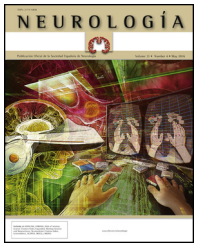
Neurología. 2016;xxx:xxx—xxx

SOCIEDAD ESPAÑOLA DE NEUROLOGIA

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW ARTICLE

Early- and late-onset Alzheimer disease: Are they the same entity?☆

P. Tellechea[a], N. Pujol[a], P. Esteve-Belloch[a], B. Echeveste[a], M.R. García-Eulate[b], J. Arbizu[c], M. Riverol[a,*]

[a] *Departamento de Neurología, Clínica Universidad de Navarra, Pamplona, Navarra, Spain*
[b] *Departamento de Radiología, Clínica Universidad de Navarra, Pamplona, Navarra, Spain*
[c] *Departamento de Medicina Nuclear, Clínica Universidad de Navarra, Pamplona, Navarra, Spain*

Received 30 April 2015; accepted 14 August 2015

KEYWORDS
Alzheimer disease;
Early-onset;
Late-onset;
Neuropsychology;
Neuropathology;
Neuroimaging

Abstract Early-onset Alzheimer disease (EOAD), which presents in patients younger than 65 years, has frequently been described as having different features from those of late-onset Alzheimer disease (LOAD). This review analyses the most recent studies comparing the clinical presentation and neuropsychological, neuropathological, genetic, and neuroimaging findings of both types in order to determine whether EOAD and LOAD are different entities or distinct forms of the same entity. We observed consistent differences between clinical findings in EOAD and in LOAD.

Fundamentally, the onset of EOAD is more likely to be marked by atypical symptoms, and cognitive assessments point to poorer executive and visuospatial functioning and praxis with less marked memory impairment. Alzheimer-type features will be more dense and widespread in neuropathology studies, with structural and functional neuroimaging showing greater and more diffuse atrophy extending to neocortical areas (especially the precuneus). In conclusion, available evidence suggests that EOAD and LOAD are 2 different forms of a single entity. LOAD is likely to be influenced by ageing-related processes.

PALABRAS CLAVE
Enfermedad de Alzheimer;
Inicio precoz;
Inicio tardío;

Enfermedad de Alzheimer de inicio precoz y de inicio tardío: ¿son la misma entidad?

Resumen La enfermedad de Alzheimer de inicio precoz (EAIP), definida como la que se manifiesta antes de los 65 años de edad, muestra ciertas características diferentes de la enfermedad de Alzheimer de inicio tardío (EAIT). Nuestro objetivo fue analizar los trabajos más actuales que

☆ Please cite this article as: Tellechea P, Pujol N, Esteve-Belloch P, Echeveste B, García-Eulate MR, Arbizu J, et al. Enfermedad de Alzheimer de inicio precoz y de inicio tardío: ¿son la misma entidad? Neurología. 2016. http://dx.doi.org/10.1016/j.nrl.2015.08.002

* Corresponding author.
E-mail address: mriverol@unav.es (M. Riverol).

Neuropsicología;
Neuropatología;
Neuroimagen

comparan la clínica, la neuropsicología, la patología, la genética y la neuroimagen de la EAIP y la EAIT, para determinar si nos enfrentamos a dos enfermedades distintas o a variantes de una misma entidad. Como resultado, hallamos consistencia en algunas características diferenciales entre los 2 cuadros clínicos. Fundamentalmente, la EAIP comienza con mayor frecuencia con una clínica atípica; la valoración cognitiva muestra mayor afectación de las funciones ejecutiva y visuoespacial y de las praxias, y menor afectación de la memoria; la neuropatología evidencia mayor densidad y una distribución más difusa de la patología tipo Alzheimer; los estudios de neuroimagen estructural y funcional muestran una afectación cortical mayor y más difusa, afectando al neocórtex (especialmente el precuneus). En conclusión, las evidencias actuales hacen pensar que la EAIP y la EAIT son variantes clínicas de una misma entidad, que en el caso de la EAIT se ve influida probablemente por factores asociados al envejecimiento.

Introduction

Alzheimer disease (AD) is the most frequent neurodegenerative disease. It presents clinically as progressive dementia that predominantly affects episodic memory.[1] Age is the main risk factor for developing AD, and in fact, prevalence of the disease is higher in older segments of the population. AD is the most frequent cause of dementia and accounts for approximately 60% of the total cases, whether before[2] or after the age of 65,[3] the age marking the arbitrary limit between early-onset and late-onset dementia.

In 1907, Alois Alzheimer described the disease now bearing his name today in a 51-year-old woman who had developed dementia with predominant language impairment and behavioural changes.[4] For years, this syndrome of early-onset dementia without amnesia was thought to define AD and distinguish it from senile dementia, which was characterised by a later onset and symptoms of amnesia and attributed to the ageing process. However, in the 1960s and 1970s, studies showed that the neuropathology underlying early-onset and senile dementia was the same; as such, both clinical variants are produced by the same disease, AD.[5,6] From that time on, once the clinical criteria for an AD diagnosis had been established, doctors were more likely to recognise the senile onset form[7] since it was far more common, while the other 'atypical' early-onset variant was almost forgotten. However, a number of recent studies have underlined the clinical heterogeneity of AD and investigated its underlying causes.

This review aims to present the similarities and differences between early-onset AD (EOAD) and late-onset AD (LOAD) with regard to the clinical features, neuropsychology, neuropathology, genetics, and neuroimaging features described to date. This will serve to clarify if there are indeed 2 different entities or 2 clinical variants of the same disease.

Clinical presentation

The most common initial clinical presentation of AD is episodic memory loss, which is accompanied by progressive impairment of other cognitive domains. Nevertheless, some patients present alterations in other cognitive areas and memory remains relatively well preserved. AD may even present as a 'focal' syndrome in which the predominant symptom is apraxia or an impairment of language, visual function, or visuospatial reasoning. This wide array of cases illustrates the heterogeneous clinical presentations of AD, and this results in major challenges and frequent diagnostic errors.[8] Some such 'atypical' syndromes can easily be mistaken for other entities, such as frontotemporal dementia (FTD), when executive or language dysfunctions are dominant; or corticobasal degeneration, when there are signs of corticobasal syndrome. Assigning the correct diagnosis to 'focal' syndromes of AD (especially when ruling out FTD in the differential diagnosis) will involve detecting any temporal lobe and posterior hemisphere symptoms (amnesia, visuospatial dysfunction) on the one hand, and on the other, verifying whether the focal deficits in these syndromes seem to be less selective (and profound) than those in FTD. Here, an exhaustive neurological examination will reveal deficits in other cognitive domains and those affecting multiple functional systems within a single domain (for example, phonology, spelling, and syntax within language).[9]

In light of this heterogeneous array, some authors have attempted to facilitate diagnosis by elaborating classification systems for specific AD subtypes: the typical form (memory loss with other deficits) and the temporal variant (with isolated memory loss) are late-onset syndromes. In contrast, the left/language variant (a nonfluent aphasia), progressive logopenic aphasia (with preserved fluency and predominant repetition deficit), right/visuoperceptive variant (including posterior cortical atrophy, which is almost always due to AD) and the frontal/executive variant are early-onset syndromes.[10] Using a similar approach, another study grouped AD patients in 3 categories: those with frontal lobe dysfunction, very early onset, and a family history; another with primarily posterior deficit (temporoparietal and/or occipital lobes) and early onset, and a third group with predominantly temporal lobe dysfunction in elderly patients.[11] Lastly, current diagnostic criteria for AD describe a typical amnestic presentation and other non-amnestic presentations, including those with predominant deficits in language, visuospatial function, and executive functions.[12]