Alzheimer's Disease and Treatment

Neuroimaging and Neuropsychological differences between Early-Onset Alzheimer and Late-Onset Alzheimer

Corresponding Author: Francesco Sciancalepore

Memory Clinic, Department of Neurology and Psychiatry, Sapienza University, Viale dell'Università, 30, 00161 Rome, Italy.

Email: sciancalepore.1679543@studenti.uniroma1.it

Introduction

Alzheimer's Disease (AD) represents the most known and widespread neurodegenerative disorder. Every day neurologists diagnose a new AD case and current estimates suggest that over 46 millions of people live with this dementia worldwide [1].

The AD history started in 1901 when Alois Alzheimer observed a patient named Auguste Deter; a 51-year-old woman with strange behavioral symptoms and memory impairments. The woman showed symptoms as memory loss, confusion, language impairment and unpredictable, agitated, aggressive and paranoid behaviour. Only five years later, when the patient passed away, neuropathology revealed neuritic plaques and neurofibrillary tangles consistent with what became known as AD. This form of dementia was initially characterized as a neurodegenerative disorder presenting in early life or midlife, with onset at younger than 65 years of age [2]. In fact, August Deter was a middle-aged woman when the first symptoms appeared. Nevertheless, in the late 1960s and early 1970s, investigators stressed the presence of similar neuritic plaques and neurofibrillary tangles in elderly individuals with dementia, thus shifting the AD focus to the far-larger numbers of patients with Late-Onset AD (LOAD) [3].

Nowadays, the main focus of interest and research has been on LOAD; however, like Auguste Deter, subjects with Early-Onset AD (EOAD) remain an important and impactful subgroup of patients with this disorder.

EOAD is defined as AD with clinical onset younger than 65 years of age and it is the most common cause of early-onset

neurodegenerative dementia [4]. Differently, LOAD refers to a form of AD in which symptoms occur after 65 years of age. At the same time, EOAD is not just LOAD occurring at a younger age, but a form of AD deeply different from the other in many aspects. For instance, EOAD differs from LOAD for the higher genetic predisposition [5]; moreover, patients with EOAD exhibit a greater risk for mortality [6] and have a longer duration of the disease before diagnosis (about 1.6 years) [7]. Additionally, several studies indicate that patients with EOAD have a potentially more aggressive clinical progression [8]. Furthermore, although these two forms refer to a single disease, many studies also report several neuroimaging and neuropsychological differences.

Neuroimaging differences

The characteristic neuropathological findings of AD are the extracellular deposition of senile- amyloid plaques and intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein. Amyloid plaques' deposition does not always follow a stereotypical pattern of progression, but often develops in the isocortex and only latterly affects subcortical structures. Neurofibrillary tangles, on the other hand, begin by affecting the transentorhinal region progressing to the limbic system and finally to the neocortex [9].

In accordance, it is important to underline that neurophysiological pattern of AD is correlated with the clinical manifestations. For this reason, since EOAD and LOAD often present different clinical features, the associated cerebral pathways also exhibit significant differences.

Temporal lobe and default mode network

The human Medial Temporal Lobe (MTL) is critically involved in episodic memory. At the same time, MTL is vulnerable to accumulation of AD amyloid plaques and neurofibrillary tangles [10,11]. MTL is a non-homogeneous brain structure which consists of several subregions, including the hippocampus and substructures along the parahippocampal gyrus. Neuroimaging studies of spontaneous fluctuations in Blood Oxygen Level-Dependent (BOLD) signal, measured by resting-state functional MRI, have consistently found that the MTL forms a crucial subsystem in the Default Mode Network (DMN), linking it with regions such as the precuneus, posterior cingulate cortex, lateral inferior parietal cortex and medial prefrontal cortex [12,13]

AD does not uniformly affect all MTL subregions. In the earliest disease stage, the neurofibrillary tangles mostly affect the medial portion of the collateral sulcus (part of perirhinal cortex) and can in later stages be found in entorhinal cortex and hippocampus [10]. In later disease stages, when tau pathology progresses towards large portions of the hippocampus and to more widespread lateral and posterior cortical areas, decreases in MTL-Posterior Medial (PM) connectivity are likely to emerge [10].

Functional neuroimaging studies have demonstrated significant cortical atrophy, hypoperfusion, and hypometabolism in EOAD in lateral temporal cortices, and significant lesions or hypometabolism in medial temporal and hippocampal regions in LOAD [14-16]. Accordingly, EOAD exhibit a diffuse neocortical atrophy with greater loss in posterior cortical midline structures (precuneus, middle and posterior cingulate) while atrophy is predominant in hippocampal regions in LOAD patients [15,17]. Several studies [18-21] found a more severe hippocampal and amygdala atrophy in LOAD than EOAD when compared to controls. Moreover, amygdala atrophy seems to be correlated with hippocampal atrophy in LOAD but not in EOAD, and more strongly in the left hemisphere, supporting the view that LOAD forms are more associated than EOAD with involvement of MTL structures.

Also, in the Anterior-Temporal Network (ATN), LOAD shows a decreased functional connectivity, especially in the posterior regions. By contrast, increased and extended connectivity of the ATN was found in EOAD, additionally involving fronto-insular regions [22].

Nevertheless, a similar functional connectivity pattern was found in the DMN. In fact, several studies [22,23] revealed that DMN connectivity was similarly reduced in both patients' groups, despite a highly distinctive pattern of structural changes, involving in particular the posterior part of the DMN in EOAD. Since has been suggested that DMN dysfunction could be tightly linked to amyloid deposition in AD [24], the identical changes of functional connectivity within the DMN in EOAD and LOAD could be explained by the vulnerability of this network to amyloid deposition likely to be similar in the two patients' groups, both in terms of topography and severity [22].

Frontal and parietal networks

Several structural and metabolic neuroimaging studies focusing on the effect of age in AD reported greater dysfunction of frontal and parietal networks in EOAD, in comparison with the late onset form of the disease [14,16,17,25]. Using FDG-PET, Kalpouzos et al. [26] found a specific frontal and inferior parietal hypometabolism in EOAD relative to LOAD patients. Other studies showed a greater reduced connectivity of a fronto-parietal executive network in EOAD patients, with a behavioral impact on executive functioning. On the other hand, LOAD exhibited an increased connectivity within the frontal networks [27]. In addition, on FDG-PET, the EOAD patients, compared to the LOAD patients, often exhibit lower metabolic activity in the parietal (left worse than right) lobes. Other studies indicate a significant parietal lobe impairment along with additional changes in other neocortical regions in EOAD than LOAD [16].

The dorsolateral frontal cortex has dense connections with the parietal lobe; a network that has been implicated in tasks of executive functioning [28], especially in EOAD [29]. There is an increasing understanding that cognition is a product of these networks and tracts, and investigations of white matter pathways indicate disruption of important parietal lobe-dorsolateral frontal tracts in AD, especially in EOAD [28]. Early involvement of the parietal lobe in EOAD would affect grey matter as well as its main dorsolateral frontal networks. Accordingly, in a study [30] a lower metabolic activity in the dorsolateral frontal regions was found in EOAD compared to LOAD. Also, a study for longitudinal changes in cortical thickness showed greater thinning in the dorsolateral frontal and inferior parietal lobule in EOAD than in LOAD [18].

Moreover, it was demonstrated that white matter atrophy in EOAD is mainly centred on the posterior and medial parietal areas, including the connections of posterior cingulate region [31]. In accordance, the involvement of medial parietal areas is considered an element of peculiarity of EOAD, distinguishing it from other early non-AD neurodegenerative diseases [32].

In conclusion, these findings suggest differences in AD-pathophysiology between EOAD and LOAD; a notion that has been debated since Auguste Deter was first encountered by Alois Alzheimer. The aforementioned studies report findings

about significant differences between EOAD and LOAD. Specifically, the results implicate the differential early involvement in parietal and frontal lobes. A possible explanation is that younger patients have a completely different distribution of neurofibrillary tangles. This could result in a different pattern of AD progression. In fact, in typical LOAD patients, the clinical progression often reflects an initial and significant impairment of temporal medial areas (as reported in the previous paragraph), while EOAD results from a significant early involvement of frontal and, mostly, of parietal areas [33].

As we will see in the next section, these different neurophysiological impairments lead to different neuropsychological alterations.

Neuropsychological differences

Several works have compared the neuropsychological profile of AD patients to establish if there are more affected cognitive domains in patients according to the age of onset of the disease. The majority of these studies have shown significant differences.

Memory

In general, studies show a greater involvement of this cognitive domain in patients with LOAD [34,35]. This is in accordance with neuroimaging findings that showed a larger MTL impairment in LOAD than EOAD. Furthermore, in some studies the memory seemed to be relatively preserved in early stages in individuals with AD compared to LOAD [36,37]. Specifically, a greater impairment of memory has been observed, both of recent events [36] and well-learned information [38] in the latter group of patients. Additionally, a worse temporal orientation was also observed in the group with LOAD [34,39] attributable to the greater loss of memory in this group of patients.

Other studies [26], instead, indicate a different qualitative affectation, predominantly a failure memory in the EOAD and a failure of the encoding in the LOAD. Moreover, a study [40] found that verbal anterograde memory was very impaired in EOAD and LOAD, but the degree of impairment was equivalent in both groups. In contrast, a specific pattern of memory dysfunction emerged, revealing that semantic memory was significantly more affected in the LOAD than in the EOAD group. A more detailed analysis of the patterns of semantic impairment revealed that LOAD patients showed a deeper semantic impairment than EOAD patients, affecting both free recall and semantic recognition [40]. However, this latter study reported that EOAD patients, while having a lesser degree of memory impairments, also show difficulties in this cognitive domain.

Overall, recent literature shows that there are distinct profiles of memory impairments associated with EOAD and LOAD. Contrary to previous studies which have reported a relative sparing of memory in EOAD [36,41], results of the current studies showed that EOAD patients presented an important verbal episodic memory impairment, similar to that found in LOAD patients [40]. Therefore, recent results do not support the view that EOAD patients show a remarkable preservation of memory in the early stage of the disease and develop difficulties at later stages of the disease [36]. Rather, they support the idea that the episodic memory impairment is present early in the disease process of EOAD, such as initially suggested by Delay and Brion [42]. This early impairment can be related to significant parietal dysfunctions in EOAD patients. In fact, the memory network is certainly mediated by the hippocampus but also by lateral and medial parietal regions [43], and degeneration of these latter regions could explain stark episodic memory impairments.

In summary, while presenting less memory impairments than LOAD subjects, studies suggest that EOAD patients can often exhibit episodic memory deficits.

Language

Patients with LOAD generally perform worse on visual confrontation naming tests, such as the Boston Naming Test [30,35]. Nevertheless, some studies found that, although the above result is true, the naming function deteriorates more quickly in EOAD [44]. Moreover, subjects with EOAD obtained lower performances in writing [35] and some studies reported more severe language impairment as a feature of EOAD [34,45]. In accordance, a study [18] revealed that EOAD patients showed more rapid cortical thinning than LOAD in the left hemisphere, including inferior frontal (Broca's area), superior temporal gyrus (Wernicke's area) and supramarginal gyrus. This involvement of language area is in agreement with the findings that suggest a more rapid decline in this cognitive domain for patients with EOAD. These findings are also consistent with studies that showed language disturbance more prevalent in EOAD than in LOAD patients, particularly in word comprehension and the rate of naming ability loss [44].

On the contrary, some studies [36,46,47] did not find significant differences between EOAD and LOAD patients in language domain.

The contradictory results are probably caused by different methods, in terms of the definition of diagnosis and language tests [48].

Executive functions

Given the greater dysfunction of frontal areas in EOAD patients, several studies often revealed this group performed worse than LOAD patients in task assessing executive functions. Accordingly, Cho et al. [18] found that the involvement of left dorsolateral frontal and cingulate areas was related to EOAD's more rapid cognitive decline in attentional (forward digit span task) and frontal-executive functions (word reading in the Stroop test). Impairment of attention in EOAD was also reported in several other studies [34,38]. In addition, it was described that EOAD patients exhibited a worse performance in response's inhibition and interference task [49] and in test assessing working memory [49]. Measures of visual attention and psychomotor speed did not yield significant differences; however, significant differences emerged on Trail Making Test A performance: LOAD patients tended to perform comparatively better than EOAD patients [49].

Other executive deficits in EOAD, compared to LOAD, have been noted and include problems with backward digits and "pull-to-stimulus" visuospatial functioning [49]. Accordingly, in one study EOAD subjects reported worse visuoconstructional abilities [40].

In summary, on executive assessments, EOAD subjects significantly perform worse than LOAD ones on a significant number of tasks, being more impaired in frontal/executive function, working memory and visuospatial function compared to LOAD patients. Results of neuropsychological tests, according to the severity of disease, seem to suggest an association of these impairments with fronto-parietal and widespread frontal dysfunction [48].

The following table resumes the main neuroimaging and neuropsychological differences between EOAD and LOAD patients described in the previous sections:

Table 1: Main neuroimaging and neuropsychological features of EOAD and LOAD patients.

	Neuroimaging features	Neuropsychological deficits
Early-Onset AD (EOAD)	- Atrophy/hypometabolism in precuneus, middle and posterior cingulate; - Reduced connectivity in DMN; - Hypometabolism in fronto-parietal networks; - White matter disruption of parietal lobe-dorsolateral frontal tracts	- Episodic memory; - Naming ability and word comprehension; - Attention; - Response inhibition (Stroop Test); - Working memory; - Visuospatial and visuoconstructional abilities
Late-Onset AD (LOAD)	- Severe atrophy in hippocampus and amygdala (MTL); - Decreased functional connectivity in ATN; - Reduced connectivity in DMN	- Semantic and episodic memory; - Temporal orientation; - Naming/visual confrontation naming abilities

Conclusions

As described in this chapter, despite part of the same disorder, EOAD and LOAD exhibit a great and significant heterogeneity. EOAD patients show a larger impairment of executive and visuospatial functions. On the other hand, LOAD subjects are characterized by greater memory deficits that also result in a worse temporal orientation. These neuropsychological differences are closely related to neuroimaging features. Accordingly, these two AD groups show a different pattern of neurophysiology: EOAD patients have a greater amyloid deposition and neurofibrillary formation in frontal and parietal areas; LOAD subjects, instead, exhibit greater neurophysiological aberrations concerning medial-temporal regions. In addition, as briefly reported in the introduction, these two AD forms also show a different disease progression with EOAD that is clinically more aggressive [8].

However, although these differences, current management for EOAD is similar to that for LOAD [50]. The management of EOAD might be different from LOAD when targeting the assessment of specific cognitive, psychological and behavioral deficits. In fact, beyond the aforementioned differences, EOAD is more often associated with a sense of an unexpected loss of independence in midlife, anticipatory grief about the future and difficulty with continued work, financial and family responsibilities than LOAD [50]. Moreover, patients and families need information and education on this form of AD and what it means in someone who is middle-aged or relatively young. Compared to patients with LOAD, those with EOAD often have higher levels of disease awareness and early generalized anxiety with a potentially increased risk of suicide [51]. These evidences suggest that treatment of EOAD might also include an age-appropriated psychosocial support, beyond the typical pharmacological treatments. Special efforts are required to provide psychological or psychiatric support and using local age-appropriate support groups and community resources, both for patients and caregivers.

In conclusion, it is becoming increasingly clear that AD is a highly heterogeneous disorder. Probably, it is not age-at-onset per se that determines the cognitive and neurophysiological profile, but some other, as yet unknown, underlying genetic and/or biological factors that predispose for both an earlier age-at-onset and a different clinical manifestation. Nevertheless, to date, further studies are needed to better investigate and understand these neuropsychological and clinical differences between EOAD and LOAD. Despite being overshadowed by LOAD, patients with EOAD (about 5% to 6% of all those with AD) are significantly different in their clinical and neurobiological features and require different management strategies. For this reason, a better understanding of neuropsychological profiles might therefore contribute to the development of personalized and more effective treatment of this complex and heterogeneous disorder known as AD.

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