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Alzheimer's Disease: Learning From the Past, Looking to the Future

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Abstract

Our understanding on the pathophysiology and clinical aspects related to Alzheimer's Disease (AD) have been largely improved since the first case recorded in the medical literature in the beginning of the 20th century. Regarding the age of onset of AD, an important change seems to have happened in the last century: from several AD cases reported in middle aged and young adults in the first half of the 20th century, the age of onset of AD seems to have increased at the end of that century and the beginning of the 21st century. Since the 1-century-long time interval is very narrow to make a hypothesis on a genetic modification, it is possible that modifiable risk factors of AD played a role in increasing the age of onset of AD. Although the exact etiology of AD remains unknown, experts currently agree that it is multifactorial, being the result of complex interactions among genetic, environmental and lifestyle factors, such as physical activity, nutrition, and smoking. In the present article, we briefly discuss how lifestyle trends in the last century may have contributed to the increase in the age of onset of AD, and propose future directions for research on AD and lifestyle factors.

Keywords

Alzheimer, historical approach, lifestyle behavior, secular trends

Alzheimer's disease (AD) was first reported in the medical literature more than 1 century ago. Since then, our understanding on the pathophysiology and clinical aspects related to this disease has been largely improved. However, several points remain to be clarified, especially with regard to the etiology of AD. Although the exact etiology of AD remains unknown, experts currently agree that it is multifactorial, being the result of complex interactions among genetic, lifestyle, environment, and contextual (eg, accidents with head injury) factors. In this article, we try to gather information about the history of AD, some particularities with regard to possible temporal changes in the presentation of this disease and secular changes in societal lifestyle behaviors; this text is intended to open new perspectives for future basic and clinical research on AD.

Between 1901 and 1906, Alois Alzheimer, a German physician, followed the intriguing medical case of Mrs Auguste D, aged 51 years at the moment of her first consultation with Dr Alzheimer. The main symptoms of Mrs Auguste D were reduced comprehension and memory, aphasia, and disorientation; memory declines will rapidly become the clinical hallmark of dementias during the 20th century. Histopathological examination of Mrs Auguste D's brain evidenced amyloid plaques and neurofibrillary tangles. In the next decades after the reporting of Auguste D's case, increasing scientific literature reported cases of patients with AD (most of them with histopathological examination to confirm AD diagnostic). Intriguingly, most of the case reports and observational studies involved middle-aged (<60 years) and young older (between 60 and 65 years) patients. Illustratively, in a necropsy-based study developed in 1958 among 17 people with AD, Letemendia and Pampiglione indicated that the average age of AD onset was 52 years (oldest age at 60 years). Even in the study by Woodard[1] in the middle 60s, a large necropsy-based study that clearly showed an association between AD prevalence and increasing age, around 10% of people with AD had developed the disease before the age of 60 (see "TEXT-FIG.1" in Woodard's original publication[1]), which seems to be a very high prevalence of the disease we currently consider as "early-onset dementia" (in 2012, only 4% of American people with AD were <65 years[2]). Although these data are only anecdotal, they suggest that an important change in the presentation of AD occurred during the 20th century (more visible after the 70s); the age of onset of AD seems to have increased. Assuming that such a change really happened and considering it as a health improvement, since the 1-century-long time interval is very narrow to make a hypothesis on a genetic modification, we would be seduced to search the answers on modifiable risk factors for AD, especially changes in lifestyle behaviors during 20th century.

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Since 2011, the Alzheimer's Association included in their annual report,[2] as risk factors for developing AD, "cardiovascular disease risk factors", such as physical activity and exercise (PA/E), nutrition, high cholesterol, and smoking. The association between cardiovascular disease and AD was probably known by physicians in the first half of the 20th century (McMenemey[3] indicated, about a AD case report [McMenemey's case 1] in a publication from 1940 "The interesting factors are the atherosclerosis of the aorta, coronary arteries, renal arterioles, and, to some extent, of the vessels of the brain"). However, one could argue that there is a potential problem with a theory that tries to associate the increase in the age of onset of AD (which can be considered as an important improvement) with secular changes in lifestyle behaviors; secular trends in lifestyle behaviors in the 20th century would theoretically lead to a worsening rather than an improvement in the presentation of AD. Indeed, temporal trends in smoking, PA/E, and nutrition showed that during the 20th century (1) the percentage of Americans who had never smoked decreased[4]; (2) the total PA/E-related energy expenditure of Americans remained mostly unchanged for adults and seems to be decreased among children and adolescents[5]; and (3) energy intake increased.[6] Therefore, based on this information one may be tempted to indicate that changes in lifestyle behaviors did not contribute to the increase in the age of onset of AD observed during the last century.

However, the relationship between lifestyle behaviors, other risk factors of AD, and AD presentation is certainly more complex than we may examine by these data trends. For example, a more comprehensive analysis on the potential role of PA/E on the etiology of AD shows us the following: at the epidemiological level, studies have demonstrated that PA/E delays onset of AD; at the tissue and cellular levels, exercise improves total brain and hippocampus volume, blood flow and brain architecture, and stimulates neurogenesis and cell survival (particularly in the hippocampus).[7] These benefits of PA/E are at least partially explained by PA/E effects at the molecular level; exercise increases the production and release of insulin growth factor 1, vascular endothelial growth factor, and brain-derived neurotrophic factor, all of them being associated with angiogenesis and/or neurogenesis and cell survival.[7] However, the possible impact of PA/E, as it is probably the case for other lifestyle behaviors, on the etiology and progression of AD is not simple to disentangle; interactions between PA/E and other aspects can change the physiological responses induced by PA/E.[7] Animal models have shown that exercise reversed the negative effects of fat diet on the neuronal plasticity at the hippocampus, which suggests the presence of a possible molecular mechanism by which lifestyle factors can interact at a molecular level. Moreover, exercise stimulated neurogenesis in rodents that exercised in group but not in isolated rodents that exercised individually, suggesting that exercise interacts with social experiences to impact brain's health. It is noteworthy that although secular trend studies in American adults showed no differences in PA/E levels during the 20th century, Americans have reduced occupational PA and increased PA/E at leisure time[5]; it is plausible to think that more pleasurable PA/E, which are more easily related to leisure time activities (in general sports practice or exercise training), would be more effective and promote more frequent and richer social contacts than occupational PA, thus improving the effects of PA/E on brain's health. This kind of detailed analysis on lifestyle secular trends may also be done for the other behaviors (eg, although energy intake increased, the percentage of fat in Americans' diet reduced[6]; high-fat diet is associated with reduced brain-derived neurotrophic factor and then reduced hippocampal plasticity).

In summary, it is likely that physiological mechanisms induced by certain lifestyle behaviors play an important role in the etiology of AD. Due to the difficulty of translating basic animal models to human research, longitudinal within-subject studies in large samples would bring about important information on etiological mechanisms AD, especially if the measures of AD biomarkers as well as individuals lifestyle behaviors are available; however, this kind of study will take long time before having conclusive results. At the meantime, investigating AD biomarkers cross-sectionally in selected populations, such as very old age regular runners/swimmers and age-matched lifelong sedentary people or very old long time smokers and age-matched never smokers, as well as the interactions among selected populations (eg, old age runners and smokers, runners nonsmokers, etc), would also shed light on this topic; following those populations up to autopsy when possible would also be relevant.

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