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Investigation and Diagnostic Methods

Use of Modern Classification Systems for the Complex Diagnostics of Alzheimer's Disease

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Objective. To compare levels of Aβ40, Aβ42, total tau protein, and tau protein phosphorylated at threonine 181 in cerebrospinal fluid (CSF) with clinical diagnoses of Alzheimer's disease (AD). **Materials and methods**. The study was conducted in 64 patients with diagnoses of dementia and Mini-Mental State Examination (MMSE) scores of 24 points or lower. All patients underwent lumbar puncture. Aβ40 and Aβ42 levels, the Aβ42/40 ratio, and levels of total Tau and Tau phosphorylated at threonine 181 were determined in CSF using a multiplex assay following the manufacturer's protocol. Concentrations were expressed in pg/ml. **Results**. Prior clinical diagnoses of AD had been made in only three patients (5%). The study revealed increased contents of AD-typical pathological proteins in the CSF in 48 subjects (75%). The data obtained indicate that the diagnosis of AD is made 10–14 times less frequently, according to global statistics, than might be expected. The discrepancy between the clinical diagnosis and laboratory data is confirmed by our study. **Conclusions**. Differences in the treatment of dementia and the development of new drugs targeting specific elements in the pathogenesis of different types of dementia require accurate and complete diagnosis of dementia, especially AD as the most common form of this disease.

Keywords: dementia, cerebrospinal fluid, β-amyloid, tau protein.

The WHO identifies dementia as a syndrome in which cognitive function deteriorates to a greater extent than seen in normal aging [1]. The four most common types of dementia are Alzheimer's disease (AD) (50–70%), vascular dementia (25–30%), Lewy body dementia (15–20%), and frontotemporal dementia [1].

AD is one of the most common neurodegenerative diseases worldwide and a leading cause of cognitive and functional decline in older adults. The prevalence of AD increases exponentially between ages 65 and 85, doubling every five years. There are many demographic and vascular risk factors which make a person more susceptible to this disease, as do the presence of the apolipoprotein E ε4 allele, a family history of AD, and previous severe head trauma [2].

The neurodegenerative process in AD is caused by the formation and aggregation of deposits of amyloid peptide. Amyloid (Aβ) is formed by the catabolism of amyloid precursor protein. This protein can be cleaved via amyloidogenic and non-amyloidogenic pathways involving transmembrane proteins with protease activity: α-, β-, and γ-secretases [3]. The most common types of Aβ formed during the processing of amyloid precursor protein are Aβ40 and Aβ42 [4]. At physiological levels, soluble Aβ (primarily Aβ40 and Aβ42) are essential for the regulation of synaptic plasticity and neuron survival. Intermediate levels of Aβ produce presynaptic enhancement of synaptic activity, while abnormally low levels have the opposite effect [2]. AD patients show progressive deposition of Aβ, with subsequent cytopathology affecting the surrounding glial cells and neurons; Aβ oligomers disrupt normal signal transduc-

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tion and cause increased neuronal excitability [2]. Aβ42 is able to stimulate the production of tumor necrosis factor-α by microglia, which leads to an inflammatory response, oxidative stress in neurons, changes in calcium homeostasis, and neurotransmitter deficiency. This results in hyperactivation of kinases, inactivation of phosphatases, and hyperphosphorylation of tau protein (Tau), which results in the formation of neurofibrillary tangles. These tangles accumulate in synapses and neuron bodies, causing neuron death by apoptosis [5]. Thus, the accumulation of Aβ triggers the progressive deposition of Tau, while Aβ dimers trigger its phosphorylation [2]. AD is therefore a secondary tauopathy, where Tau accumulation is caused by Aβ deposition.

The correctness of the diagnosis of AD and the differential diagnosis of other types of dementia are urgent points, as different approaches are needed for different types of dementia. In approximately one third of cases, clinical and pathological anatomical diagnoses of AD do not coincide, such that the proportion of AD diagnoses made posthumously is increasing [6, 7].

In AD, the amount of Aβ42 in the cerebrospinal fluid (CSF) is inversely related to the total and phosphorylated Tau (pTau) levels [8]. Several meta-analyses have analyzed levels of Aβ40, Aβ42, total Tau (tTau), and Tau phosphorylated at threonine 181 (pTau181) in the CSF [8, 9]. A meta-analysis reported 20 years ago showed that patients with AD have a decreased Aβ42 concentration and an increased Tau concentration in the CSF [9]. Twenty years on, these data have only just been confirmed in a large number of studies. A meta-analysis by Li et al. [10] found that Aβ42, tTau, pTau, and the Tau/Aβ42 ratio in the CSF had significant influences on the progression of AD. CSF levels of the biochemical markers Aβ42, tTau, and pTau181 have demonstrated diagnostic accuracy for mild cognitive impairment and AD dementia [11].

The aim of the present work was to estimate Aβ40, Aβ42, the Aβ 42/40 ratio, t-tau, and pTau181 in the CSF of patients with dementia and to evaluate the correspondence of signs of AD in the CSF with the clinical diagnosis.

Materials and Methods. The study included patients observed in the department of gerontology, Alekseev Psychiatric Clinical Hospital No. 1, from June 2022 to August 2022. The study included 64 patients (46 women aged 75 ± 10.4 years and 18 men aged 69 ± 12.5 years) with dementia. All diagnoses were made on the basis of results of standard interdisciplinary consultations involving neurologists, neuropsychologists, and psychiatrists. Diagnoses were determined in accordance with the International Classification of Diseases (ICD-10). Diagnosis F02.8 "Dementia in other specified diseases classified elsewhere" was made in 53 patients, F00 "Dementia in Alzheimer's disease" in three, F01 "Vascular dementia" in three, F02.00 "Dementia in Pick disease" in one, F03.10 "Presenile dementia, unspecified" in one, and F06 "Other mental disorders due to brain damage and dysfunction or physical illness" in three. All participants underwent standardized neurological examination and neuropsychological testing.

The Mini-Mental State Examination (MMSE) was used to assess cognitive function [12]. Dementia was diagnosed when scores were 24 or lower.

CSF was collected by lumbar puncture with a sterile needle; the CSF volume was at least 1 ml. CSF samples were centrifuged (1500 rpm) for 15 minutes within 1 h of collection and supernatants were collected. Samples were stored at –80°C.

Aβ40, Aβ42, the Aβ42/40 ratio, tTau, and pTau181 were estimated in CSF using a multiplex assay with the MILLIPLEX MAP Human Amyloid Beta and Tau Magnetic Bead Panel kit following the manufacturer's protocol. Concentrations were expressed in pg/ml.

Imaging data were harvested from each patient's medical records if acquired no more than 6 months before the patient was included in the study.

Informed consent was obtained from all participants. The study was conducted in accordance with the recommendations of the Declaration of Helsinki. Procedures involving experiments on humans were carried out in compliance with the ethical standards of Protocol No. 1 of January 25, 2022 of the Ethics Committee of the Alekseev Psychiatric Clinical Hospital No. 1, Moscow Health Department.

Protein concentrations were compared using ANOVA and Fisher's test. Correlation analysis was run using Pearson correlation. All data had normal distributions, as confirmed using the Shapiro–Wilk test.

Results. CSF protein contents (pg/ml) are presented in Fig. 1. Differences between men and women were found in Aβ42 content and the Aβ42/40 ratio ($p = 0.042$ and $p = 0.014$).

Correlation analysis of protein content with age and MMSE scores was then carried out (Table 1). Correlation analysis showed that there was no relationship between protein contents and the extent of decline in cognitive functions. Correlations of markers with each other and with age were identified.

Indicators of AD in the CSF were defined in terms of the A/T/N classification system – Aβ, pTau, and neurodegeneration (corresponding to tTau in the CSF) [13]. The following variants were distinguished: normal ($A^-T^-N^-$), without pathological changes characteristic of AD ($A^-T^-N^+$, $A^-T^+N^-$, $A^-T^+N^+$), and AD ($A^+T^-N^-$, $A^+T^-N^+$, $A^+T^+N^-$, $A^+T^+N^+$). The following values were used for cutoffs: Aβ42 < 1013 pg/ml, pTau > 64 pg/ml, tTau > 3252 pg/ml. These values were selected in accordance with the techniques used for estimation of biomarkers [14].

Classification results showed that 75% of patients had signs of AD, while 20% had no signs of AD. Three patients (5%) had normal CSF protein levels: a 68-year-old woman with a total MMSE score of 9 and neuroimaging showing cerebral microangiopathy and a 75-year-old woman with a total MMSE score of 15. Both patients had diagnoses of

TABLE 1. Correlation Analysis of CSF Protein Concentrations with Age and MMSE Scores

Indicator	Aβ40	Aβ42	42/40	tTau	pTau181	MMSE
Aβ42	0.633*	–				
42/40	–0.236 *	0.538	–			
tTau	0.587*	0.056	–0.487*	–		
pTau181	0.517*	–0.064	–0.585*	0.839*	–	
MMSE	0.060	0.037	0.083	0.016	–0.160	–
Age	0.506*	–0.039	–0.636*	0.356	0.427	–0.124

*$p < 0.05$.

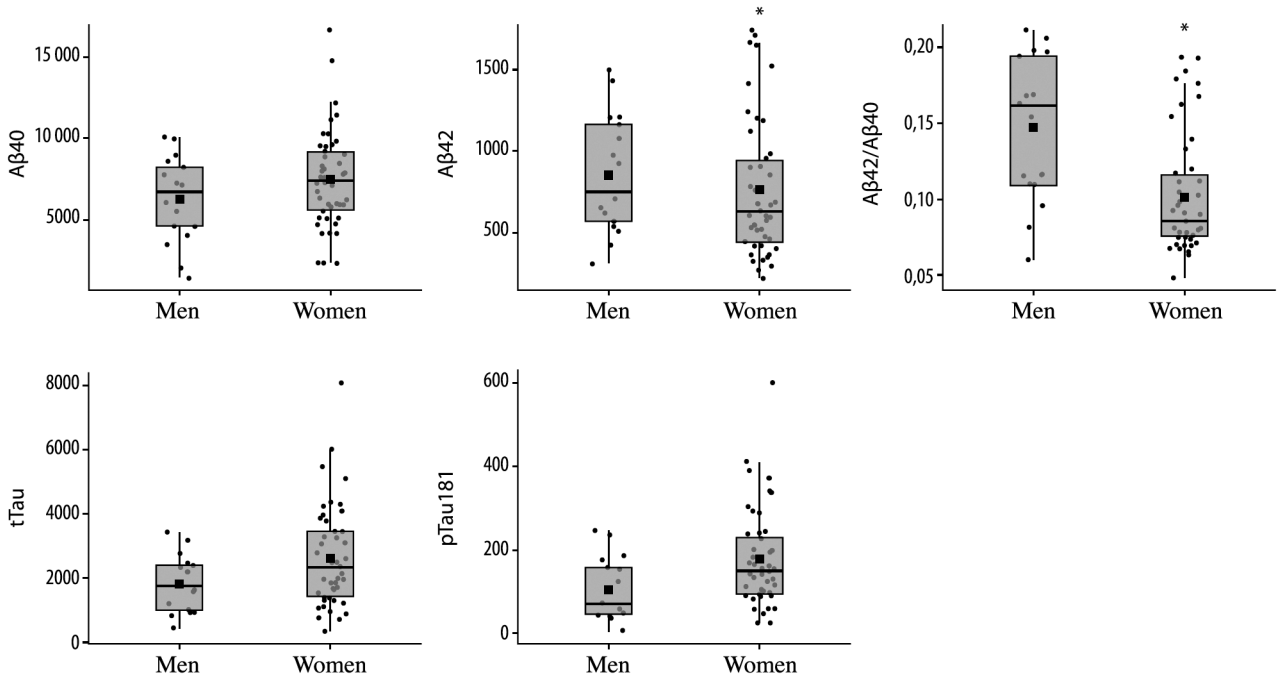

Fig. 1. CSF protein concentrations. *$p < 0.05$.

F02.8 "Dementia in other specified diseases classified elsewhere." The third patient had a total MMSE score of 7, no CT/MRI data, and a diagnosis of F06.828 "Organic brain disease of complex origin with pronounced mnestic-intellectual decline."

Biomarker categories on the Alzheimer's disease spectrum $A^+T^{+/-}N^{+/-}$ could be divided into "pathological changes in AD" ($A^+T^-N^-$), AD ($A^+T^+N^{+/-}$), and "AD and associated putative non-Alzheimer's pathological changes" ($A^+T^-N^+$) [15]. The distribution of patients according to the A/T/N classification was as follows: $A^+T^+N^+$ in 19%, $A^+T^+N^-$ in 39%, $A^+T^-N^-$ in 17%, $A^-T^+N^+$ in 6%, $A^-T^+N^-$ in 14%, and $A^-T^-N^-$ in 5%. Quantitative protein measurements in different patient groups are presented in Fig. 2.

The next stage consisted of analysis of the relationship between diagnoses made by doctors, CSF protein contents, and CT/MRI disease indicators. Data from 50 patients were analyzed, as there were no imaging studies or medical history data in 14 cases. Analysis of CT/MRI results identified vascular pathology and histories of acute cerebrovascular accident. Diagnosis F02.8* "Dementia in other specified diseases classified elsewhere" were made in 82% of patients ($n = 41$). Table 2 shows nine patients who had other diagnoses. All patients diagnosed with AD had CSF signs of AD. The patient with Pick disease (F02.00) had all the signs of this disease according to the medical history, though a decrease in Aβ was detected with a normal level of Tau in the CSF. Patients with diagnoses F03.10 and F06.328 had signs of vascular disorders and also signs of AD in the CSF.

Figure 3 plots the correspondences between vascular abnormalities on CT/MRI and the contents of pathological proteins in the CSF.

The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for preclinical AD are based on the concept that AD biomarkers follow a specific temporal sequence, with β-amyloidosis occurring before tau-related neurodegeneration, which in turn is a direct correlate of clinical symptoms. Our study identified six patients with

TABLE 2. Correspondence Between CT/MRI Vascular Lesions and Concentrations of Pathological Proteins in the CSF

Diagnosis	Vascular lesions (CT/MRI)	CSF	A/T/N classification
F00.00* Early-onset AD dementia	Chronic cerebral ischemia	AD	$A^+T^+N^+$
F00.04* Early-onset AD dementia	None, history of epilepsy	AD	$A^+T^+N^-$
F00.24* Late-onset AD dementia	Cerebral microangiopathy	AD	$A^+T^+N^-$
F01.04 Acute-onset vascular dementia with other mixed symptoms	ACVA	AD	$A^+T^+N^-$
F01.94 Vascular dementia with episodes of confusion	None	AD	$A^+T^+N^+$
F02.00* Dementia in Pick disease	Yes	AD	$A^+T^+N^-$
F03.10 Presenile dementia unspecified	Chronic cerebral ischemia	AD	$A^+T^-N^-$
F06.21 Delusional (schizotypic) disorder related to vascular brain disease	None	No AD	$A^-T^-N^-$
F06.328 Psychotic depressive disorder associated with mixed diseases	Vascular encephalopathy	AD	$A^+T^-N^-$

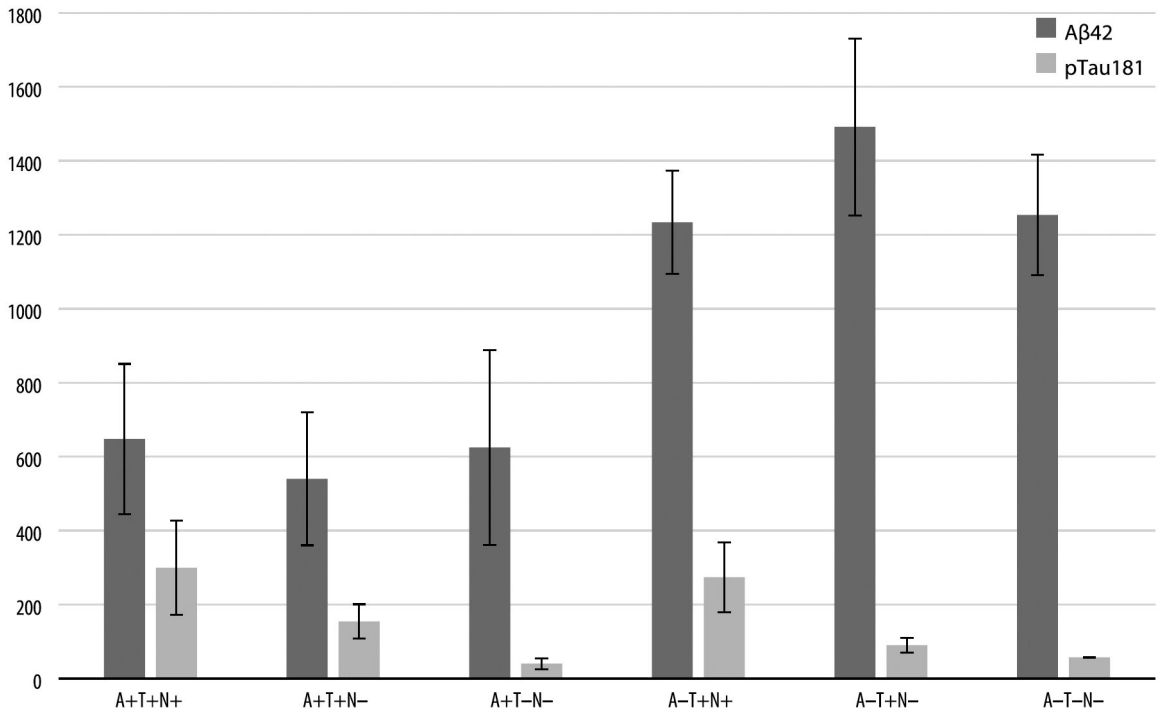

Fig. 2. CSF protein concentrations in patients separated using the A/T/N classification system.

normal Tau levels and reduced Aβ levels. The $A^-T^-N^+$ profile is expected in pathologies such as ischemic cerebrovascular disease or hippocampal sclerosis, while the $A^-T^+N^+$ profile is expected in primary age-related tauopathy [16].

It should be noted that our study had no patients with $A^+T^-N^+$, which corresponds to the profile "AD and associated putative non-Alzheimer's pathological changes," which could be seen as a dementia of mixed nature.

Discussion. CSF marker concentrations provide an objective indicator for the differential diagnosis of disease. According to the A/T/N classification, the prevalence of AD in our sample was 75%, which is consistent with global data. Comparison of biochemical markers in the CSF revealed differences in Aβ concentrations between men and women. Analogous sex-related differences have also been noted in the literature [17]: female sex is a risk factor for AD [18].

The present study found no correlation with clinical data (total MMSE score). However, the literature does not show a clear correlation between the CSF Aβ level and the severity of cognitive impairment [19, 20]. Aβ, but not Tau, was found to correlate with patient age. This indirectly shows an increase in the prevalence of AD with age in patients [21].

The diagnosis of dementia in mixed-type AD corresponds to ICD-10 code F00.2. Despite this, the vast ma-

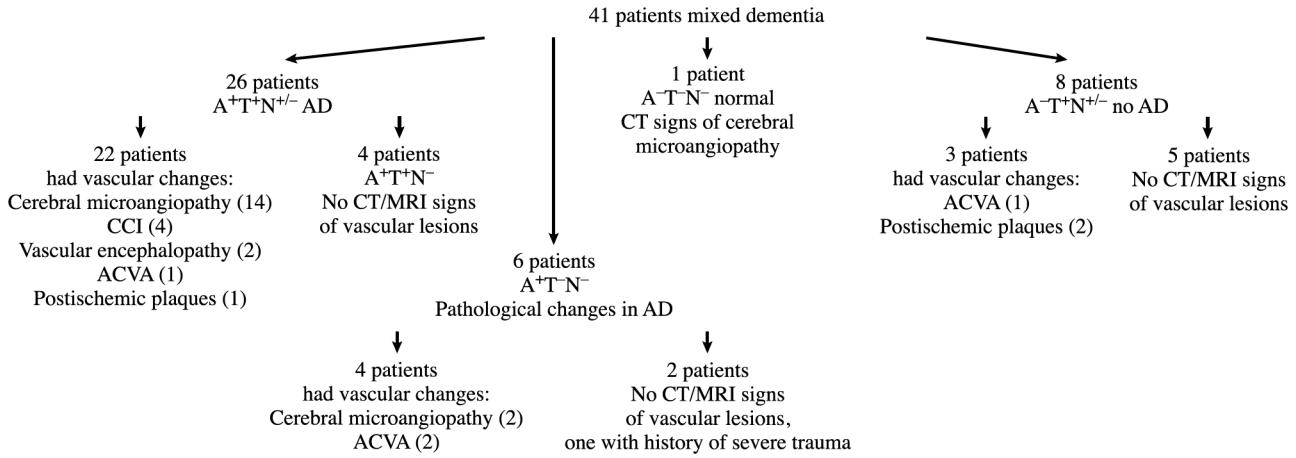

Fig. 3. Relationship between vascular impairments on CT/MRI and pathological proteins in CSF in patients with diagnoses of F02.8*.

jority of study participants were diagnosed with F02.8 "Dementia in other specified diseases classified elsewhere." Code F02.8 includes an extensive list of types of dementia, including dementia due to other organic diseases. However, clinical guidelines [18] indicate that AD accounts for 60–70% of all dementias. In our study, this diagnosis was made in only three of 64 patients, which is not consistent with global data. In addition, mixed dementia is too vague a term; a combination of degenerative and cerebrovascular pathological processes occurs in the vast majority of cases, because of their advanced age and the presence of concomitant pathology. However, this does not indicate that this pathological process is not a consequence of AD [18]. It was also shown that "Alzheimer's disease with cerebrovascular disease" is a more correct diagnosis and will be coded in the next version of the ICD with code 6D80.2.

Vascular disorders accompany AD. Furthermore, the presence of any vascular disorders is not a differential diagnosis of vascular dementia. Not only risk factors for vascular diseases, but also even histories of stroke can lead to the development of AD rather than vascular dementia [22]. The factor defining the hereditary predisposition to AD – the ε4 allele of the apolipoprotein E gene – is also a risk factor for the development of cardiovascular diseases [22]. Postmortem materials from patients with AD show Aβ deposition in vessels (70–90% of cases), which points to resulting disturbances in cerebral perfusion [18]. Assessment of disorders as being of mixed nature requires not only the presence of vascular abnormalities, morphological and/or neuroimaging features, but also clinical signs of the two diseases [23]. The author points out that use of this approach will identify dementia of mixed etiology in no more than 15% of cases. Other authors [24] have expressed doubts regarding the validity of the concept of mixed dementia and have challenged the view of this nosology as a simple co-occurrence of various pure forms of dementia.

Vascular deposition of Aβ can lead to decreased clearance of Aβ from the brain, development of neuroinflammation, and, ultimately, neurodegeneration [25]. Aβ has been shown to be able to contribute to disruption of the blood coagulation and fibrinolytic systems [26], which may also contribute to the occurrence of vascular disorders associated with AD.

The most common pathology on CT/MRI in the present study was cerebral angiopathy. All these patients had CSF signs of AD, and all patients with chronic cerebral ischemia (CII) and vascular encephalopathy also had signs of AD. The present study included no patients with $A^+T^-N^+$, corresponding to "AD with other non-Alzheimer's pathology," which could be seen as a mixed-type dementia.

Clinical guidelines [18] do not advise the routine use of CSF markers and indicate that CSF examination should be performed for abnormal proteins in patients with early-onset or atypical AD. However, this study shows that diagnoses of AD are made significantly less frequently than the average incidence of the disease.

Differential diagnosis is important in clinical practice. A diagnosis reflecting the type of dementia can form the basis for individualized treatment and assessment of prognosis. The main drugs for the treatment of both vascular dementia and Alzheimer's-type dementia include two groups: anticholinesterase drugs and a glutamate NMDA receptor antagonist. Treatment of mild to moderate dementia should begin with anticholinesterase drugs (donepezil, galantamine, rivastigmine), while the glutamate NMDA receptor antagonist memantine should be used in severe dementia [18, 27, 28]. Conversely, memantine has been shown to be effective in patients with mild to moderate dementia of vascular origin [29]. Thus, diagnosis of AD and "vascular dementia" determines the first-line drug depending on the severity of symptoms, which directly influences treatment efficacy. In addition, new drugs under development may have different efficacies in different types of dementia [30].

Conclusions. Analysis of CSF for pathological proteins in the present study identified 75% of patients with AD and pathological changes in AD, which is consistent with

WHO data. All patients with clinical diagnoses of AD also CSF signs of AD. AD is often accompanied by vascular disorders, which was also found in this study. While active research on targeted drugs for the treatment of dementia aimed at particular pathogenetic pathways of the disease is under way, an important task for clinical specialists is that of obtaining more accurate and complete pathogenetic diagnoses, especially of AD, as the most common type of dementia.

The authors declare no conflict of interest.

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