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Original Research

# Characteristics of the Clinical and Neuroimaging Picture in Patients with Early-Onset Alzheimer's Disease

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The most common cause of severe cognitive impairment in adults is Alzheimer's disease (AD). Depending on the age of onset, AD is divided into early (<65 years) and late (≥65 years) forms. Early-onset AD (EOAD) is significantly less common than late-onset AD, accounting for only about 5–10% of cases. However, its medical and social significance as a disease leading to loss of ability to work and legal capacity, as well as premature death in patients aged 40–64 years, is extremely high. Patients with EOAD, as compared with late-onset AD (LOAD), have a greater number of atypical clinical variants: 25% and 6–12.5%, respectively, which complicates the differential diagnosis of EOAD against other neurodegenerative diseases. Nonetheless, the typical amnestic variant predominates in both LOAD and EOAD. Also, patients with EOAD have characteristic neuroimaging features: brain MRI scans from patients with EOAD often have more severe parietal atrophy and less severe hippocampal atrophy than those from patients with LOAD. This report addresses the features of the clinical and neuroimaging picture in patients with EOAD. A clinical case of a patient with EOAD is presented.

**Keywords:** early-onset Alzheimer's disease, clinical picture, MRI of the brain, neuroimaging, clinical case.

Dementia is currently one of the most significant problems facing the healthcare system in the 21st century [1]. Dementia is a syndrome in which the key clinical manifestation consists of severe cognitive deficits impairing the patient's capacity. It is estimated that more than 55 million people around the world suffer from some form of dementia. At the same time, in the context of an aging global population, the prevalence of dementia is steadily increasing [2, 3].

The leading causes of severe cognitive impairments (CI) include Alzheimer's disease (AD), which accounts for 60–80% of all cases of dementia [2]. AD is a progressive neurodegenerative disease predominantly due to abnormal processing and polymerization of proteins which are normally soluble. The main pathogenetic changes in AD are the deposition of β-amyloid (Aβ) and hyperphosphorylated tau protein. Accumulation of these proteins leads to neuron dysfunction and death [4].

It should be noted that age is the most significant biological risk factor for the development of AD. Depending on the age of onset of AD, early (<65 years) and late (≥65 years) forms are discriminated [5–8]. Despite the fact that AD is currently better known as a disease of older people, it was originally described in 1906 by Alois Alzheimer in a patient aged 51 years [9]. The term "Alzheimer's disease," which was introduced by Kraepelin, came to be understood as a disease whose clinical picture included impairment of cognitive functions developing in patients under 65 years of age. Subsequent studies showed that patients of different ages had similar pathomorphological changes, i.e., Aβ accumulation, such that the more common late-onset form of the disease could be classified as AD [10, 11].

The incidence of early-onset AD (EOAD) is significantly lower than that of the later-onset form of the disease, at about 5–10% [3, 7, 12]. However, the relevance of the

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problem of AD in younger patients is emphasized by the facts that the disease is extremely unexpected by the patient and leads to professional failure at working age, psychological problems due to loss of independence, financial difficulties, limitation or severance of social contacts and possible negative reactions from society, disruption of family obligations (for example, inability to care for small children or elderly parents, difficulties in performing household tasks), and "loss of self" [1, 5, 13].

In contrast to data on the prevalence of late-onset AD (LOAD), there is only limited information on the incidence of EOAD. A small number of epidemiological studies have shown that the prevalence of EOAD in the 45–65-year age group is 24 cases per 100,000 population per year, while the incidence is 6.3 cases per 100,000 population per year [3, 13, 14]. Moreover, both indicators increase exponentially as people approach age 65 years. The first symptoms in patients with EOAD usually occur between ages 30 years and 65 years [7]; mean age at onset is 54–56 years [3, 5, 15].

Hereditary and sporadic cases of AD are identified. Unlike LOAD, which is a complex disease with a heterogeneous etiology, EOAD is considered to be an almost entirely genetically determined disease, where there is a heritable predisposition ranging from 92% to 100% [16]. Thus, 35–60% of patients with EOAD have at least one first-degree relative with the same disease [3, 17]. Only 10–15% of EOAD cases can be explained by known mutations in the Aβ precursor protein (*APP*), presenilin-1 (*PSEN1*), or presenilin-2 (*PSEN2*) genes; these are characterized by Mendelian inheritance with autosomal dominant transmission and high penetrance (>85%) [17, 18–20]. The most common mutations are those in the *PSEN1* gene, which occur in 30–70% of cases, while 10–15% of cases involve mutations in the *APP* gene and fewer than 5% involve the *PSEN2* gene. At the same time, a large number of cases of EOAD remain unexplained but are probably due to the presence of other as yet identified genetic variants [3, 19]. As a result, studies are actively addressing the roles of other genes not displaying Mendelian-type inheritance.

The presence of homozygosity for the ε4 allele of the apolipoprotein E (*APOE*) gene, which is an independent genetic risk factor for the development of EOAD, has also been shown to led to significant increases in the risk of developing EOAD [7, 21, 22]. Improvements in genetic research methods have led to the identification of a number of genes which may underlie the development of EOAD; these include the sortilin-related receptor gene *SORL1* [23, 24], the trigger receptor gene expressed on myeloid cells *TREM2* [25], the serine protease gene *HTRA1* [26], etc. [12].

A feature of the clinical picture of patients with EOAD is the more marked heterogeneity of symptoms as compared with patients with LOAD [3, 7, 12, 27]. Nonetheless, the typical amnestic variant is predominant in both LOAD and EOAD. The LEADS study (The Longitudinal Early-Onset Alzheimer's Disease Study), which included 600 patients with EOAD aged 40–64 years, showed that 81% of patients had the amnestic variant of EOAD [28]. Around 25% of cases of EOAD (according to some studies up to 64% [29]) show an atypical clinical picture, characterized by relatively intact memory in the presence of disorders in other cognitive domains such as executive functions, speech, counting, visuospatial functions, and praxis; behavioral disorders may also be observed, mostly apparent as the presence of apathy-abulia syndrome [3, 7, 30].In contrast, atypical forms of LOAD are detected in only 6–12.5% of patients [29, 31].

Atypical variants of EOAD include posterior cortical atrophy, the logopenic variant of primary progressive aphasia, frontal (behavioral/dysregulatory) and biparietal variants with progressive ideomotor apraxia and visuospatial impairment, and the corticobasal variant [5, 32–34]. These variants of AD have the same pathological and biochemical markers as the classic amnestic variant of AD, though the primary pathological process affects particular limited areas of the cerebral cortex, resulting in heterogeneity in the clinical and neuroimaging picture [5].

Thus, given the significantly lower prevalence of LOAD as compared with LOAD, there is insufficient awareness among the population and medical specialists regarding possible very early disease onset, the diversity of the clinical picture, and the heterogeneity of neuroimaging data, while there are limitations on t ability to use expensive and invasive AD biomarkers and difficulties in the differential diagnosis of EOAD against other neurodegenerative diseases, resulting in erroneous or late diagnosis (the mean delay is 1.6 years [35]) and leads to untimely prescription of drug therapy. In this regard, further study of the features of EOAD, along with consideration of even individual clinical cases of patients with EOAD, is relevant.

**Clinical Case.** Patient M, 43 years old, requested a specialist outpatient appointment at the Federal Brain and Neurotechnologies Center, Federal Medical Biological Agency of Russia, and attended with his wife complaining of a progressive decline in memory for recent events noted over the previous two years. Over the previous year, the patient had started to notice difficulties in understanding rapid oral speech and experienced word selection difficulties when speaking, with the result that he had become unable to cope with his occupational duties. The patient had attended the clinic at his place of residence with these complaints to see a therapist and a neurologist; dementia was identified and the patient was prescribed memantine 10 mg in the morning and rivastigmine (Exelon) 9.5 $cm^2$ patch once daily. There were no episodes of disorientation. The patient could maintain personal hygiene and take care of himself. The patient's wife did the household chores: the patient did not cook on his own, but continued to provide periodic help with cleaning around the house.

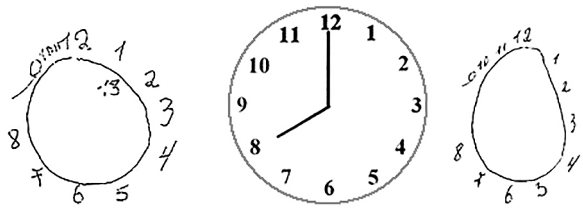
*Life history*: The patient had higher education and was currently not working. He was married with no children. There were no occupational hazards. He had been seen for

a heart defect in childhood (nature unknown). He denied injuries, surgeries, infections, and other chronic diseases. He smoked one pack of cigarettes per day and did not abuse alcohol. Family history: he stated that his mother had not had diseases with CI; he had difficulty in relation to family history of his father and other relatives. There had been no contact with infectious patients and the patient had not traveled abroad in the last six months. There was no history of allergy.

*Examination*: the patient was clearly conscious, communicative, and oriented in time and his own personality. Orientation in place: the patient knew that he was in a hospital in Moscow, but could not give the address of the hospital (he stated that he came to the hospital with his wife and did not remember the address); he was also unable to say which floor he was on but did not remember the fact of going up in an elevator. At the appointment, the patient's emotional background was flat and there was a reduction in insight into his condition. In conversation the patient spoke little, answered questions on the point raised, and followed simple instructions. Somatic status: nothing remarkable. Neurological status: no cerebral or meningeal symptoms detected. Cranial innervation intact. No limb paresis. Muscle tone normal. Tendon reflexes brisk and symmetrical. No pathological reflexes detected. Coordination tests performed satisfactorily. Stable Romberg test. Gait unremarkable. No sensory disorders identified. No loss of control of pelvic functions.

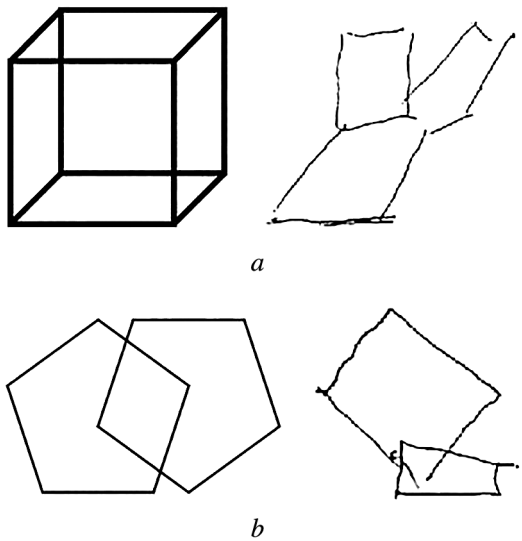
Neuropsychological examination: the patient's attitude to the assessment was positive, he sought to complete all the tasks set, and had reduced insight into errors made during testing. Instructions were remembered for very short periods of time. Psychometric scales for cognitive functions: the patient scored 8 points on the Mini Mental State Examination (MMSE) (normal 29–30 points), which corresponds to severe CI (moderate degree of dementia). The patient scored 12 points on the Montreal Cognitive Assessment Scale (MoCA) (normal 26–30 points), corresponding to severe CI. Memory assessment subtest (memorization of five words from the MoCA scale), immediate recall: first attempt – unable to name a single word; second attempt – named three words; impairment to delayed reproduction noted – without prompts the patient could not remember a single word and reproduction did not improve when the patient was given category prompts; when multiple choice prompts were used, the patient was able to name only one word, while false recognitions were noted in other cases. The patient scored 10 points on the Frontal Assessment Battery (normal 16–18 points), which corresponds to severe frontal dysfunction.

Neuropsychological status showed a marked decrease in auditory-verbal memory in the 10-word memorization test: 3–3–3–2–2 on direct reproduction (normal 9–10) and 0 on delayed reproduction (normal 9–10). Memory for remote events and autobiographical memory were relatively preserved (according to the patient's wife). The clock drawing and copying tests were used to assess visuospatial



*a* *b*

Fig. 1. Assessment of visuospatial functions (clock drawing and copying tests). *a*) clock drawing test; *b*) clock copying test.



*a*

*b*

Fig. 2. Assessment of visual-spatial functions (copying geometric shapes). *a*) cube; *b*) pentagons.

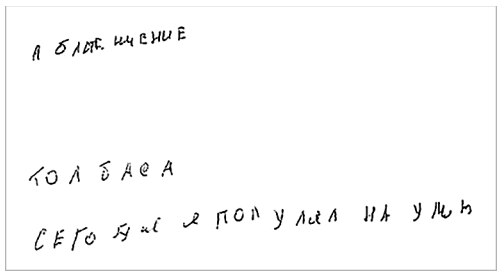


Fig. 3. Change in patient E's handwriting.

functions. The patient scored 2 points on the clock drawing test (the circle was closed and all numbers from 1 to 12 were included, though the numbers were positioned outside the circle and were drawn with unequal intervals, and there were no hands); the patient scored 2 points on the clock copying test (similar errors were made), which corresponds to severe visuospatial impairments (Fig. 1). Constructive apraxia and impairment to visual-spatial gnosis were noted: there were severe difficulties in copying geometric figures, i.e., pentagons and cubes (Fig. 2). Dynamic praxis was assessed in the "fist-edge-palm" test; the patient correctly performed three series in a row with a doctor but was unable to perform it independently. Visual subject gnosis was preserved. Tactile gnosis was preserved. Assessment of ex-

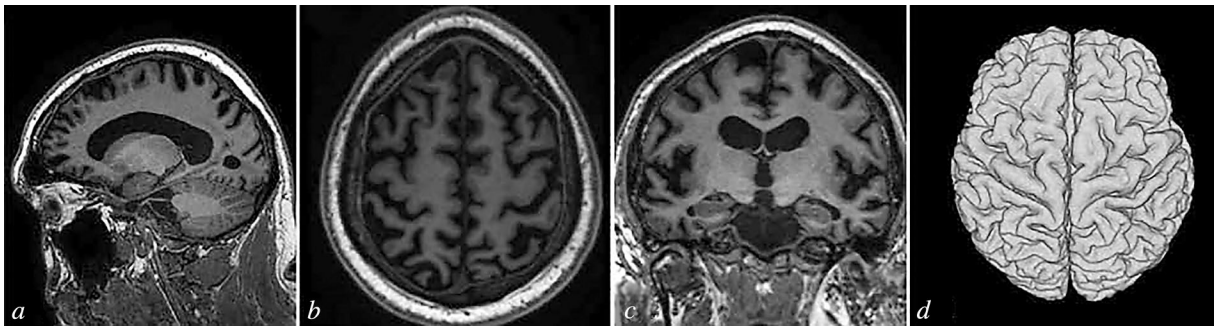



Fig. 4. Brain MRI, T1-weighted images. *a*) Sagittal section. Cortical atrophy, most marked in the frontal and parietal lobes; *b*) axial section. Cortical atrophy, most marked in the frontal and parietal lobes; *c*) coronal section. Moderate decrease in the volume of the entorhinal cortex. Hippocampus volume preserved. Cortical atrophy in the frontal and temporal lobes; *d*) volumetric reconstruction demonstrating atrophic changes in the cerebral cortex.

ecutive functions: the patient performed the number-letter binding test (TMT-B) from the MoCA scale with errors (only joined numbers in order); he had difficulties in generalizing pairs of words – train and bicycle, clock and ruler. Schulte test for evaluation of the function of attention: the patient's work efficiency was 162.4 sec (normal 40–50 sec; severe decrease), the degree of work warming up was 0.76 (normal ≤1; no deviation), and psychological stability was 1.12 (normal ≤1; severe decrease), which indicates a severe slowdown in mental processing speed. Automated counting without errors; unable to perform a single counting operation – acalculia. Speech, as the highest mental function, was preserved. The patient fully understood spoken speech. The patient's own speech was phrasal. Reading and writing were impaired, with individual letters missing (Fig. 3). Speech fluency was reduced: the patient scored four words in the literal associations test (words starting with the letter L) (normal 12 words or more), and two words in the categorical associations test (animals) (normal 15 words or more). The presence of anxious-depressive disorders was evaluated using the Hospital Anxiety and Depression Scale: no anxiety or depressive disorders were detected.

Data from laboratory and instrumented research methods: general blood tests and general urine tests were within normal limits. Thyroid hormones and blood biochemistry were within normal limits. Folic acid 11.9 nM (normal 6–39 nM). Vitamin B12 262 pM (normal 142–725 pM). Test for HIV, syphilis, and hepatitis negative.

ECG: heart rate (HR) was 62 bpm, normal sinus rhythm.

Ultrasound duplex scanning of the brachiocephalic arteries (USDS of the BCA) showed minor atherosclerotic changes without hemodynamically significant stenoses.

Electroencephalography (EEG) showed a background of diffuse changes in electrical activity with slowing of basic rhythmic activity and signs of moderate dysfunction of the median nonspecific structures of the brain.

Brain MRI scans were performed on a Discovery MR750w tomograph with a magnetic field strength of 3.0 T (GE Healthcare, USA) using a 32-channel head coil. Global cortical atrophy was revealed (2 points on the GCA scale) and cortical volume was decreased, mainly in the frontal and temporal lobes and the parietal lobe/precuneus region (Fig. 4). There were no significant atrophic changes in the hippocampus (1 point on the medial temporal lobe atrophy scale (MTA)); the volume of the entorhinal cortex was moderately reduced (2 points on the entorhinal cortex atrophy scale (ERICA)). The changes detected were symmetrical between the hemispheres. The volumes of the basal ganglia, brainstem structures, and cerebellum corresponded to age norms. Isolated small foci of gliosis, presumably of vascular origin, were detected in the white matter of both hemispheres. The MRI pattern was potentially consistent with a neurodegenerative disease (possibly AD).

Thus, the complaints, histories, somatic and neurological status, neuropsychological status, laboratory diagnostics to exclude causes of reversible CI, and data from instrumented studies led to a diagnosis of possible AD with early onset and severe CI of neurodegenerative nature. The patient was given advice to control risk factors which could have adverse influences on cognitive status, along with regular moderate physical activity, social activity, cognitive training, stopping smoking, and a healthy diet (Mediterranean diet). The dose of Akatinol Memantine was increased to 15 mg in the morning once daily in the first week and 20 mg in the morning once daily from the 2nd week and thereafter. The rivastigmine (Exelon) dose was increased to a 13.3 $cm^2$ patch once daily in the long term. The patient was prescribed choline alfoscerate 800 mg in the morning and 400 mg in the afternoon for six months. Follow-up observations by a neurologist, re-evaluation of neuropsychic status after six months, and genetic testing were advised.

**Discussion.** We present here a young patient with CI increasing over the previous two years, reaching the level of moderate dementia at the time of presentation, which was confirmed by results from integrative assessment of cognitive functions. This clinical case can be interpreted as rapidly progressive dementia (RPD), which is understood by most researchers as the development of cognitive decline with rapid progression to the level of dementia over a relatively short period of time, of no more than two years (up

to four years according to some studies) [36, 37]. The best-known diseases whose clinical picture includes the development of RPD include Creutzfeldt–Jakob disease, which is a prion neurodegenerative disease. Many authors have noted that in patients without prion diseases, AD is one of the most common diagnoses in patients with RPD (16–51%) [36–39]. Approximately 30% of cases of AD experience rapid progression; studies have shown that deterioration in cognitive status develops more rapidly in EOAD than LOAD [40–42]. EOAD is also responsible for a large number of premature deaths in people aged 40–64 years [43]. Patients with EOAD have a potentially more aggressive clinical course [44], as seen in our patient.

Researchers have noted that a feature of patients with EOAD as compared with LOAD is the presence of a "purer" pathology, i.e., fewer comorbidities and risk factors [45, 46]. With the exception of a heart defect, for which he was seen by specialists only in early childhood, no other chronic clinically significant diseases were found in the patient presented here.

The patient's neuropsychological status showed a neurodegenerative disease profile characteristic of Alzheimer's-type CI, as indicated by: impairment of immediate and delayed reproduction with incorrect recognitions and ineffective hints; impairment of clock-drawing and -copying, as well as figure-copying; a marked decrease in speech fluency, and, to a greater extent, decreases in naming categorical associations.

Neuropsychological test results demonstrated that the patient presented here had severe primary hippocampal memory impairments, gross impairment of visuospatial functions, signs of constructive and dynamic apraxia, impaired executive functions, deterioration of neurodynamic processes, acalculia, and impaired reading and writing, which is to be expected given the global atrophy and predominantly fronto-parieto-temporal localization of atrophic changes on the brain MRI scan.

Despite the fact that the literature has noted a higher frequency of atypical variants of the clinical picture in patients with EOAD than LOAD [3, 7, 29–31], the primary features in the present patient were memory disorders, with subsequent addition of disorders of other cognitive functions, which is consistent with the diagnosis of the classic amnestic variant of EOAD.

On the one hand, gross impairments of visuospatial functions and praxis may be characteristic of the atypical biparietal variant of the disease, with progressive ideomotor apraxia, as well as visuospatial impairments; marked executive dysfunction can be seen in the frontal variant; impairments in reading, writing, counting, and visuospatial functions are characteristic of posterior cortical atrophy, while decreased speech fluency and word-finding difficulties are typical of the logopenic variant of primary progressive aphasia [5, 12, 32, 34]. Although our patient had the above symptoms, it is difficult to identify the leading symptom except for the memory disorders mentioned above. In addition, in atypical variants, defects of semantic memory are less common and long-term preservation of memory functions is more typical [47, 48]. However, the patient presented here, conversely, showed predominance of severe memory deficit combined with other CI, which can probably be explained by the advanced stage of the disease, which is generally characterized by the presence not only of memory disorders but also other cognitive functions.

In addition, in EOAD, where frontal dysfunction is noted at onset and MRI brain scans demonstrate the presence of atrophy predominantly in the frontotemporal regions, difficulties arise in the differential diagnosis against frontotemporal dementia. However, EOAD is characterized by the presence of marked behavioral disorders, while early and severe memory impairment is generally a criterion for excluding this clinical diagnosis [49].

Data obtained from MRI brain scans are interesting, as no significant hippocampal atrophy was observed as defined by the MTA scale. However, brain MRI showed that patients with EOAD display more widespread cortical atrophy, predominantly affecting the parietal cortex, as compared with patients with LOAD, in whom atrophy is more limited to the temporal regions; patients with EOAD have less severe hippocampal atrophy [34, 50, 51], as in the patient examined here. It should be noted that the literature contains data showing that the MTA scale may have lower sensitivity and specificity in identifying AD than the ERICA scale, which assesses the volume of the entorhinal cortex and parahippocampal gyrus, the width of the collateral sulcus, and the width of the fissure between the entorhinal cortex and the tentorium cerebelli [52, 53]. Thus, an ERICA score of ≥2 points provides higher diagnostic accuracy (91%) than the MTA score (74%), with a sensitivity of 83% versus 57% and a specificity of 98% versus 92% for the diagnosis of dementia due to the AD [53]. The present patient had a score of 1 point on the MTA scale and 2 points on the ERICA scale, which indicates AD with high probability.

Studies have shown that the hippocampus is not the only vulnerable brain structure in AD; the entorhinal cortex is also vulnerable, showing damage in the form of early histological changes in AD, including the formation of neurofibrillary tangles and cell death. The entorhinal cortex is a region of the brain located in the medial temporal lobe and plays a significant role in the implementation of memory processes [54]. The patient presented here displayed a decrease in the volume of the entorhinal cortex, and this could probably explain the presence of marked memory loss even in the absence of significant hippocampal atrophy. In addition, the present patient showed atrophy in the precuneus, which is typical for patients with EOAD. The precuneus is part of the associative cerebral cortex, responsible for the processes of spatially oriented behavior, including episodic memory [55].

Confirmation of the diagnosis of EOAD was based on assessment of complaints, medical history, neuropsycho-

logical status, and neuroimaging data. The diagnosis was also supported by the absence of changes in somatic and neurological status, along with laboratory diagnostic data excluding causes of reversible CI. More accurate diagnosis undoubtedly requires lumbar puncture with determination of biomarkers of AD in the cerebrospinal fluid, along with positron emission tomography. However, given the high cost and invasiveness of these methods, the absence of neurological and behavioral disorders characteristic of other neurodegenerative disorders in the patient described here, and the presence of a typical clinical picture of AD, the need for these research methods in this particular case is dubious, so they were not performed.

**Conclusions.** The frequency of EOAD is lower than the prevalence of LOAD. However, the medical and social significance of EOAD is extremely high, as this disease develops in people of working age and leads to disability, and it is also a cause of premature death in young patients. This increases the relevance of studying EOAD with the aims of improving the diagnosis of this disease and the early prescription of appropriate therapy. A typical clinical picture with the presence of severe memory disturbances predominates in both LOAD and EOAD. However, atypical variants of the clinical course are more common in EOAD, which makes differential diagnosis against other neurodegenerative diseases difficult. Brain MRI findings in patients with EOAD may also demonstrate neuroimaging features, such as more severe parietal atrophy and less severe hippocampal atrophy than patients with LOAD, which must be taken into account when making a diagnosis. Improvements in knowledge and increasing awareness among medical professionals regarding the possible clinical manifestations and neuroimaging changes in EOAD are important.

The authors declare no conflict of interest.

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