[4–9]

The concept of cognitive reserve refers to differences between individuals in how tasks are performed, which may allow some people to be more resilient to brain changes than others, suggesting that certain experiences in a person's life may decrease risk of dementia. Epidemiological studies suggest that life experiences, including academic and professional achievements, and leisure activities, can increase cognitive reserve.[10] In the last century, women have had fewer opportunities to access higher education and professional achievement, therefore, fewer opportunities to increase their cognitive reserve. As a result, women are much more affected by this risk factor than men.[4]

There are studies that propose menopause as a female-related risk factor for Alzheimer's disease. The concept has been proposed that perimenopause is a state of bioenergetic transition characterized by a decline in mitochondrial activity and a shift in energy source from glucose to lipids, which may result in brain remodeling, loss of synaptic spines, and neurodegeneration. Supporting this proposal are neuroimaging data demonstrating that, compared to premenopausal women, perimenopausal and postmenopausal women experience reductions in glucose metabolism like that caused by Alzheimer's disease.[4,11–18] Regarding hormone replacement therapy after menopause, studies suggest that starting hormone therapy at an older age may have adverse consequences. Observational data show that women who started hormone therapy shortly after menopause or at a younger age have a lower risk of AD than women who started hormone therapy later.[4,19–23]

There is also the issue of diagnostic tests, which may not be suitable for an early diagnosis of AD in females. The most frequently used tests to diagnose Alzheimer's disease are those of verbal memory, such as memorizing lists of words, for example. However, there is a female advantage in verbal memory, which may be partially explained by steroid hormones such as estradiol. Studies from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort show a female advantage in verbal memory, not only during normal cognitive aging, but also during mild cognitive impairment, even if women present levels of impairment due to the disease (hippocampal atrophy, cerebral hypometabolism, deposition of Aβ) similar to that of a man. In advanced stages of the disease, this female advantage has been eliminated. Therefore, these findings may indicate that the female

advantage in verbal memory acts as a form of cognitive reserve, allowing women to maintain cognitive performance in the early stages of the disease. This female advantage can be functionally useful, however, it can delay the diagnosis of mild cognitive impairment, so that patients already have more severe impairment by the time they are finally diagnosed, limiting the opportunity for early intervention. Furthermore, if women are, in fact, diagnosed at a more advanced stage than men, they can be expected to deteriorate more quickly.[4,24–30]

The ε4 allele of the APOE gene is a major genetic risk factor for Alzheimer's disease, and is associated with abnormal accumulation of the Aβ protein. The apoE protein is involved in the transport of cholesterol and other lipids in the peripheral region of the brain, and it has been shown that the apoE4 protein is less effective in the clearance of Aβ and contributes to a diminished response to neuronal injury when compared to the apoE2 and apoE3 proteins. Although the mechanisms underlying the interaction between sex and APOE genotype remain unclear, research suggests that women with the APOE ε4 genotype may experience higher rates of Alzheimer's disease, greater impairment of brain integrity, and accelerated longitudinal decline at a given level of age evolution of the disease. Women who carry the ε4 allele had an increased risk of progression on the Clinical Dementia Rating scale when compared to men with the ε4 allele and also to ε4-negative women (i.e., women who do not carry the allele). Several studies have shown that women with the APOE ε4 genotype showed faster cognitive decline than men of any APOE genotype and also than ε4-negative women. Therefore, such data suggest that the APOE ε4 allele interacts with the sex of individuals, influencing the risk of dementia due to Alzheimer's disease.[4,31–40] There are many studies being carried out in search of more assertive diagnoses for Alzheimer's disease, one of which is through saliva.[41–43] Age is the most important factor,[43,44] although gender also deserves to be assessed, given the higher prevalence of AD in females.

Conclusion

Therefore, it is concluded that sex and gender can influence the risk of development, clinical presentation, and progression of Alzheimer's disease. Therefore, considering such sex and gender differences represents an opportunity to increase early diagnosis rates among female patients and to improve disease treatment according to the individuals' sex. It is important that health professionals, especially those working in Primary Care, know the morbidity and mortality profile of the pathology, so that they know how to identify which population subgroups are more predisposed to developing the disease, and can apply appropriate diagnostic tests for each subgroup.

For example, develop and apply early diagnostic tests that do not involve verbal memory for female patients, as there is an advantage of this in relation to verbal memory, which can delay diagnosis, limiting the opportunity for early intervention. Considering sex and gender differences in Alzheimer's disease is a strategy that must be implemented in health care, as it represents an opportunity to improve the diagnosis, management, assessment of progression, and treatment of the pathology.

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Conflicts of interest

The authors declare to have no conflict of interest.

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