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Evaluation of β Amyloids and Tau Protein Biomarkers for Alzheimer's Disease in Serum of Alzheimer Patients

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Abstract

Background: β Amyloids and tau proteins are well-known markers of Alzheimer's Disease (AD). The goal of this study was to investigate the difference in the amounts of β amyloids [$A\beta_{(1-42)}$ and $A\beta_{(1-40)}$] and tau protein in the blood serum of AD patients and controls participants in order to find more usable non-invasive AD biomarkers.

Materials and methods: Following medical assessments, physical examinations, and regular blood tests to rule out other known causes to memory impairment, a total of 25 AD participants, aged 50–84 years, and 25 healthy age-matched controls, were initially chosen. The Mini-Mental State Examination (MMSE) was used to assess cognitive impairment in all subjects, as well as standard magnetic resonance imaging. We used the ELISA technique to evaluate the blood serum levels of beta amyloid [$A\beta_{(1-42)}$ and $A\beta_{(1-40)}$], tau protein and the ratio of $A\beta_{(1-42)}/A\beta_{(1-40)}$ in AD patients and control participants.

Main findings: This study showed that tau protein, $A\beta_{(1-42)}$ and ratio of $A\beta_{(1-42)}/A\beta_{(1-40)}$ were significantly elevated in AD patients when compared to control participants. However, $A\beta_{(1-40)}$ were significantly decreased in AD patients when compared to control participants.

Principle conclusion: Our results indicated that elevated levels of tau protein, $A\beta_{(1-42)}$ and ratio of $A\beta_{(1-42)}/A\beta_{(1-40)}$ and decreased levels of $A\beta_{(1-40)}$ can be used to β diagnose AD pathogenicity. As a result, blood-based biomarkers are predicted to provide crucial therapeutic solutions to promote early detection and screening for AD.

Keywords: Alzheimer's disease • Blood serum • Beta amyloid peptide • Tau protein

Introduction

Alzheimer's Disease (AD) is a chronic neurological illness that affects around 35.6 million people globally [1,2]. This illness is characterized by cognitive impairment, behaviourally progressing dementia, aberrant protein accumulation and synaptic dysfunction [3]. The primary neuropathological hallmarks of AD are β amyloid (Aβ) plaques and Neurofibrillary Tangles (NFTs) in the brain, which are comprised of tau protein [4,5]. Both Aβ accumulation and tau aggregation in NFTs are thought to contribute directly to AD neuro-degeneration and cognitive impairment [6]. Many researches indicated that Aβ is a significant element in the early stages of the disease [5], and tau pathology being a subsequent effect. Although, recent research suggests that tau pathology is more essential than previously assumed, as it emerges earlier in childhood, even before Aβ deposition in certain people [5,7].

Microtubule-Associated Protein Tau (MAPT) or as known tau protein can help to maintain axonal microtubule structure, which is important for axonal cytoskeleton stability [8]. Tau is prevalent in the central nervous system and has several phosphorylation sites. Microtubule stability, distribution, and function in neurons are all affected by phosphorylation state of tau protein [9]. When the tau protein is hyperphosphorylated, it detaches from the microtubule, causing axonal morphology and dynamic transport function to be disturbed and disrupted [10,11]. $A\beta_{(1-42)}$ is the most abundant component of Aβ plaques, and its abundance correlates adversely with the load of Aβ deposits in brain tissue, whereas $A\beta_{(1-40)}$ is a more soluble, less amyloidogenic form that may even protect against Aβ deposition [12]. Some researchers have yet to demonstrate a link between blood $A\beta_{(1-42)}$ and $A\beta_{(1-40)}$ concentrations and the existence of AD [13-15], while other studies' findings have countered this theory [16-18].

At the present time, only post-mortem verification of Aβ deposits (plaques) and NFTs allows for a precise AD diagnosis; and hence, clinicians depend on clinical diagnosing criteria, such as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's and Related Disorders Association (NINCDS-ADRDA) guidelines; however, the diagnostic accuracy of these AD criteria is poor [19,20]. As a result, accurate biomarkers that capable of identifying AD pathology are necessary. Nowadays, current biomarkers for AD are based on Cerebrospinal Fluid (CSF) or neuroimaging. As shown in a 2016 meta-analysis of fluid AD biomarkers [21], CSF $A\beta_{(1-42)}$ and tau can identify AD patients from controls [22]. Furthermore, higher CSF tau protein and $A\beta_{(1-42)}$ levels are a key indicator of AD [22]. CSF sample and analysis, on the other hand, are intrusive, painful, time-consuming, and costly [23,24]. As a result, blood is a more appropriate goal for AD biomarker analysis, and various authors have explored tau protein levels in the blood of AD patients [25,26]. Previous research has found that plasma tau levels correlate with brain tau levels [27,28] and also that plasma tau levels are notably higher in the serum of

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AD patients [29-32]. Furthermore, another research found a link between plasma tau levels and CSF total tau or phosphorylated tau (T181) levels [33], indicating the relevance of serum tau measurements in the diagnosis of AD. A recent research also found that tau/$A\beta_{(1-42)}$ levels in plasma were highly predictive of brain tau deposition and were linked to changes in cerebral Aβ deposition, brain glucose metabolism and hippocampus volume change [34]. Nevertheless, there was significant variance among the few available studies on AD serum markers, demanding more investigation for diagnostic reliability and relationship with clinical characteristics such as cognitive impairment.

Aβ and tau proteins are well-known markers of AD. As a result, the goal of this study is to look at variations in the concentrations of Aβ [$A\beta_{(1-42)}$ and $A\beta_{(1-40)}$] and tau protein in the blood serum of AD patients and control participants in order to develop more usable non-invasive AD biomarkers.

Materials and Methods

Participants

A randomized controlled trial applied on total of 25 participants (aged 50–84 years) and 25 healthy age matched controls who were recruited from private clinics in Mansoura, Egypt A total of 25 participants (aged 50–84 years) and 25 healthy age-matched controls were recruited from private clinics in Mansoura, Egypt. Before taking part in the study, all subjects provided informed consent. Individuals with subjective cognitive impairments were first tested and pre-screened for cognitive impairment using the Mini-Mental State Examination (MMSE), which had a cut-off score of 23 points, and then scanned for optical coherence tomography.

Mini-Mental State Examination (MMSE)

Considering the MMSE score might indicate the severity of cognitive impairment, it is reasonable that the relation between this psychological test and OCT parameters could be relevant information for clinical evaluation and monitoring of cognitively impaired individuals. The brief cognitive evaluations required are typically paper-and-pencil tests that take no more than 10 minutes to finish, involve major mental abilities, yield an objective score, and examine functions such as registration (repeating named prompts), awareness and calculation, remember, language, ability to follow simple instructions, and orientation [35]. MMSE was first launched in 1975 [36]. In order to distinguish organic psychiatric patients from functional psychiatric patients [36,37], a healthcare professional asks a patient a series of questions meant to evaluate a variety of ordinary mental functions during the MMSE. The MMSE has a maximum score of 30 points. A score of 20 to 24 signifies mild dementia, a score of 13 to 20 implies moderate dementia, and a score of less than 12 reveals severe dementia. A person with AD's MMSE score drops by two to four points every year on average. The MMSE has several advantages, including quick administration, the accessibility of different language translations, and elevated levels of acceptability as a diagnostic tool among health professionals and researchers [38].

Inclusion and exclusion criteria

Patients with comorbidities were not permitted to take part. A physical examination, routine blood tests (e.g., complete blood cell count, vitamin B-12 levels, thyroid function tests, and creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and C-reactive protein) were performed on all participants to rule out other known contributors to memory impairment. To rule out the likelihood of overt cerebrovascular illness, routine Magnetic Resonance Imaging (MRI) scans were also done. Control patients got medical examinations to rule out major medical conditions (e.g. Type 1 diabetes mellitus, significant hypertension, or cardiovascular disease). All clinical evaluations were performed by specialists who had been unaware of the patients' genetic status; however, the blinded condition could not be achieved for obviously demented people. Table 1 summarizes the clinical and demographic characteristics of the study population.

Table 1. Demographic characteristics and baseline measures for controls and patients with Alzheimer Disease (AD).

	Controls (n=25)	AD participants (n=25)	P value
Men/Women	11/14	12/13	
Age, mean ± SD	65.4 ± 8.5	69.96 ± 7.94	0.0338
MMSE score (0-30), mean ± SD	28.52 ± 0.92	21 ± 2.22	<0.0001*
Duration of illness, mean ± SD	Not applicable	2.2 ± 0.96	
RBCs count (106/mm3), mean ± SD	3.44 ± 0.13	3.39 ± 0.18	0.2611
WBCs count (103/mm3), mean ± SD	6.95 ± 0.82	7.002 ± 0.66	0.8218
Platelets count (103/mm3), mean ± SD	99.19 ± 5.03	101.6 ± 17.63	0.5087
Serum ALT (IU/L), mean ± SD	30.53 ± 3.19	30.49 ± 2.54	0.7846
Serum AST (IU/L), mean ± SD	35.95 ± 2.68	36.77 ± 4.43	0.4367
T3 (pg/ml), mean ± SD	3.05 ± 0.39	3.15 ± 0.36	0.3234
T4(ng/dL), mean ± SD	1.27 ± 0.16	0.25 ± 0.09	0.5764
TSH (IU/ml), mean ± SD	2.22 ± 0.13	2.26 ± 0.14	0.3589
CRP (mg/L), mean ± SD	3.7 ± 0.24	3.76 ± 0.25	0.41
Vitamin B12 (pg/ml), mean ± SD	373.3 ± 34.14	378.1 ± 38.75	0.6394
Creatinine (mg/dL), mean ± SD	0.83 ± 0.08	0.83 ± 0.09	0.9404

Note: *Statistically significant from control group ($p<0.05$)

Abbreviations: MMSE: Mini-Mental State Examination; RBCs: Red Blood Cells count; WBCs: White Blood Cells count; ALT: Alanine Transferase; AST: Aspartate Transferase; T3: Triiodothyronine; T4: Tetra-iodothyronine; TSH: Thyroid Stimulating Hormone; CRP: C-Reactive Protein

Separation of serum

Each participant's blood sample was withdrawn in ten milliliters (mL) through vein puncture into sterile vacutainers with separator gel and clot promoter without EDTA under strict aseptic conditions and kept at room temperature for 30 minutes. The samples subsequently were clotted for 30–40 minutes at room temperature before becoming centrifuged at 1000 g for 20 minutes at 4°C to collect the supernatants (serums).

Assays of serum

Assays were performed on blood serum samples from AD patients and control participants that had been stored in -70°C freezers for varying lengths of time without being disturbed. Temperature management in the low temperature freezers is checked regularly.

Enzyme-linked immune-sorbent assay

The supernatant remaining after blood centrifugation was used to estimate protein levels in serum using commercially available ELISA kits according to the method of Bradford [39]. An Enzyme-Linked Immuno-Sorbent Assay (ELISA) plate reader was used to measure all ELISA kits (Stat Fax 2200, Awareness Technologies, Florida, USA). Triplicate samples were taken. The concentration was determined using the standard curve. All experimental methods were carried out in accordance with the manufacturers' instructions.

Assessment tauopathy related enzymes

Human MAPT: A sandwich enzyme immunoassay technique was used to assess the concentration of human MAPT in serum samples of AD patients and control participants by a human MAPT ELISA assay kit (Shanghai Sunred biological technology Co., Shanghai, China, Cat. No. 201-12-4259).

Human $A\beta_{(1-40)}$: A sandwich enzyme immunoassay technique was used to assess the concentration of human $A\beta_{(1-40)}$ in serum samples of AD patients and control participants by a human $A\beta_{(1-40)}$ ELISA assay kit (Shanghai Sunred Biological Technology Co., Shanghai, China, Cat. No. 201-12-1231).

Human $A\beta_{(1-42)}$: A sandwich enzyme immunoassay technique was used to assess the concentration of human $A\beta_{(1-42)}$ in serum samples of AD patients and control participants by a human $A\beta_{(1-42)}$ ELISA assay kit (Shanghai Sunred Biological Technology Co., Shanghai, China, Cat. No. 201-12-1265).

Statistical analysis

Data were expressed as mean ± SD. Comparisons between control and AD groups were performed by student t-test using GraphPad instat 3.0. Significance was defined as P<0.05. The graphs were made using GraphPad Prism 8.0.

Results

Baseline and global measures

This study included 25 AD patients and 25 control participants. Their baseline data was presented in Table 1. There was no significant difference between the two groups in demographic data such as age (p=0.0338). There were no significant difference between the studied groups in their baseline laboratory data such as red blood cells count (p=0.2611), white blood cells count (p=0.8218), platelets count (p=0.5087), alanine aminotransferase level (p=0.7846), aspartate aminotransferase level (p=0.4367), tri-iodothyronine level (p=0.3234), tetra-iodothyronine level (p=0.5764), thyroid stimulating hormone level (p=0.3589), C-reactive protein level (p=0.41), vitamin B-12 level (p=0.6394), serum creatinine level (p=0.9404). These laboratory tests were made to exclude secondary cause of dementia. Assessment of the MMSE scale was performed once in the control group and in the AD group. The obtained results from MMSE test were comparable in AD group and statistically significantly lower than in the control group.

Serum tau protein level

The concentration of tau protein in the serum of AD patients was significantly higher by 70% when compared with tau protein concentration in serum of control participants (Figure 1).

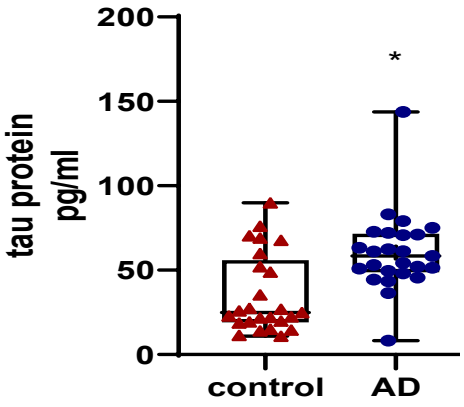

Figure 1. Scatter graphs of tau protein levels in serum samples of AD patients and control participants.
Note: Data are presented as mean ± SD (n=25) *Statistically significant from control group (p<0.05)

Serum $A\beta_{(1-40)}$ protein level

The concentration of $A\beta_{(1-40)}$ protein in the serum of AD patients was significantly lower by 16.5% when compared with $A\beta_{(1-40)}$ protein concentration in serum of control participants (Figure 2).

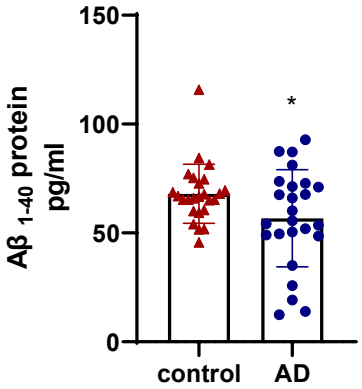

Figure 2. Scatter graphs of Aβ 1-40 protein levels in serum samples of AD patients and control participants.
Note: Data are presented as mean ± SD (n=25) *Statistically significant from control group (p<0.05)

Serum $A\beta_{(1-42)}$ protein level

The concentration of $A\beta_{(1-42)}$ protein in the serum of AD patients was significantly higher by 65% when compared with $A\beta_{(1-42)}$ protein concentration in serum of control participants (Figure 3).

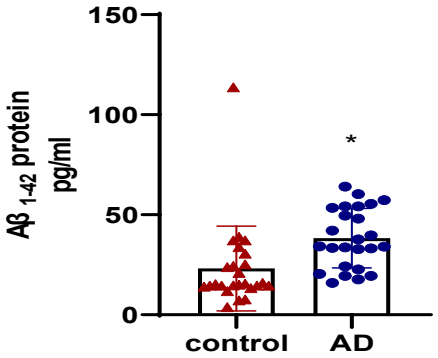

Figure 3. Scatter graphs of Aβ 1-42 protein levels in serum samples of AD patients and control participants.
Note: Data are presented as mean ± SD (n=25) *Statistically significant from control group (p<0.05)

The ratio of blood serum concentration of $A\beta_{(1-42)}/A\beta_{(1-40)}$ proteins

The ratio of $A\beta_{(1-42)}/A\beta_{(1-40)}$ in serum samples of AD patients was 2.3 folds higher than $A\beta_{(1-42)}/A\beta_{(1-40)}$ concentration in serum samples of control participants (Figure 4).

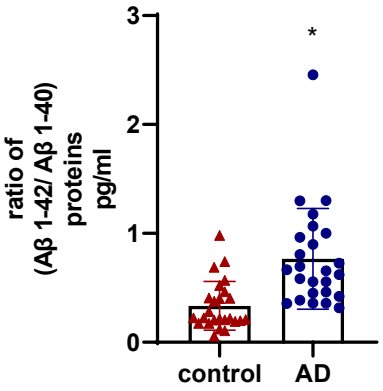

Figure 4. Scatter graphs of ratio of $A\beta_{1-42}$/ $A\beta_{1-40}$ protein levels in serum samples of AD patients and control participants.

Note: Data are presented as mean ± SD (n=25) *Statistically significant from control group ($p<0.05$)

Discussion

Powerful translational finding suggests that disease-modifying therapies for neurodegenerative diseases, including AD, are now more likely to achieve significant effectiveness if initiated as early as possible in the disease process, by relatively well maintaining of neuronal networks homeostasis [40-42]. There is a strong need for blood-based biomarker-guided studies in cognitively normal persons at risk for AD. Blood-based biomarkers are expected to aid in the early diagnosis and classification of people based on their underlying unique pathophysiology at certain time points throughout illness development, as well as to enable accurate biological staging [40,42,43]. Herein, our data show that the plasma tau protein, $A\beta_{(1-42)}$ protein and ratio of plasma $A\beta_{(1-40)}/A\beta_{(1-42)}$ was significantly higher in AD patients while plasma $A\beta_{(1-40)}$ was significantly decreased in AD patients when compared to control participants.

The tau protein is a phosphoprotein that is encoded by the Microtubule-Associated Protein Tau (MAPT) gene *via* alternative splicing [44-48]. In AD, NFTs form in the brain in a regular and hierarchical structure that begins in layer II of the entorhinal cortex, travels through the limbic and association regions, and eventually reaches the hippocampus and neo-cortex [49]. Pathological tau can spread from cell to cell, spreading the disease from impacted to connecting healthy parts of the brain [50,51]. Tau protein combines with tubulin and preserves microtubule integrity through phosphorylation. Tau has 79 phosphorylation sites, the phosphorylation status of which is controlled by tau kinases and phosphatases [52]. Inhibition in this process leads to hyperphosphorylation of tau at these precise locations, resulting in the development of NFTs and neuronal cell death [53]. It was reported that tauopathy was produced in recipient animals by injecting brain extracts from mice or humans with tauopathy into the brains of wild-type animals, and it spread from the injection site across neuronal connections [54-60]. Though the ELISA method for measuring CSF tau in AD patients is well established, the sensitivity and specificity vary throughout researches [22,25]. Previous research found a link between high levels of plasma tau and poor logical memory, total grey matter volume, hippocampal and grey matter thickness [25]. A high tau level had been linked to the development of AD and a considerable mortality rate. In the instance of AD patients, the production of NFTs in the brain was found to be associated with increasing amounts of hyperphosphorylated tau protein [61]. High tau protein phosphorylation has also been linked to a quicker development of moderate cognitive decline to AD and rapid cognitive decline in AD [62,63]. Here, we measured elevated level of tau protein in serum of AD patients compared to controls participants by ELISA technique. These proteins' high sensitivity and specificity may be effective in diagnosing the AD condition with high accuracy by eliminating false positive and false negative findings.

Aβ is a proteolytic component of Amyloid Precursor Protein (APP), which is abundantly expressed in neurons and is physiologically involved in various functions including neurite outgrowth, axonal guiding regulation, synapses function, plasticity regulation, involvement in initial nervous system development, and neuroprotective effects [64-66]. APP can be processed in two ways: in the non-amyloidogenic pathway, APP is first cleaved by α-secretase, and then by γ-secretase, which cuts the protein inside the Aβ domain. However, in the amyloidogenic pathway, APP is broken sequentially by β-and γ-secretase before being released extracellularly as Aβ pieces of varying lengths, but primarily consisting of 40 [$A\beta_{(1-40)}$] or 42 [$A\beta_{(1-42)}$] amino acid residues [67]. Once generated, monomeric Aβ can combine into various assemblies, giving rise to insoluble oligomers, protofibrils, as well as Aβ fibrils, which can then assemble into Aβ plaques, although monomeric and oligomeric forms of Aβ remain soluble. Since these several states of Aβ coexist in the AD brain, it is difficult to distinguish the most significant and hazardous forms in terms of etiology. Despite the fact that *in vivo* studies have shown that Aβ plaques cause neuronal death, neuronal degeneration, and impair normal neuritic functions [68-70]. Here, we found that AD patients had decreased levels of $A\beta_{(1-40)}$ when compared to control participants. These results were in agreement with previous studies which found decreased levels of $A\beta_{(1-40)}$ in AD patients [71-77]. The drop in plasma $A\beta_{(1-40)}$ levels during AD might be explained by a reduction in Aβ elimination from the brain (CSF) to the peripheral fluids (blood) due to changes in blood-brain barrier permeability, glymphatic system, or cerebrovascular or microglial activation issues associated with The condition or older age [77]. On the contrary, we found elevated levels of $A\beta_{(1-42)}$ in AD patients when compared to control participants. These results were in agreement with previous studies which found elevated levels of $A\beta_{(1-42)}$ in AD patients [78-80]. Our findings suggest that two plasma biomarkers [$A\beta_{(1-40)}$ and $A\beta_{(1-42)}$] may be utilized to predict cerebral Aβ deposition with high accuracy. These findings provide an exciting basis for future research targeted at building a blood-based analysis platform that might expand worldwide accessibility since it would be less expensive and time-consuming than assessing brain amyloidosis using Aβ-positron emission tomography scanning equipment.

While AD biomarkers assessed in CSF are clearly indicative of AD pathophysiology, the challenges associated with their use, such as invasiveness of techniques, increased cost, limited access to scanners and cyclotrons, and limited convenience as a screening tool, have hindered their widespread use in clinical and research settings [81,82]. Blood-based biomarkers, on the other hand, would be a widely recognized and practical strategy if they exhibited sensitivity and specificity equivalent to neuroimaging and CSF indicators [82,83]. Lately, the relevance of the CSF $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio as a new biomarker has emerged as a method to alleviate biases associated with pre-analytical or analytical factors [84-86], to improve the diagnostic performance of CSF biomarkers, particularly in conflicting cases as well as for use in clinical routine [84,86,87]. Although everyone's baseline amount of Aβ peptides vary [88], recent research combining positron emission tomography Aβ imaging and CSF biomarkers found that the $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio produced greater correlation than $A\beta_{(1-42)}$ alone [89,90]. However, only a few studies have reported on the $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio in the serum of AD patients. In our study we measured the level of $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio in serum of AD patients and control participants. We found that AD is associated with higher $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio level when compared to control participants. According to previous research, the plasma $A\beta_{(1-42)}/A\beta_{(1-40)}$ ratio is the strongest predictor of cerebral Aβ amyloidosis [91]. So, this ratio can be used as an early and easy predictive tool of AD pathogenesis.

On the whole, blood-based biomarkers are projected to allow essential clinical solutions prompted by the global threat of the expanding AD epidemic [92,93]. They will support early screening and identification of individuals who are very unlikely to develop AD-related pathophysiology, as well as increase the likelihood that individuals with AD pathophysiology

are chosen for further investigations using more specific, expensive, and/or more invasive methods with limited accessibility (such as positron emission tomography imaging or CSF assessment). The widespread availability of blood-based biomarkers will also open the way for a more cost-effective, resource-efficient, and time-efficient multistep diagnostic workup, as well as aid the retooling of drug Research and Development processes, from proofs of pharmacology through clinical trial design [42,94].

Conclusion

Blood-based biomarkers will be a widely known and practical approach for prediction of AD with high sensitivity and specificity equivalent to neuroimaging and CSF indicators. They will support early screening and identification of individuals who are very unlikely to develop AD-related pathophysiology. The extensive availability of blood-based biomarkers will also open the way for a cheaper and time-saver multistep diagnostic tool. In our study, we found that elevated levels of tau protein, $A\beta_{(1–42)}$ protein, ratio of $A\beta_{(1-42)}/A\beta_{(1-40)}$ proteins and reduced level of $A\beta_{(1-40)}$ protein were highly sensitive and specific markers that differentiate healthy individuals from patients with AD.

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Disclosure

The authors declare no conflict of interest.

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