Journal of Alzheimer's Disease 91 (2023) 923–924
DOI 10.3233/JAD-230016
IOS Press



Editorial

# Alzheimer's Disease: Not Just for the Aged?

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Pre-press 23 January 2023

Age is critical in diagnosis of Alzheimer's disease (AD). Since the first AD case was reported in 1906 [1], it is widely recognized that AD occurs mainly in the elderly, and the pathogenic gene mutation carriers, including presenilin-1 (*PS1*), presenilin-2 (*PS2*), and amyloid precursor protein (*APP*), always present with much earlier onset age than sporadic AD patients. Such phenomenon is more obvious in the cases with very early onset age, which is supported by the fact that almost all the previously reported patients (<30 years) had pathogenic mutations, and the youngest onset age was 21 among them [2]. For sporadic AD, *APOE* allele ε4 is the most important genetic risk factor, which is associated with earlier age of onset [3]. However, it is the first time to report a 19-year-old young adult diagnosed with probable AD, without the above known pathogenic gene mutations or *APOE* ε4 allele [4]. Such a very early-onset AD without any genetic background inspired my great interest and further thinking of the conventional perspective, pathogenic mechanisms, and limitations of current technologies of genetic testing in the field of AD.

The patient reported in this study [4] mainly presented with memory decline, especially episodic memory loss, supported by the results of the Wechsler Memory Scale and World Health Organization-University of California Los Angeles Auditory Verbal Learning Test. Furthermore, cerebrospinal fluid (CSF) biomarkers showed a decrease in the $A\beta_{1\text{-}42/1\text{-}40}$ ratio, an increase in p-tau, and mild atrophy in bilateral hippocampus, as indicated by brain MRI scans, all of which met the diagnostic criteria for AD. However, some results do not conform with the recent AD diagnostic criteria proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) [5] and the International Working Group [6], such as negative PET results. I agree with the authors' view that this phenomenon is not enough to rule out the diagnosis of AD. As the authors described in the discussion section, divergent forms of amyloid and tau, the accuracy of the PET itself, young age, and fast metabolism related issues should be considered comprehensively to explain the reason for negative PET results, especially for such a young patient. Furthermore, either PET or CSF can be used to verify amyloid pathology, and they are not always consistent. Even in AD patients, PET scans are not 100% positive [7]. The cut-off values for each biomarker are yet to be established using large cohort studies for different ethnic groups. The authors finally make a diagnosis of AD and I personally think is reasonable.

AD is a neurodegenerative disease and tends to occur in the elderly. Though autosomal dominant early-onset AD (EOAD) accounts for only 10% of all EOAD cases [3], it is rare that EOAD without known pathogenic gene mutations occurs earlier than 30 years old. The etiology of sporadic EOAD is still unclear, though it is generally held that most of them are predominantly polygenic. Furthermore, it is confusing if and how it is distinct from late-onset AD (LOAD), though many hypothesize that it is just an extreme case of LOAD with accumulation of related

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ISSN 1387-2877/$35.00 

variants (e.g., *SORL1*, *TREM2*, *ABCA7*, *APOE*) or the presence of unknown genetic or environmental factors (e.g., stroke, brain trauma, chronic stress, depression) [8, 9].

This case report has some limitations that should be pointed out. Although this patient can be considered positive for AD, the possibility of genetic mutations cannot be ruled out. With advances in gene detection technology and analysis ability, we may find novel pathogenic mutations in yet unknown genes or *de novo* mutations. Long-term follow-up of the patient is needed to further support the diagnosis. In addition, compared with patients diagnosed with AD in the traditional sense, longitudinal changes of memory impairment and response to drugs of the patient reported in the study need further attention and research. Memory impairment in young adults is a complex disorder influenced by genetic factors (e.g., pathogenic or risk gene mutations, epigenetics) [8, 9], environmental factors (e.g., exposure of lead) [10], and unhealthy lifestyle (e.g., unhealthy diet, alcohol misuse, smoking, physical inactivity) [11].

Taken together, this is a very interesting case, and no one in the world has reported such an early AD case without known pathogenic gene mutations previously, which attracts widely attention to AD in young people.

## ACKNOWLEDGMENTS

The author has no acknowledgments to report.

## FUNDING

The author has no funding to report.

## CONFLICT OF INTEREST

George Perry has equity in Synaptogenix and is an advisor for both Synaptogenix and Nervgen. The topic of this editorial does not overlap the area of consulting. He is also the Editor-in-Chief of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

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