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REVIEW

Cerebrospinal fluid biomarkers for understanding multiple aspects of Alzheimer's disease pathogenesis

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Abstract

Alzheimer's disease (AD) is a multifactorial age-related brain disease. Numerous pathological events run forth in the brain leading to AD. There is an initial long, dormant phase before the clinical symptoms become evident. There is a need to diagnose the disease at the preclinical stage since therapeutic interventions are most likely to be effective if initiated early. Undoubtedly, the core cerebrospinal fluid (CSF) biomarkers have a good diagnostic accuracy and have been used in clinical trials as end point measures. However, looking into the multifactorial nature of AD and the overlapping pathology with other forms of dementia, it is important to integrate the core CSF biomarkers with a broader panel of other biomarkers reflecting different aspects of pathology. The review is focused upon a panel of biomarkers that relate to different aspects of AD pathology, as well as various studies that have evaluated their diagnostic potential. The panel includes markers of neurodegeneration: neurofilament light chain and visinin-like protein (VILIP-1); markers of amyloidogenesis and brain amyloidosis: apolipoproteins; markers of inflammation: YKL-40 and monocyte chemoattractant protein 1; marker of synaptic dysfunction: neurogranin. These markers can highlight on the state and stage-associated changes that occur in AD brain with disease progression. A combination of these biomarkers would not only aid in preclinical diagnosis, but would also help in identifying early brain changes during the onset of disease. Successful treatment strategies can be devised by understanding the contribution of these markers in different aspects of disease pathogenesis.

Keywords Diagnosis · Neurofilament light · Neurodegeneration · Synaptic dysfunction · Neurogranin · Fatty acid-binding proteins · Neuroinflammation

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease whose pathology starts decades before the clinical symptoms appear [1]. The preclinical stage represents a dormant phase where neuropathological changes are accumulating but the person has normal cognition [2]. Numerous biochemical pathways have been described to explain the pathogenesis of AD. Starting with the identification of amyloid beta (Aβ) in 1985, as the main component of

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amyloid plaques [3], our understanding of Aβ and amyloid precursor protein (APP) metabolism, and tau pathology (neurofibrillary tangles and neuropil threads) has improved with time. Thorough research has been carried out to understand other aspects of AD pathogenesis and thereafter, numerous hypotheses have been put forth. AD may, therefore, be considered a result of a number of pathological changes in the brain, such as amyloidosis, neurodegeneration, inflammation, synaptic dysfunction, disruption of neuronal signaling and neuronal membranes, oxidative stress and mitochondrial dysfunction [4]. These changes direct the trajectory of preclinical AD to AD dementia and make AD a multifaceted disease.

Several AD drug trials have failed, probably because the treatments are initiated at an advanced stage where damage is too severe, and the drug is not able to demonstrate a clinical benefit because the brain is too compromised to benefit from a treatment [5–7]. It is imperative to initiate an early treatment and ensure that the correct patient population is included in the clinical trials. Therefore, there is an urgent need to diagnose AD and initiate treatment at the preclinical stage, so as to obtain a clinical benefit. The first step in devising successful treatment strategies is to identify biomarkers for accurate diagnosis of AD, and thereafter develop therapeutic strategies. It is essential to find an ideal biomarker that should also help in monitoring the mechanism of action and the biochemical effects of the treatment drug [8]. As per the regulatory bodies such as Food and Drug Administration (FDA) and European Medicine Agency (EMA), exploration and validation of a biomarker should be integrated with drug development to accelerate the journey towards development of an effective therapeutic intervention [9]. Clinical trials that aim at evaluating the effectiveness of therapeutic strategies can come up with reliable results when the therapeutic effect of these agents is monitored using markers that reflect over the molecular changes of the disease. As far as AD is concerned the promising markers in this context are the cerebrospinal fluid (CSF) markers [8]. The CSF biomarkers are the potential candidates to facilitate early diagnosis of AD because the AD pathological hallmarks start decades before the appearance of cognitive symptoms [10]. The core CSF biomarkers [CSF Aβ-42, total tau (T-tau) and phosphorylated tau (P-tau)] have been extensively studied and validated in relation to AD pathology, conversion and progression. There is a further need to explore and evaluate additional CSF biomarkers, which can aid in early and accurate diagnosis of AD, as well as in monitoring the downstream effects of a therapeutic intervention. As seen from the high failure rate of AD drug trials, it is extremely essential to explore additional CSF biomarkers which reflect on individual pathologies, meet the regulatory qualification and can help to enrich the clinical trial populations.

The CSF biomarkers as a part of AD diagnostic criteria

The biomarkers of AD have been divided into three main categories: the biomarkers of amyloid deposition (A), tau pathology (T) and neurodegeneration (N) (A/T/N) [11]. The biomarkers of amyloid accumulation include abnormal tracer retention on amyloid positron emission tomography (PET) imaging and CSF Aβ-42. The biomarkers of tau pathology include CSF P-tau or tau PET. The biomarkers of neurodegeneration include CSF T-tau and ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and brain atrophy via magnetic resonance imaging (MRI). The brain imaging techniques have been used as end points in clinical trials [12]. However, the limited accessibility, lack of molecular specificity, exposure to radioactivity and cost factor involved in neuroimaging markers particularly Aβ imaging, restricts their use in routine analysis [13]. Therefore, the CSF is being extensively studied worldwide, in AD biomarker research. The CSF is in direct contact with the brain and the biochemical changes occurring in the brain are reflected in it [14]. The CSF biomarkers have a causal relation to AD pathology and may provide an insight into the different aspects of AD pathogenesis. The core CSF biomarkers (decreased CSF Aβ-42 and elevated T-tau and P-tau) have shown a high specificity and sensitivity for AD diagnosis [15]. CSF Aβ-42 correlates well with Aβ pathology [16], whilst the correlation of the tau markers with pathology is less clear; recent data indicate that CSF T-tau and P-tau may be markers of a neuronal reaction to Aβ pathology, which with time will translate into full-blown pathology (neurodegeneration and tangle pathology) [17]. In any case, these markers are quite specific for identifying an individual with preclinical AD [18].

In the recent years, with the advances in our understanding of AD pathophysiology, it has become evident that the relation between clinical symptoms and disease pathology varies, and the cognitive impairment evolves gradually. As a result, in 2011 the National Institute on Aging (NIA) and the Alzheimer's Association (AA) revised the diagnostic and research criteria for AD and included the CSF biomarkers in addition to the imaging markers [19]. In 2014, the International Working Group (IWG) reanalysed the pathological and topographical biomarkers of AD. Diagnostic changes were proposed for typical, atypical, mixed and preclinical AD. According to this, the pathological markers such as decreased CSF Aβ-42 and elevated T-tau and P-tau were considered as specific makers of disease pathology [18].

The need of additional CSF biomarkers

The research on core CSF biomarkers (CSF Aβ-42, T-tau and P-tau) began nearly 2 decades ago. Reduced CSF Aβ and elevated T-tau and P-tau were found in the CSF of AD patients. [20, 21]. This created a pathway for further research to look over into the diagnostic potential of these biomarkers, which reflect upon brain amyloidosis and neurodegeneration. Today, these biomarkers are extensively used in diagnosis and clinical trials. They have a high enough diagnostic accuracy and reflect upon the neuropathological hallmarks of AD: the neurofibrillary tangles and amyloid plaques [22]. Additional biomarkers are still needed to complement the core biomarkers for early diagnosis and prognosis of AD and get a better insight into the different pathogenic pathways associated with the AD.

The core CSF biomarkers are relatively stable in clinical AD and, therefore, do not serve as good markers in studying disease progression [23, 24]. The CSF Aβ-42 is sharply reduced in the preclinical phase of AD while the levels are found to be constant in the subsequent phases [25]. The altered levels of these core markers do not predict the rate of cognition decline as they do not correlate with the Mini Mental Status Examination (MMSE) [26]. In another multi-center longitudinal study, it was found that there was lack of association between the changes in CSF biomarkers and the rate of change or decline in cognition over a period of 4 years [27]. In addition, these markers do not perform well enough in differentiating AD from other forms of dementia due to partially coinciding pathologies [28]. The therapeutic strategies that aim at reducing amyloid load have failed to show a clinical benefit in spite of clearing Aβ [29]. Studies have shown that the reduced levels of CSF Aβ negatively correlate with the brain amyloid load [30]. However, this association does not match with the clinical diagnosis of AD. The discordance has been found mainly in the cognitively normal participants, which have reduced CSF Aβ but are amyloid negative as seen by PET. Therefore, CSF Aβ levels are altered in the preclinical stage [31–34]. This has led to the contamination of cohort groups due to the inclusion of CSF Aβ positives in the control group. This necessitates the need for exploration and evaluation of additional or novel biomarkers that aid in accurate diagnosis, correlate with cognitive function, but also help in better understanding the disease progression and different aspects of AD pathology.

AD is a multifaceted disease, and AD dementia is a result of a number of pathological changes in the brain (Fig. 1). Numerous proteins or other biomolecules play significant roles in these pathological pathways. A reduction or elevation of their levels in the CSF is associated with a pathological change, which can directly highlight upon the extent of damage, or can occur as a protective response against the damage. A detailed understanding of disease pathogenesis at molecular level through CSF biomarkers can help in designing new efficacious chemical entities for treatment. In addition, biomarkers can serve as targets for therapeutic agents aimed to combat the associated pathological change. In context of a clinical trial, a biomarker can serve as a surrogate end point. The time consuming end points associated with the ongoing trails in AD can be reduced with the application of additional makers [35, 36]. An early diagnosis aided through CSF biomarkers would ensure cohort uniformity through recruitment of correct patient population. This would help in improving clinical trial design and interpretation [37]. The clinical stages of AD are well defined and understood, but it is important to identify and understand the different pathophysiological stages of AD. CSF biomarkers would help in understanding and identifying these stages. To bring advancement in the field of AD biomarker and therapeutic research, it is of utmost important that new biomarkers in relation to AD pathogenesis be explored in the CSF and their potential to diagnose AD at preclinical stage be evaluated in well-established cohorts.

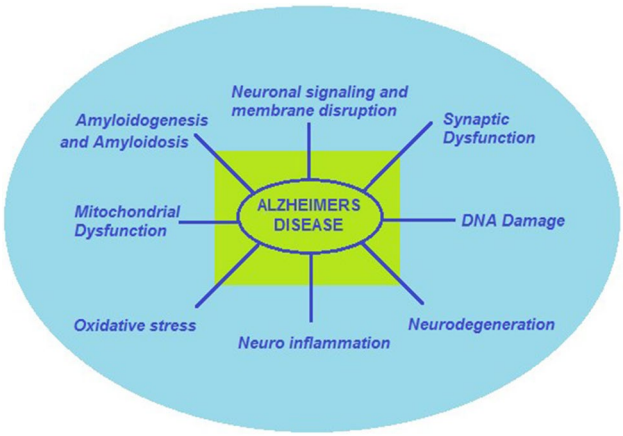

Fig. 1 Alzheimer's disease: a multifaceted disease

This review highlights upon the various CSF biomarkers that reflect upon different aspects of multifaceted AD, and also highlights upon the different studies conducted on these biomarkers in the past. Each biomarker helps to track different pathological events. An assessment of the levels of these markers in CSF might reveal an independent information or might unfold the association between individual pathologies. Altogether, the CSF measure of the biomarkers that relate to individual AD pathologies such as brain amyloidosis, neurodegeneration, synaptic dysfunction and neuroinflammation can help in better understanding the disease pathogenesis, accurate diagnosis and prognosis and thereby help in devising effective treatment strategies (Fig. 2).

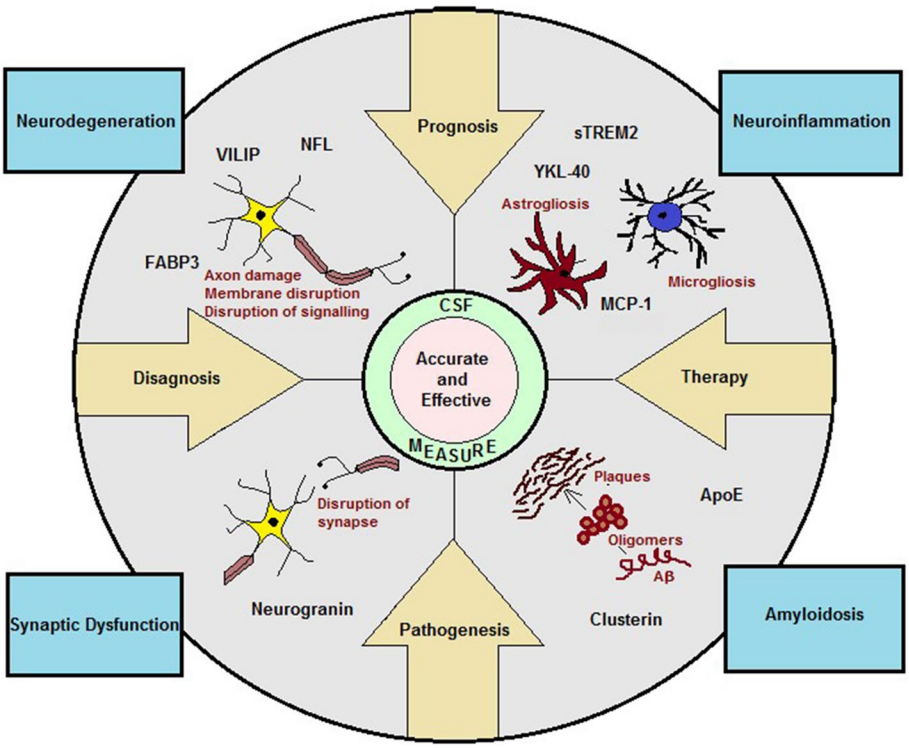

Fig. 2 CSF biomarkers for Alzheimer's disease (AD) diagnosis and understanding different aspects of pathology

The biomarkers of amyloidogenesis and brain amyloidosis

Apolipoprotein E (ApoE)

Role in AD pathogenesis

ApoE is a glycoprotein, which is highly expressed in the liver and the Central Nervous System (CNS) [38]. In the CNS, it is mainly expressed by astrocytes and to some extent by the microglia [39, 40]. It is a constituent of lipoproteins, and in the CNS it is mainly confined to the HDL (high-density lipoproteins) [41]. In the brain, apoE plays a vital role in regulating cholesterol metabolism and transport [42]. ApoE plays a significant role in AD pathogenesis by affecting amyloid and tau pathology, and the isoforms have a differential role in pathogenesis

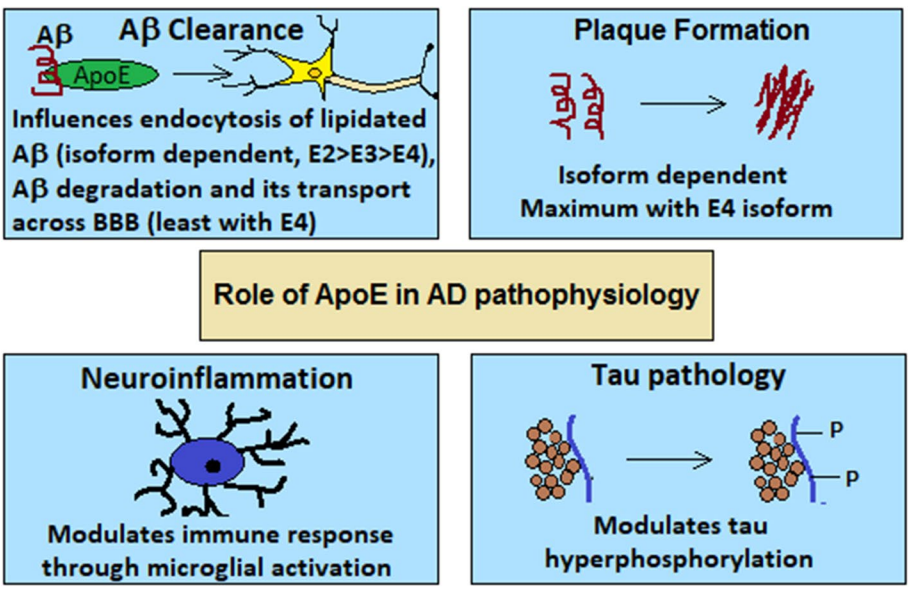

Fig. 3 Role of apoE in the pathophysiology of AD (*AD* Alzheimer's disease, *ApoE* apolipoprotein E, *Aβ* amyloid beta)

(Fig. 3). Genome wide association studies (GWAS) have revealed that *APOE* locus, on chromosome 19, with ε4 variant as the major genetic risk for late onset Alzheimer's disease (LOAD) [43, 44]. In response to neuronal injury, the expression of apoE is upregulated [45]. The three isoforms of apoE (E2, E3, E4) differentially affect cholesterol transport, metabolism and synaptic plasticity, repair and neurite growth. The E4 isoform is least effective in regulating cholesterol transport, efflux and synaptic plasticity [46, 47].

ApoE mediates clearance of Aβ in an isoform-dependent manner, through endocytosis of Aβ lipoprotein complexes, by affecting proteolytic degradation of Aβ and its transport across BBB. Lipidated apoE binds to Aβ to form Aβ lipoprotein complexes [48] and facilitates endocytosis of these complexes. ApoE binds with its receptors, low-density lipoprotein receptor (LDLR) and lipoprotein receptor-related protein (LRP1), and mediates the endocytosis of lipoproteins [49]. The three isoforms bind differentially with Aβ (E2 > E3 > E4), and differentially influence the lipidation of Aβ and hence the endocytosis [50]. ApoE also regulates proteolytic degradation of Aβ, and among the isoforms E4 isoform is the least efficient in promoting the degradation [51]. ApoE also influences Aβ clearance by regulating its transport across BBB, in an isoform-dependent manner. The E2 and E3 isoforms mediate faster clearance of Aβ through the BBB as compared to E4 [52]. This could be attributed to the effect of apoE on the integrity of tight junctions in BBB, which is impaired in the apoE4-BBB model and apoE4 knock-in mice [53]. ApoE also affects accumulation of Aβ by promoting formation of Aβ filaments [54]. The presence of apoE is essential for Aβ accumulation, which is isoform dependent. The E4 isoform promotes much higher accumulation than E2 and E3 [55, 56]. No amyloid deposits were found in $APOE^{(-/-)}$ transgenic mice ($APP^{V717F+/-}$), that overexpresses the amyloid precursor protein, as compared to $APOE^{(-/+)}$ and $APOE^{(+/+)}$ [55]. Significant differences in Aβ deposition have been found in PDAPP mice (which develop age-dependent Aβ accumulation), according to the apoE isoform expressed. The amyloid load in hippocampus was two times higher in E4 mice compared to E3 and 4.6 times higher than E2 mice [56].

Neurodegeneration in AD is also influenced by apoE. ApoE affects neuroinflammation, and tau-mediated neurodegeneration. ApoE4 exacerbates neuronal death and modulates microglial activation [57], and overexpression of apoE4 results in tau hyperphosphorylation [58]. Higher tau levels have been found in P301S/E4 tau transgenic mice compared with P301S/E2 and P301S/E3 mice. The brain atrophy and neuroinflammation were much more in E4 mice as compared to E2 and E3 [57]. Recent data also suggest intriguing interactions between apoE isoforms and the activation state of disease-associated microglia, which may be part of the disease-promoting effect of apoE4 [59].

CSF biomarker studies pertaining to ApoE

ApoE is a major apolipoprotein found in the CSF [60]. Numerous studies have evaluated the levels of apoE in the CSF, so as to establish it as a potential marker (Table 1). To evaluate the CSF levels, researches have used methods such as enzyme-linked immuno sorbent assay (ELISA), mass spectrometry, multiplex assays and flow cytometry. Studies on CSF levels of apoE in AD show inconsistent results, with either decreased [61–64] or elevated [65–67] levels as compared to controls. As per some studies *APOE* genotype may influence CSF ApoE levels. Higher CSF levels of apoE have been reported in individuals having *APOE* ε4 alleles [68]. Strong positive correlations have been found between CSF apoE levels and CSF tau in AD patients as compared to controls [65]. The correlation between CSF apoE levels and CSF tau are also *APOE* genotype dependent [69]. The correlation between the two markers suggests that altered apoE levels in CSF could be attributed to the neurodegeneration in AD or vice versa. ApoE binds to protein tau in an isoform-dependent manner [70]. The association of apoE CSF levels with genotype, and genotype-dependent correlation between ApoE and CSF Tau, suggests that neurodegeneration is isoform influenced.

Thus, quantification of apoE levels can highlight upon state of amyloid and tau pathology in AD brains. Owing to the significant role of apoE in AD pathogenesis, further studies should be conducted in well-established cohorts to establish apoE as a potential CSF diagnostic and theragnostic biomarker. There have been inconsistencies with regard to CSF apoE levels. However, these inconsistencies could be attributed to a number of factors such as sample variability, variability in method or technique of analysis or unequal gender distribution in study groups.

Clusterin

Role in AD pathogenesis

Clusterin also called apolipoprotein J is a stress-induced chaperone glycoprotein which can stabilize stressed protein structures. It does so by binding to the hydrophobic surfaces of the partially unfolded proteins [77, 78]. In the brain, it is highly expressed by astrocytes [79]. It plays varied roles in AD pathology. Genome wide association studies (GWAS) have revealed that single nucleotide polymorphisms (SNP's) associated with clusterin (*CLU*) gene are associated with AD [80]. Genetic variations have been located by resequencing of *CLU*-coding exons. These variations can lead to non-synonymous substitutions,

Table 1 Studies conducted to evaluate the role of apoE as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with APOE genotype/core markers	Analysis method
Van Harten et al. [71]	Non-demented individuals ($n=430$) classified into subjective cognitive decline (SCD, $n=207$) or mild cognitive impairment (MCI, $n=213$)	CSF levels were higher in MCI compared to SCD at baseline, on stratification of MCI and SCD into ε4 and non-ε4 carriers and significant difference was seen only in ε4 carriers	CSF levels were strongly associated with CSF T-tau and P-tau in *APOE* ε4 carriers	ELISA
Johansson et al. [72]	AD ($n=29$), other dementias ($n=4$), stable cognitive function (SMCI, $n=13$) and healthy controls ($n=18$)	CSF levels were significantly elevated in AD compared to other dementia and lower as compared to healthy controls	ApoE levels in CSF were not associated with *APOE* genotype	Luminex multiplex assay
Rezeli et al. [73]	AD ($n=13$) and non-AD ($n=12$)	No significant difference between study groups	ApoE levels in CSF were not associated with *APOE* genotype; CSF levels positively correlated with P-tau in ε4 non-carriers	Mass spectrometry
Richens et al. [74]	AD ($n=10$) and controls ($n=18$)	No significant difference between study groups		Luminex multiplex assay
Toledo et al. [75]	Normal controls ($n=92$), MCI ($n=149$) and AD ($n=69$)	CSF apoE levels were associated with cognitive decline and atrophy rate	Results were only significant in the group without the ε4 allele	Luminex multiplex assay
Perrin et al. [76]	Cognitively normal [clinical dementia rating (CDR 0, $n=24$) and mild AD or probable AD (CDR 1, $n=24$)]	Did not differ significantly between the two groups		ELISA
Zhang et al. [61]	AD ($n=48$), Parkinson's disease (PD, $n=40$), controls ($n=95$)	Reduced in AD as compared to controls, but did not differ from PD		Multiplex assay
Hesse et al. [68]	AD patients ($n=55$) and normal controls ($n=21$)	Reduced in AD as compared to the controls	Individuals having ε4 allele had higher apoE levels	ELISA
Fukuyama et al. [66]	AD patients, $n=25$ [early onset Alzheimer's disease (EOAD) and late onset Alzheimer's disease (LOAD)] and normal controls ($n=36$)	ApoE levels were reduced with age in normal controls and increased in AD (more distinctly in EOAD). The elevated levels were positively correlated with decline in cognition		ELISA
Pirttilä et al. [64]	AD ($n=25$); classified as *APOE* ε4 positive ($n=16$) and negatives ($n=9$), and as mild ($n=16$) and moderate dementia ($n=9$)	ApoE levels decreased with time in ε4 positives and in both mild and moderate dementia		ELISA
Lindh et al. [65]	AD ($n=18$), MCI ($n=9$), other dementia disorders (ODD, $n=9$) and age-matched healthy controls	Elevated in AD, MCI and ODD as compared to healthy controls and significantly increased in AD at follow-up	CSF levels significantly correlated with CSF tau in AD	ELISA
Merched et al. [67]	AD ($n=38$), controls ($n=31$) and those suffering from other neurological disorders ($n=47$)	Significantly elevated in patients with LOAD as compared to controls and other neurological disorders		ELISA
Landen et al. [63]	EOAD ($n=23$), LOAD ($n=31$), frontotemporal dementia (FTD, $n=16$), vascular dementia (VaD, $n=25$) and controls ($n=25$)	Significantly reduced in all the groups compared to the controls, in EOAD compared to LOAD and FTD	ApoE levels in CSF were not influenced by *APOE* genotype	ELISA

Table 1 (continued)

Study	Study groups	CSF levels in AD/study groups	Association with APOE genotype/core markers	Analysis method
Blennow et al. [62]	AD ($n=11$), FTD ($n=10$) and controls ($n=10$)	Significantly reduced in AD as compared to the controls and FTD group. Also, significantly reduced in FTD as compared to controls		ELISA

insertions or deletion in β chain of clusterin affecting its further processing and functioning [81].

Clusterin affects amyloid pathology in multiple ways. It interacts with the Aβ peptides to form complexes. The antibodies specific to clusterin strongly stain the amyloid deposits in AD brain [82]. This interaction keeps Aβ solubilized and prevents its fibrillation, and also regulates its transport across the BBB [83–85]. The binding of clusterin with Aβ increases its clearance through BBB. A study on mice models has shown that Aβ clearance is increased by 83%, when bound to clusterin [85]. Another study conducted on Tg6799 mouse has found reduction in amyloid plaques and severity of cerebral amyloid angiopathy, upon intravenous administration of clusterin [86]. Clusterin levels are increased in response to Aβ accumulation. Higher intracellular clusterin levels were found upon exposure of Aβ in APP/PSEN1 mice and hippocampal neurons [87]. The levels are significantly increased in frontal cortex and in the hippocampus in AD [88]. The elevated levels are localized to the regions abundant in Aβ [89]. This could be attributed as a protective response to combat the excessive Aβ deposition within the brain tissue. It likely suppresses Aβ deposition in conjunction with ApoE. This is evident through the results obtained from a study conducted on PDAPP transgenic mice, to look at the influence of apoE and clusterin on Aβ accumulation. Aβ accumulation was higher and early in $apoE^{(-/-)}$ and $clusterin^{(-/-)}$ mice. In addition, the Aβ levels were elevated in CSF and brain interstitial fluid, in such mice [90].

It acts as a neuroprotectant by combating oxidative stress and apoptosis [91]. It prevents the mitochondrial transfer of activated Bcl-2-associated X (Bax) protein, a member of Bcl-2 protein family, which is known to accelerate apoptosis. Clusterin is also involved in double-stranded DNA break repair [92–94]. Clusterin also influences inflammation and immune response. The expression of clusterin by astrocytes is increased on treatment with Interleukin 2 [95]. It inhibits the membrane binding of membrane attack complex and regulates the nuclear factor kappa light chain enhancer of activated B cell (NF-κB) pathway [96, 97]. NF-κB is a transcription factor, whose activation causes reactivation of astrocytes, increases the expression of inflammatory mediators such as cytokines and free radicals [97]. Therefore, NF-κB is an inducer of neuroinflammation. Clusterin inhibits the NF-κB activity by stabilizing inhibitors of NF-κB (IκBs) [98].Therefore, clusterin plays varied roles in AD pathology and serves as neuroprotectant by combating apoptosis, regulating inflammation and immune response and preventing aggregation of Aβ (Fig. 4). It can certainly serve a potential stage and state AD biomarker.

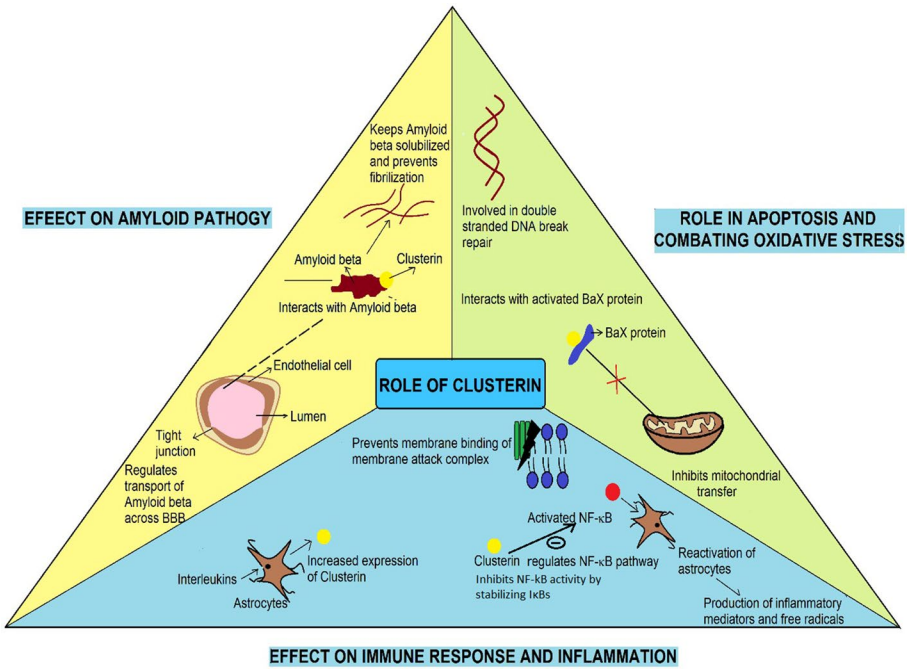

Fig. 4 Varied roles of clusterin in AD pathology (*Bax protein* Bcl-2-associated X protein, *BBB* blood brain barrier, *DNA* deoxyribonucleic acid, *NF-κB* nuclear factor kappa light chain enhancer of activated B cells, *IκBs* inhibitors of NF-κB). Yellow circle in the figure represents clusterin

CSF biomarker studies pertaining to clusterin

Numerous studies have evaluated the diagnostic potential of clusterin in CSF using different methods such as ELISA, mass spectrometry and multiplex assays. Most of the studies have reported that clusterin is significantly increased in CSF of AD patients (Table 2). The increased levels of clusterin could be attributed as a defence against neurodegeneration. CSF clusterin levels correlate well with the core CSF biomarkers (T-tau and P-tau, and Aβ-42), and are also significantly associated with CSF tau/Aβ ratio [99–101]. CSF clusterin levels were found to be associated with the entorhinal cortex atrophy rate among CSF Aβ-42-positive individuals. [102]. These correlations very likely suggest that CSF clusterin levels are elevated in relation to the pathological changes in the brain. Elevation in CSF levels of clusterin and the correlation with core biomarkers suggest that elevated levels of clusterin could be attributed as a protective response to the amyloidosis and increased neurodegeneration in the AD brain. Looking at the role of clusterin in AD pathogenesis, a further exploration of its role as an AD biomarker is needed in the CSF.

Aβ oligomers (AβOs)

Role in AD pathogenesis and biomarker studies

Neurodegeneration is a result of self-association of Aβ molecules and not just caused by the presence of Aβ. The oligomers of Aβ can be even more toxic than fibrillar Aβ aggregates [107]. They affect synapse composition, shape and density, thereby play a significant role in synaptic degeneration in AD [108]. Administration of cell-derived AβOs inhibit long-term potentiation of synaptic transmission, induced in rats [109]. The CSF levels of AβOs have been quantified in AD. Using a sensitive assay, it has been found that CSF levels of AβOs significantly increase in AD patients as compared to aged controls [110]. Lower levels of CSF AβOs have been reported in AD patients as compared to those with other forms of dementia [111]. In another study the ratio of AβOs/Aβ-42 was found to be significantly elevated in AD as compared to the non-AD group [112]. The diagnostic potential of AβOs in AD should be further explored using well-established cohorts.

Biomarkers of neuroinflammation

YKL-40/chitinase-3-like protein 1 (CHI3L1)

Role in AD pathogenesis

YKL-40 is a glycoprotein belonging to the family of 18 glycosyl hydrolases. It is also called human cartilage glycoprotein-39 (HC gp-39) or chitinase-3-like-1 protein (CHI3L1). It binds with chitin but does not have a chitinase activity [113]. It is secreted by the chondrocytes, synovial cells, vascular smooth muscle cells, macrophages and neutrophils [114, 115]. It is named based on the first three terminal amino acids: tyrosine (Y), lysine (K), and leucine (L) [115, 116]. YKL-40 plays a key role in inflammation, therefore, influences AD pathology. In

Table 2 Studies conducted to evaluate the role of clusterin as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with APOE genotype/core markers	Analysis method
Deming et al. [99]	AD ($n=300$) and controls ($n=373$)	Clusterin CSF levels were significantly elevated in AD	CSF levels were not associated with *APOE* genotype	Multiplex immunoassay
Prikrylova Vranova et al. [103]	PD ($n=23$), Parkinson's disease dementia (PDD, $n=18$), dementia with Lewy bodies (DLB, $n=15$), AD ($n=18$), progressive supranuclear palsy (PSP, $n=16$), multiple system atrophy (MSA, $n=12$) and control group ($n=21$)	No significant difference between AD and other diagnostic groups		ELISA
Jongbloed et al. [100]	Subjective memory complainers (SMC, $n=17$) and volunteers ($n=14$)	The clusterin CSF levels were reduced in SMC. The difference in the CSF levels between study groups was more clear with the CSF clusterin/plasma ratio	Significant positive correlation with CSF T-tau and P-tau	ELISA
Sihlbom et al. [104]	AD ($n=17$) and controls ($n=16$)	The clusterin CSF levels were elevated in AD		Mass spectrometry
Nilselid et al. [101]	AD ($n=99$) and controls ($n=39$)	The clusterin CSF levels (native and deglycosylated) were elevated in AD	Both native and deglycosylated clusterin levels positively corrected with CSF tau and Aβ-42	ELISA
Finehout et al. [105]	AD ($n=34$) and controls (non-AD, $n=34$)	The clusterin CSF levels were elevated in AD		Mass spectrometry
Lidstrom et al. [106]	AD ($n=32$), VaD ($n=20$), PD ($n=17$) and controls; longitudinal samples from patients with acute stroke	The clusterin CSF levels did not differ significantly in AD, VaD, PD or acute stroke, as compared to controls	CSF clusterin levels did not depend on the *APOE* ε4 status in AD	ELISA

response to neuroinflammation, the expression of YKL-40 is increased and is localized to astrocytes in the region of inflammation [117]. It is expressed by the microglia, and the expression of YKL-40 messenger ribonucleic acid (mRNA) is increased in AD [118]. Microglia and astrocytes are associated with senile plaques in AD and play a key role in immune response in the brain [119]. The microglia are activated in response to neurodegeneration. The plaque-associated activated microglia are large and mostly phagocytic [120]. They constantly scavenge the plaques, damaged neurons, infectious agents and promote inflammation in damaged tissue [121, 122]. Aβ, either alone or together with inflammatory mediators, sets up an activation cycle to activate the microglia and thereby generate an immune response in the brain [123]. Microglial activation thereby plays an important role in AD [124]. Therefore, microglial-expressed protein YKL-40 is a potential marker of neuroinflammation and plays a significant role in AD pathogenesis.

CSF biomarker studies pertaining to YKL-40

The CSF levels of YKL-40 are elevated in AD. Through numerous studies, it has been have found that increased levels of YKL-40 in CSF have prognostic and diagnostic utility as a biomarker for AD. YKL-40 aids in preclinical AD diagnosis and discriminating cognitively normal individuals from mild cognitive impairment (MCI) or AD patients (Table 3). The role of YKL-40 is also seen in differential diagnosis of dementia [125]. The levels of YKL-40 have been found to significantly correlate with MMSE scores [126]. Studies suggest YKL-40 is elevated early in the AD continuum and can serve as a valuable neuroinflammatory marker to detect early pathological changes and can even be used to study disease progression. The association of CSF YKL-40 with CSF T-tau and P-tau (Table 3) indicates that YKL-40 can help in tracking the neuroinflammation associated to neurodegeneration. Being a potential diagnostic and prognostic marker, it can serve as a target to combat AD-associated neuroinflammation. YKL-40 levels are consistently increased with age. This suggests that neuroinflammation occurs normally with aging. However, the still higher increase in ε4 carriers suggest that neuroinflammation is exacerbated with amyloidosis and neurodegeneration [127]. On the contrary, a recent study also indicates that inflammation could be driven by amyloidosis but, independent of the *APOE* ε4 status. In this study, the CSF levels were elevated in Aβ-positive individuals (low CSF Aβ), who were *APOE* ε4 non-carriers [128]. Therefore, YKL-40 can be used as a potential marker to stage the neuroinflammation associated with AD.

Monocyte chemoattractant protein 1 (MCP-1)

Role in AD pathogenesis

Chemokines are low-molecular weight cytokines. They are secondary inflammatory mediators induced by the primary mediators such as interleukin-1. These act as chemoattractants and direct leucocytes to the site of inflammation. They express their action through guanine nucleotide-associated protein (G protein)-coupled receptors. There are approximately 50 cytokines which are classified into four families; CC cytokines (have 2 adjacent cysteine residues at the N terminal), CXC cytokines (have two terminal cysteine residues separated by one amino acid), C cytokines (have 2 cysteine residues in total, one at N terminal and other at the downstream) and CX_3C cytokines (have 2 cysteine residues separated by 3 amino acids at the N terminal) [134, 135]. Inflammation plays a significant role in AD pathogenesis. The cytokines and chemokines, being inflammatory mediators, are involved in AD pathogenesis. They are released by the astrocytes, which play a role in Aβ generation and degeneration [136]. The production of chemokines is increased in response to Aβ and plays an important role in migration of astrocytes. The treatment of neonatal astrocytes with Aβ significantly increased the production of MCP-1. In the same study, it was found that astrocytes from adult mice migrate in response to MCP-1, indicating the role of MCP-1 in astrogliosis and degradation of Aβ [137]. Deficiency of chemokine receptors in transgenic mice models has shown to promote early Aβ accumulation [138]. The astrocytes proliferate in response to neurodegeneration and increase the deposition of toxic Aβ [139]. Aβ itself increases the expression of chemokines and cytokines by astrocytes, by reactivating them. There is a continuous cycle of activation and reactivation of astrocytes leading to inflammation and neuronal injury. [140, 141]. Therefore, the chemokines being mediators of inflammation play a significant role in AD pathogenesis.

CSF biomarker studies pertaining to MCP-1

Many studies have demonstrated the role of CC chemokine, MCP-1 or CCL2 in AD diagnosis. Studies have reported elevated CSF levels of MCP-1 in AD (Table 4). MCP-1 levels in CSF are positively correlated with the decrease in MMSE scores and higher baseline levels predict a faster rate of cognitive decline in AD [142–144]. Therefore, MCP-1 could serve as a marker of cognitive decline along the AD continuum. MCP-1 plays an important role in AD-associated neuroinflammation and can serve a potential biomarker to track the same.

Table 3 Studies conducted to evaluate the role of YKL-40 as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers/APOE genotype	Analysis method
Gispert et al. [129]	Controls ($n=49$), preclinical AD ($n=19$), MCI due to AD ($n=27$), mild AD dementia ($n=15$)	Elevated in preclinical AD, AD and MCI	Increased in *APOE* ε4 carriers within a study group; positively associated with P-tau	ELISA
Hoglund et al. [128]	Healthy older individuals, $n=129$ (divided into high CSF Aβ, $n=86$ and low CSF Aβ, $n=43$)	No difference between two groups	Significantly elevated in *APOE* ε4 non-carriers who were Aβ positive	ELISA
Gispert et al. [130]	Normal controls ($n=53$), preclinical AD (CSF Aβ < 500 pg/mL, $n=20$), MCI due to AD ($n=28$), mild AD dementia ($n=15$)	Significantly increased in MCI due to AD compared to controls	No association with Aβ-42; positive linear association with P-tau	ELISA
Janelidze et al. [124]	Healthy controls ($n=53$), stable mild cognitive impairment (sMCI, $n=62$), MCI who later developed AD (MCI-AD, $n=35$), AD dementia ($n=74$), PDD/DLB ($n=47$), vascular dementia (VaD, $n=34$), and FTD ($n=33$)	Significantly increased compared to healthy controls and sMCI. Elevated as compared with DLB, PDD but not with VaD or FTD.	Positively correlated with Aβ-42 in AD patients and with tau in all diagnostic groups	ELISA
Wennström et al. [125]	AD patients with mild to moderate dementia ($n=49$), PD ($n=61$), DLB ($n=36$) and non-demented controls ($n=44$)	Elevated compared to non-demented controls, DLB and PD patients	Not associated with CSF P-tau, T-tau or Aβ-42	ELISA
Hellwig et al. [131]	AD dementia ($n=39$), MCI due to AD ($n=13$), MCI not due to AD ($n=29$), non-AD dementia ($n=14$)	Significantly elevated in AD compared to MCI not due to AD or non-AD dementia. Also elevated in MCI-AD	Significant correlation with T-tau and P-tau in the non-AD group; no association CSF with Aβ	ELISA
Kester et al. [132]	Cognitively normal ($n=37$), MCI ($n=61$), AD ($n=65$)	Elevated in MCI and AD baseline levels in MCI-predicted progression to AD. Longitudinally increased in AD and MCI		ELISA
Alcolea et al. [133]	Cognitively normal controls ($n=80$) and amnestic MCI ($n=27$)	Elevated significantly in amnesic MCI as compared to controls	Strong correlation with T-tau and P-tau; no correlation between YKL-40 and Aβ-42	ELISA
Sutphen et al. [127]	Cognitively normal middle-aged individuals (CDR 0, $n=169$), classified as early, mid and late	Significantly elevated in mid and late middle-aged individuals	Biomarker changes more evident in ε4 carriers	ELISA

Table 4 Studies conducted to evaluate the role of MCP-1 as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers/APOE genotype	Analysis method
Janelidze et al. [145]	Cognitively normal ($n=315$), MCI ($n=449$) and AD ($n=57$)	Study participants were divided into Aβ positives and negatives. MCP-1 levels were not influenced by Aβ status		Electrochemiluminescence immunoassay [meso scale discovery, (MSD)]
Wennström et al. [125]	AD patients with mild to moderate dementia ($n=49$), PD ($n=61$), DLB ($n=36$) and non-demented controls ($n=44$)	Elevated compared to non-demented controls; difference not detectable on age correction		Electrochemiluminescence immunoassay (MSD)
Rosén et al. [146]	AD ($n=25$) and controls ($n=25$)	No significant difference between AD and controls		MSD assay
Westin et al. [142]	Controls ($n=30$) and MCI ($n=119$)	Elevated in sMCI and even in MCI to AD converters; higher baseline values predict rate of future cognitive decline		Electrochemiluminescence immunoassay (MSD)
Correa et al. [147]	AD ($n=22$) and healthy controls ($n=27$)	Significantly elevated in AD	Positively correlated with CSF P-tau and Aβ	ELISA
Choi et al. [148]	AD ($n=11$), PD ($n=8$), healthy controls ($n=13$)	Elevated in AD and PD but not significantly as compared to controls		Multiplex immunoassay (Luminex xMAP technology)
Galimberti et al. [143]	Amnestic MCI ($n=38$), AD ($n=36$), subjects with non-inflammatory affections of the nervous system ($n=41$)	Significantly elevated in MCI and AD compared to controls		ELISA
Blasko et al. [144]	AD ($n=23$), FTD ($n=5$), alcohol dementia ($n=10$), major depression ($n=11$) and healthy controls ($n=27$)	Significantly increased in AD compared to controls (no difference in case of older controls	Positive correlation with T-tau but not with Aβ and P-tau	ELISA

Biomarker of synaptic dysfunction

Neurogranin

Role in AD pathogenesis

Neurogranin is a calmodulin-binding, postsynaptic protein found in the dendrites [149]. It plays an important role in memory potentiation. It binds with calmodulin and releases the same when intracellular concentration of calcium increases. The released calmodulin binds with the calcium ions and activates a signal transduction pathway [150]. Synaptic dysfunction is linked to decline in cognition and occurs prior to neuronal degeneration [151, 152]. The brain levels of synaptic proteins including neurogranin are reduced in AD at an early stage. The synaptic dysfunction in terms of reduction in synapses is also seen in MCI which is higher in mild AD. Thus, synaptic dysfunction occurs early in AD and indicates disease progression [153–157]. Neurogranin regulates the calcium-dependent postsynaptic signaling triggered by calmodulin [158]. It has been found that neurogranin [$Ng^{(+/+)}$] mice exhibit greater intracellular calcium concentration as compared to $Ng^{(-/-)}$ mice upon tetanic stimulation [159]. Expression of neurogranin reduces with aging [160]. Reduced brain levels of neurogranin can cause a dysregulation of post-synaptic signaling. Reduced neurogranin mRNA expression has been reported in hippocampal and retrosplenial regions of the brain in aged mice [160]. Therefore, a reduction of synaptic proteins such as neurogranin in the brain relates to synaptic dysfunction and the CSF levels of such proteins can be used for disease diagnosis and monitor the progression.

CSF biomarker studies pertaining to neurogranin

In the past few years, a number of researchers have evaluated the diagnostic and prognostic potential of the biomarker neurogranin. A number of assay methods have been developed to quantify neurogranin in the CSF and have reported elevated neurogranin levels in AD (Table 5). In a study conducted on various synaptic proteins including neurogranin in post-mortem brain samples, it was found that synaptic proteins discriminated dementia cases from controls with over 90% sensitivity and specificity [161]. The CSF neurogranin levels correlate with brain atrophy and amyloid load and also help in predicting decline in cognition. The CSF levels differ significantly between stable MCI (sMCI) and MCI to AD converters and between sMCI and AD [162–165]. Increased CSF levels of neurogranin are specific to AD and not seen in other neurodegenerative diseases [166, 167]. Therefore, it is a promising biomarker for early AD diagnosis, predicting progression and distinguishing AD from other forms of dementia. It can act as a theragnostic marker, which can help in monitoring biochemical effects of drugs used to improve synaptic function. Since, synaptic dysfunction is associated to cognitive decline, neurogranin can help in staging the rate of cognitive decline along the AD continuum. However, large longitudinal studies are needed to further validate the role of neurogranin in AD diagnosis and prognosis.

Biomarker of altered microglial activity

Soluble ectodomain of triggering receptor expressed on myeloid cells (sTREM2)

Role in AD pathogenesis

Ectodomain of triggering receptor expressed on myeloid cells (TREM2) is a transmembrane glycoprotein immune receptor expressed in a number of cells such as dendritic cells, osteoclasts, tissue macrophages and the microglia. It contains an ectodomain with three N-glycosylation residues, a transmembrane sequence and a short intracellular tail. Its functions are mediated via DNAX-activating protein of 12 kDa (DAP12) signaling [172, 173]. In the brain, it is expressed by the microglial cells and regulates microglial-mediated phagocytosis and clearance of apoptotic neurons [174, 175]. It plays an important role in regulating immune responses in the brain and the production of inflammatory cytokines [176, 177]. TREM2 is upregulated in mice with mutant APP and amyloid deposition [178]. The mutations associated with the *TREM2* gene are associated with an increased risk for AD. GWAS, next generation sequencing, Sanger sequencing and genotyping have revealed that R47H *TREM2* variant is a risk factor for AD, which can increase the risk of developing AD by two- to fourfold [179–182]. This can be associated to tau pathology, since carriers of the risk variant were found to possess higher levels of T-tau [183]. It has also been found that mutations in *TREM2* reduce Aβ clearance [184]. TREM2 undergoes regulated membrane proteolytic processing by ADAM 10 (A disintegrin and metalloproteinase domain-containing protein 10) and γ secretase, and releases the soluble ectodomain sTREM2 into the extracellular space [185]. The sTREM2 is detectable in the CSF and the levels have been quantified in different neurological disorders such as AD, frontotemporal dementia (FTD) and multiple sclerosis [186, 187]. Since, TREM2 regulates microgliosis, the soluble fragment of the protein, sTREM2, could play a role in regulating TREM2-mediated microgliosis. The exact biological role of the soluble fragment is unclear. However, using in vitro and in vivo models, Zhong

Table 5 Studies conducted to evaluate the role of neurogranin as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers/ APOE genotype	Analysis method
Hoglund et al. [128]	Healthy older individuals, $n=129$ (divided into high CSF Aβ, $n=86$ and low CSF Aβ, $n=43$)	Significantly elevated in Aβ-positive group	Significantly elevated in *APOE* ε4 non-carriers who were Aβ positive	MSD assay
Tarawneh et al. [165]	Cognitively normal controls (CDR 0, $n=207$) and AD (CDR: 0.5, 1, 2.; $n=95$), non-AD dementias ($n=19$)	Significantly elevated in participants with CDR ≥ 0.5 compared to CDR 0 and non-AD dementias	Positively correlated with CSF T-tau and P-tau	Two-site immunoassay (Erenna Singulex)
Mattsson et al. [168]	AD ($n=93$), MCI ($n=187$) and controls ($n=109$)	Significantly predicted AD vs. controls; elevated in AD	CSF neurogranin levels were associated with Aβ positivity in all the groups; correlated strongly with T-tau	Electrochemiluminescence immunoassay (MSD)
Sanfilippo et al. [169]	Healthy controls ($n=44$), MCI ($n=50$), prodromal AD ($n=36$), AD ($n=25$), major depressive disorder (MDD, $n=6$)	Significantly elevated in AD, prodromal AD vs. controls and MDD; significantly elevated in prodromal AD vs. MCI	Correlated positively with CSF T-tau and P-tau	ELISA
De Vos et al. [170]	Healthy controls ($n=29$), MCI due to AD ($n=20$), AD MCI due to AD ($n=20$), AD, MCI due to AD and AD with high tau levels ($n=19$)	Significantly elevated in MCI vs. controls but not in AD; no significant differences between MCI and AD	Correlated with T-tau in MCI and AD but not with Aβ-42	ELISA
Kester et al. [164]	Cognitively normal ($n=37$), MCI ($n=61$) and AD ($n=65$)	Significantly elevated in AD compared to controls; no difference between MCI and AD, MCI and cognitively normal	Strong positive correction with CSF T-tau and P-tau	Sandwich immunoassay (Erenna Singulex)
Kvartsberg et al. [163]	Three cohorts consisting of AD ($n=100$), MCI ($n=40$) and controls ($n=80$)	Significantly elevated in AD vs. controls (using both methods); significantly elevated in MCI-AD vs. sMCI, AD vs. sMCI	Strong positive correction with CSF T-tau and P-tau in AD and controls	Mass spectrometry and ELISA
Hellwig et al. [131]	AD dementia ($n=39$), MCI due to AD ($n=13$), MCI not due to AD ($n=29$), non-AD dementia ($n=14$)	Significantly increased in AD, MCI due to AD compared to MCI not due to AD	Moderate correlation with CSF T-tau and P-tau but not with Aβ-42	MSD assay
Portelius et al. [162]	Cognitively normal ($n=110$), MCI ($n=173$) and AD ($n=95$)	Significantly elevated in progressive MCI, AD vs. controls	Negatively correlated with CSF Aβ-42 in sMCI, progressive MCI and AD; strong positive correlation with CSF T-tau and P-tau in all the study groups	Electrochemiluminescence immunoassay (MSD)
Thorsell et al. [171]	Study 1: AD ($n=11$) and controls ($n=9$); study 2: AD ($n=10$), MCI ($n=10$) and controls ($n=11$)	Significantly increased in AD compared to controls, no significant difference between MCI vs. AD or controls	Positive correlation with CSF T-tau and P-tau in AD (study 1), all groups together (study 2); negative correlation with CSF Aβ-42 in MCI	Immunoblot analysis

et al. have shown that sTREM2 promotes microglial survival and induces production of inflammatory cytokines [188]. In this study, it was found that administration of sTREM2-fc fusion protein increased the microglial viability, in both *TREM2* knockout mice as well as wild type. Administration of sTREM2 reduced the microglial apoptosis induced by removal of granulocyte macrophage colony-stimulating factor (GM-CSF), in both knock out and wild mice. In addition, it was found that sTREM2 treatment activates the microglia by increased expression of inflammatory cytokines [188]. A significant reduction in microgliosis as well as microglial clustering around Aβ plaques has been found in Trem2$^{-/-}$5XFAD mice as compared to the controls [189]. Therefore, sTREM2 likely plays a role in microgliosis, but further studies are needed to affirmatively elucidate the exact role of sTREM2.

CSF biomarker studies pertaining to sTREM2

Numerous studies have revealed that CSF levels of sTREM2 are altered in AD (Table 6). The levels are elevated in dominantly inherited AD cases years before the onset of symptoms [190], which highlights that microgliosis occurs prior to the onset of symptoms and later to brain amyloidosis. The Nasu–Hakola disease (NHD) *TREM2* mutation carriers have lower CSF levels of sTREM2 [187]. This signifies that there is altered protein production in mutation carriers. Studied have found the CSF levels of TREM2 are increased in AD at early stage and correlate well with the markers of neurodegeneration and tau pathology. Therefore, microgliosis is most likely an early event that occurs along the AD and occurs in response to neurodegeneration. The CSF levels are lesser in AD as compared to MCI who later developed AD (MCI-AD). Thus, microgliosis increases from the preclinical AD to MCI-AD and there after reduces in AD, probably due to reduction in immune response [191]. Higher CSF levels in MCI patients are associated to increased gray matter volume. This reflects upon the protective response of microglia in response to neurodegeneration [192]. The role of TREM2 in regulating brain immune response, microgliosis and inflammation needs to be further explored. The CSF levels of sTREM2 can help in tracking the altered microgliosis along the disease trajectory and can serve as a potential stage biomarker for identifying early stages of AD and as theragnostic marker to monitor therapeutic effects of drugs administered at an early stage.

Biomarkers reflecting neuronal membrane disruption (neurodegeneration)

Fatty acid-binding protein 3 (FABP3) or heart-type fatty acid-binding protein (HFABP)

Role in AD pathogenesis

The fatty acid-binding proteins (FABPs) are transport proteins for fatty acids and other lipophilic biomolecules. FABP3 is mainly expressed in the heart and skeletal muscles but has also been isolated from the brain [196]. In the brain, FABPs bind to long-chain polyunsaturated fatty acids (PUFA), such as docosahexaenoic acid (DHA) and arachidonic acid (ARA) and is involved in the transport of these fatty acids. These fatty acids are indispensable for maintaining neuronal membrane integrity, neurite growth and synapse formation. The DHA and ARA modulate neural membrane fluidity and permeability [197, 198]. The dietary supplementation of DHA has been found to improve spatial memory and reduce Aβ deposition in mice [199]. DHA also prevents Aβ-induced neuronal damage in vivo and in vitro [200]. Since HFABP or FABP3 regulates the transport of DHA and other fatty acids, it is likely to be associated with AD pathogenesis. The brain levels of FABP3 are reduced in such neurodegenerative diseases, which could be associated to altered signal transduction and membrane integrity [201]. FABPs are released following a cellular injury [202, 203]. Therefore, like other FABP's, HFABP is likely to be associated with cellular dysfunction associated with AD. FABP3 is also associated with dopaminergic system and changes in dopaminergic system are likely to be associated with AD. It binds and regulates the dopaminergic D_2 receptors, and overexpression of FABP3 promotes α-synuclein oligomerization [204–206]. Catalepsy behavior induced by haloperidol administration was found to be significantly increased in FABP3 knockout mice as compared to the wild type, indicating that FABP3 regulates D_2 receptors [204]. In the same study, it was found that over expression of FABP3 increased D_2 receptor sensitivity [204]. The association of FABP3 with dopaminergic system also signifies the role of FABP3 in AD pathogenesis.

CSF biomarker studies pertaining to FABP3

The CSF levels of FABP3 are elevated in AD and is a potential diagnostic marker for differential diagnosis of neurodegenerative diseases (Table 7). The elevated levels are significantly associated with brain atrophy in cases with low Aβ-42 and reflect on lipid dyshomeostasis in

Table 6 Studies conducted to evaluate the role of sTREM2 as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers/APOE genotype	Analysis method
Gispert et al. [129]	Controls ($n=49$), preclinical AD ($n=19$), MCI due to AD ($n=27$), mild AD dementia ($n=15$)	Elevated in AD and MCI (however, no significant difference upon age correction)	Positively associated with CSF P-tau, no significant difference between *APOE* ε4 carriers and non-carriers in any study group	ELISA
Heslegrave et al. [193]	AD ($n=37$) and cognitively normal controls ($n=22$)	Significantly elevated in AD	Significant positive correlation with CSF T-tau and P-tau but not with CSF Aβ-42	Mass spectrometry
Suarez-Calvet et al. [194]	Controls ($n=150$), preclinical AD ($n=63$), MCI due to AD ($n=111$) and AD dementia ($n=200$)	Significantly elevated in MCI-AD compared to controls and AD dementia	Positively correlated with CSF T-tau and P-tau (stronger in preclinical AD, MCI due to AD and AD); not affected by APOE ε4 status	ELISA (MSD platform)
Henjum et al. [195]	Cohort 1: controls ($n=50$), MCI ($n=21$) and AD ($n=29$); cohort 2: controls ($n=25$) and AD ($n=25$)	No statistical difference among the diagnostic groups	Positively correlated with CSF Aβ-42, T-tau and P-tau among controls	ELISA
Piccio et al. [187]	Cognitive normal ($n=107$), AD ($n=73$), FTD and *TREM2* risk variant carriers ($n=40$)	Significantly elevated in AD compared to controls (all non *TREM2* risk variant carriers)	Highly correlated with CSF T-tau and P-tau levels but not with CSF Aβ-42	ELISA
Gispert et al. [192]	Cognitively normal controls ($n=45$), preclinical AD ($n=19$), MCI due to AD ($n=27$), and mild AD ($n=23$)	Highest levels in MCI-AD; significantly higher than the controls and preclinical AD	Positively correlated with CSF T-tau and P-tau in all diagnostic groups	ELISA (MSD platform)

Table 7 Studies conducted to evaluate the role of FABP3 as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers/APOE genotype	Analysis method
Hoglund et al. [128]	Healthy older individuals, $n=129$ (divided into high CSF Aβ, $n=86$ and low CSF Aβ, $n=43$)	Significantly elevated in Aβ-positive group	Elevated significantly in *APOE* ε4 non-carriers who were Aβ positive	Electrochemiluminescence immunoassay (MSD)
Bjerke et al. [210]	Non-demented women ($n=86$)	Elevated in those who developed dementia and AD at follow-up; higher baseline levels associated to development of dementia	Strong correlation with CSF T-tau and P-tau at baseline	Electrochemiluminescence immunoassay (MSD)
Biscetti et al. [211]	AD ($n=48$), PD ($n=54$), DLB ($n=40$), PDD ($n=21$), other neurological disorders (OND) as controls ($n=47$)	Significantly elevated in AD, DLB compared to PD and OND	Significantly correlated with CSF T-tau levels CSF	ELISA
Chiasserini et al. [212]	AD ($n=40$), PD ($n=58$), OND	Significantly elevated in AD compared to PD and OND	Positively correlated with CSF T-tau, P-tau but not with Aβ	Immunoassay
Guo et al. [208]	Healthy controls ($n=92$), MCI ($n=149$), AD ($n=60$)	Significantly elevated in AD compared to controls		Multiplex immunoassay (Luminex xMAP technology)
Desikan et al. [207]	Cognitively normal ($n=90$), amnestic MCI ($n=139$) and probable AD ($n=66$)	Elevated in AD and MCI compared to controls	Significantly associated with CSF P-tau	Multiplex immunoassay (Luminex xMAP technology)

the CNS [207]. Therefore, elevated FABP3 levels in CSF might be associated to brain amyloidosis. The diagnostic accuracy of the core CSF biomarkers has been found to be increased in conjunction with FABP3. In addition, FABP3 and the ratio of FABP3/Aβ-42 are useful in predicting the progression of MCI subjects to AD. [208, 209]. In a recent study involving healthy aged individuals, the CSF levels of FABP3 were significantly elevated in Aβ-positive individuals (low CSF Aβ), compared to negative individuals (high CSF Aβ) [128]. Therefore, it is a good biomarker for predicting disease progression in early stages of disease and can help in identifying healthy aged individuals at risk of developing AD. The elevated CSF levels correlate with core markers of neuro degeneration (Table 7). The elevated levels in AD could likely be associated to the destruction of neurons.

Biomarkers of neuronal structure and signaling disruption (markers of neurodegeneration)

Neurofilament light chain protein (NFL): marker of axonal degeneration

Role in AD pathogenesis

Neurofilaments are the proteins particularly found in neuronal axons. They are 10 nm in diameter and are essential for the axonal growth and the transmission of impulses along the axons [213]. These are heteropolymers composed of four subunits, namely neurofilament heavy, medium and light polypeptides and α-internexin [214]. Being elastic and fibrous, they maintain the shape of neurons and act as neuroskeletal supports [215]. NFL plays a role in protecting neurites from dystrophy and regulates pathways generating Aβ [216]. Significantly higher neocortical Aβ deposition was found in APP/PS1 $NFL^{(-/-)}$ mice as compared to APP/PS1 $NFL^{(+/+)}$ mice. The dystrophic neurites were also significantly higher in $NFL^{(-/-)}$ mice, in regions surrounding the plaques. In addition, higher microgliosis was found in such regions, in $NFL^{(-/-)}$ mice as compared to $NFL^{(+/+)}$ mice [216]. Neurofilaments are likely to be released from neuronal axons in response to neuronal damage in neurodegenerative diseases. NFL is mainly located in myelinated axons and white matter changes are associated with increased NFL levels in the CSF. Therefore, elevated levels of NFL in the CSF reflect on axonal degeneration [217] (Fig. 5). NFL is a specific biomarker of axonal degeneration, whose levels have been found to be elevated in a wide range of neurodegenerative diseases including AD. It is not a disease-specific biomarker but can aid in differential diagnosis of neurodegenerative disorders since its levels are elevated in FTD as compared to AD [218]. High CSF NFL levels predict high hippocampal atrophy rate in cognitively healthy older adults as well those at risk of AD [219]. In case of AD, it can help in tracking the different dynamic changes along the disease continuum.

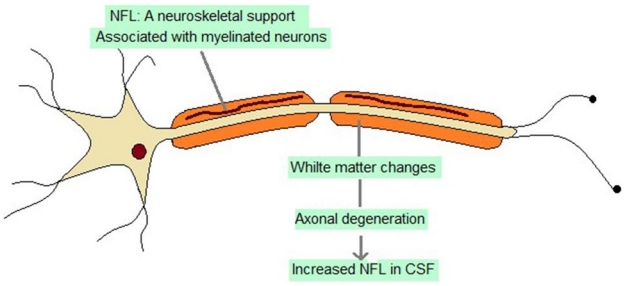

Fig. 5 Role of NFL in AD pathogenesis (*NFL* neurofilament light chain, *CSF* cerebrospinal fluid)

CSF biomarker studies pertaining to NFL

The CSF levels of NFL are elevated in a wide range of neurodegenerative diseases including AD as compared to normal controls (Table 8). NFL levels are significantly elevated in AD compared to sMCI, and higher CSF levels in AD are associated with cognitive decline, white matter change, brain atrophy, and lower FDG-PET. The change in CSF levels and these associations are independent of Aβ positivity [168, 220]. Therefore, NFL reflects upon neuronal or axonal degeneration independent of Aβ pathology. Since the CSF levels of NFL are significantly elevated in AD compared to sMCI and associated to brain atrophy and cognitive decline, it can be used as potential biomarker to study disease progression and severity along the AD continuum. In addition, the diagnostic performance of core CSF biomarkers in differential diagnosis of early onset Alzheimer's disease (EOAD) and FTD is improved in conjunction with the CSF levels of NFL [221]. Hence, it also has a potential to differentially diagnose a range of neurodegenerative diseases. But, the potential of NFL to identify individuals at risk of developing AD or its potential to identify preclinical AD needs to be further explored.

Visinin-like protein 1 (VILIP-1): marker of neuronal injury

Role in AD pathogenesis

VILIP-1 belongs to a large family of calcium-binding proteins called neuronal calcium sensors (NCSs) [224]. The VIPIL-1 protein is encoded by the visinin-like 1 (VSNL1) gene and contains 191 amino acids and weighs 22 kDa [225]. VILPI-1 is distributed in different regions of the brain [226].

Table 8 Studies conducted to evaluate the role of NFL as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers	Analysis method
Hoglund et al. [128]	Healthy older individuals, $n=129$ (divided into high CSF Aβ, $n=86$ and low CSF Aβ, $n=43$)	No difference between the two groups		ELISA
Zetterberg et al. [220]	AD ($n=95$), MCI ($n=192$) and cognitively normal individuals ($n=110$)	Significantly elevated in AD, sMCI, MCI-AD as compared to controls; AD vs sMCI	Baselines levels correlated with low CSF Aβ, T-tau and P-tau	ELISA
Mattsson et al. [168]	AD ($n=93$), MCI ($n=187$) and controls ($n=109$)	Elevated; Significantly predicted AD vs. controls	CSF NFL levels are not associated with Aβ positivity; correlated with T-tau	ELISA
Scherling et al. [222]	Normal controls ($n=47$), AD ($n=50$) various other neurodegenerative disorders such as FTD ($n=79$), PD ($n=6$) etc	Elevated significantly in AD as compared to normal controls; also in all FTD subgroups compared to normal controls and AD		ELISA
Skillback et al. [218]	Healthy controls ($n=107$), EOAD ($n=223$), LOAD ($n=1194$) FTD ($n=146$), DLB ($n=114$), PDD ($n=45$), VaD ($n=465$), mixed AD and VaD ($n=517$), other dementias ($n=108$), dementia not specified ($n=437$)	Elevated in all groups as compared to controls; highest in FTD; significantly elevated in EOAD and LOAD compared to controls		ELISA
Sjögren et al. [217]	Normal controls ($n=20$), AD ($n=22$), subcortical vascular dementia (SVD, $n=9$)	Increased in AD and SVD compared with controls		ELISA
Rosengren et al. [223]	Healthy controls ($n=39$), AD ($n=37$), FTD ($n=5$) and VaD ($n=20$)	Increased in AD, compared with controls; in FTD and VaD compared to AD and healthy controls		ELISA

The calcium ions (Ca^{2+}) are involved in neuronal signaling and the NCSs mediate the action of these ions. In response to a high intracellular concentration of Ca^{2+}, VILIP-1 gets reversibly translocated to the membrane components of the cell. This reversible interaction of VILIP-1 modulates signaling cascade in the neurons via activation of specific membrane-bound targets [227, 228]. Therefore, VILIP-1 plays an important role in neuronal signaling. The VILIP-1 regulates neuron ion channels, neuronal growth, survival, synaptic plasticity and activates cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP) signaling pathways [225]. Neurodegenerative disorders such as AD are associated with disturbed Ca^{2+} homeostasis in the neurons, which affect neuronal signaling by causing excessive activation of receptors, weakening the Ca^{2+} buffering capacity of neurons and deregulating the Ca^{2+} channels [229]. Aβ modulates this disturbed Ca^{2+} homeostasis by increasing the influx of Ca^{2+} by forming channels [230]. The NCSs such as VILIP-1 play a significant role in AD pathogenesis. The intracellular expression of VILIP-1 is reduced in AD brains as compared to controls. VILIP-1 has been found to be associated with extracellular plaques and NFTs in the brains of AD patients and its expression is associated with enhanced hyper phosphorylation of tau protein and cell death [231, 232]. In mild AD, there is a considerable loss of neurons in the entorhinal cortex [233, 234]. The levels of VILIP-1 are reduced in the entorhinal cortex of AD patients [235]. Therefore, it is a marker of neuronal injury. Figure 6 depicts the role of VILIP-1 in AD pathogenesis.

This signifies that VILIP-1 is neurotoxic under a disturbed Ca^{2+} homeostasis. In AD, its intracellular expression is reduced. Increased expression promotes hyperphosphorylation and cell death which is reduced by calcium buffer protein. A disturbed Ca^{2+} balance causes the loss of vulnerable neurons and thereby the release of VILIP-1 extracellularly [225, 231, 232, 236].

CSF biomarker studies pertaining to VILIP-1

Numerous studies have been conducted to illustrate its role as a potential CSF diagnostic, prognostic and a differential biomarker. CSF levels of VILIP-1 aid in the early diagnosis of AD, distinguish AD from MCI, helps in identifying the patients with MCI likely to progress to AD, and in differentiating AD from other forms of dementia (Table 9). When used in combination with the core CSF markers, the diagnostic performance is improved [237]. VILIP-1 and VILIP-1/Aβ-42 ratio negatively correlates with MMSE [237, 238]. Baseline CSF levels of VILIP-1 are associated with rate of whole brain and regional brain atrophy in AD. VILIP-1 and the ratio of VILIP-1/Aβ-42 correlate significantly with the brain amyloid load. Therefore, VILIP-1 and the ratio of VILIP-1/Aβ-42 help in predicting the future cognitive decline. [239–243]. VILIP-1 can be used as a surrogate marker of neurodegeneration but, larger longitudinal studies are needed to validate the same. It can help in tracking the protective effects of neuroprotective therapeutic interventions.

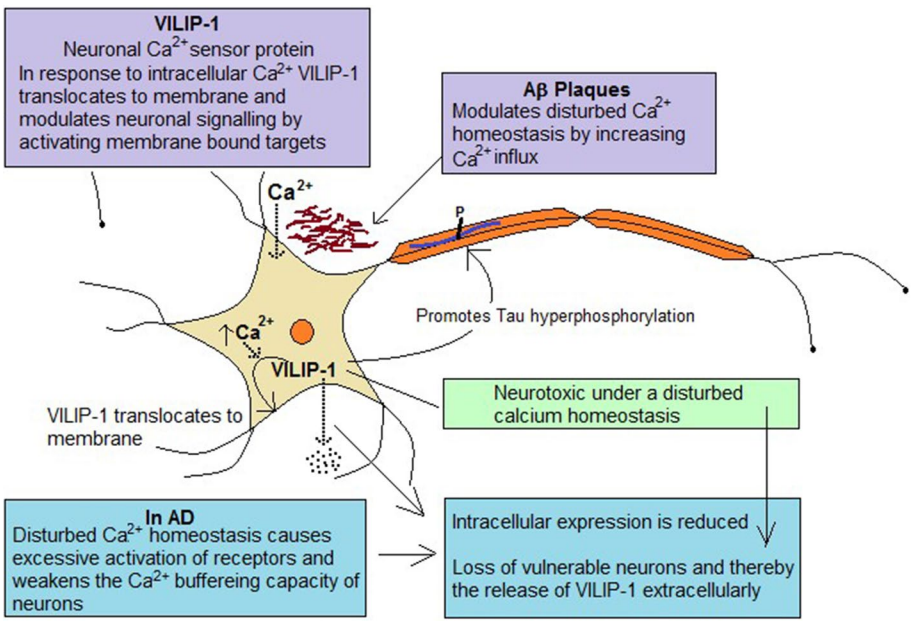

Fig. 6 The role of VILIP-1 in AD pathogenesis (*Aβ* amyloid beta, *AD* Alzheimer's disease)

Table 9 Studies conducted to evaluate the role of VILIP-1 as a potential CSF biomarker

Study	Study groups	CSF levels in AD/study groups	Association with core biomarkers	Analysis method
Hoglund et al. [128]	Healthy older individuals, $n=129$ (divided into high CSF Aβ, $n=86$ and low CSF Aβ, $n=43$)	No difference between the two groups	Significantly elevated in *APOE* ε4 non-carriers who were Aβ positive	ELISA
Babic Leko et al. [238]	Healthy controls ($n=9$), AD ($n=109$), MCI ($n=45$), VaD ($n=9$), FTD ($n=18$), DLB ($n=5$), other dementias	Significantly elevated in AD vs. controls, MCI and DLB; no difference in AD vs. VaD and FTD	Positive correlation with CSF T-tau and P-tau in a mixed group of (healthy controls, AD, MCI) as well as in AD and MCI	ELISA
Mroczko et al. [240]	Cognitively normal controls ($n=18$), AD ($n=33$), MCI ($n=15$)	Significantly elevated in AD vs. controls and MCI; also elevated in MCI vs. controls but not significantly	Significantly correlated with CSF P-tau in AD and controls; with Aβ-42 in controls	ELISA
Kester et al. [132]	Cognitively normal ($n=37$), MCI ($n=61$), AD ($n=65$)	Elevated in AD and MCI vs. normal controls but not significantly; baseline levels in MCI predicted progression to AD. Longitudinally increased in AD and MCI		Microparticle based immunoassay (Erenna Singulex)
Tarawneh et al. [242]	Normal controls (CDR 0, $n=64$) and AD ($n=23$)	Significantly elevated in AD vs. controls		Microparticle based immunoassay (Erenna Singulex)
Sutphen et al. [127]	Cognitively normal middle-aged individuals (CDR 0, $n=169$), classified as early, mid and late	Significantly elevated in late middle-aged individuals as compared to early and mid in non-ε4 carriers;	Biomarker changes more evident in ε4 carriers longitudinally	Microparticle based immunoassay (Erenna Singulex)
Luo et al. [239]	Normal controls ($n=40$), AD ($n=61$), DLB ($n=32$)	Significantly elevated in AD vs. controls and DLB	Positively correlated with T-tau and P-tau	ELISA
Tarawneh et al. [243]	Normal controls (CDR 0, $n=211$) and AD (CDR 0.5 and 1, $n=60$)	Significantly elevated in AD vs. controls		Microparticle based immunoassay (Erenna Singulex)
Tarawneh et al. [241]	Cognitively normal controls ($n=211$), AD ($n=98$), other dementias ($n=19$)	Significantly elevated in AD vs. controls and other dementias	Correlated with T-tau and P-tau	Microparticle based immunoassay (Erenna Singulex)
Lee et al. [237]	Controls ($n=24$) and AD ($n=33$)	Significantly elevated in AD vs. controls	Strong positive correlation with CSF T-tau and P-tau; higher levels associated with *APOE* ε4 genotype	ELISA

Conclusion

The multifaceted AD dementia is an amalgam of different pathological changes in the brain. The different pathological changes may represent a hierarchy of events that occur one after another or may follow their own trajectory, which ultimately leads to dementia due to AD. To get a deeper insight into different aspects of disease pathogenesis biomolecules/proteins involved in the associated biochemical pathways need to be explored and evaluated as disease biomarkers for disease diagnosis, prognosis and therapy. The CSF biomarkers would serve as reliable measures, to assess the time course of AD and the associated pathological changes along the continuum of the disease. A number of biomarkers in relation to different AD-associated pathological changes have been discussed in the current manuscript. They together or alone can aid in an accurate AD diagnosis starting from the preclinical phase and thereby can give a clear picture of the pathological changes that occur across the disease continuum. The use of multiple biomarkers can help in understanding the association of individual pathologies [244], and may provide an understanding about how one pathological change influences the other. Hence, these biomarkers in conjunction can improve the accuracy of diagnosis. It has been found that a biomarker model consisting of the biomarkers T-tau, NFL, neurogranin reflecting upon neurodegeneration, axonal damage and synaptic dysfunction, respectively, has a higher diagnostic accuracy (area under the receiver-operating curve (AUC) 85.5%) in classifying AD and controls [168]. The combination of CSF biomarkers, including YKL-40 could distinguish cognitively normal participants with clinical dementia rating (CDR) score of 0 from those with CDR > 0 with AUC 0.896 [76].

The CSF levels of these biomarkers change likely with the pathological change or event in the AD brain. The elevated CSF levels of clusterin can highlight upon the role of clusterin in binding with Aβ and preventing its fibrillization or its role in promoting the formation of soluble toxic Aβ oligomers. An elevated CSF levels of biomarkers YKL-40 and MCP-1 highlight upon neuroinflammation as a protective response to brain damage. These proteins are expressed by the astrocytes, which are activated in response to neurodegeneration and thereafter release inflammatory mediators. Elevated levels of sTREM2 highlight upon brain microgliosis as a response to phagocytise-accumulated Aβ. Therefore, these novel biomarkers can help in tracking inflammatory processes related to AD neurodegeneration. They can help in tracking stage and state-associated neuroinflammation in AD and combating the same with the therapeutic agents. Inflammation is associated with a number of psychiatric disorders [245]. These biomarkers can help in understanding the association of psychiatric disorders such as depression with AD. The dynamic changes in levels of VILIP-1, a biomarker of neuronal injury and NFL, a biomarker of axonal damage can alone or in conjunction provide an insight into the longitudinal cognitive changes associated with neurodegeneration. The cognitive decline associated with synaptic degeneration can be well accounted via CSF measure of neurogranin.

Hence, it can be concluded that the CSF biomarkers will certainly benefit in diagnosing AD at an early stage with much higher diagnostic accuracy either alone, together or in conjunction with the core CSF biomarkers. This would also aid in understanding the disease pathogenesis and progression. They can account for the lag between preclinical and clinical AD, and can act as indices of pathological change. They can serve as end point measures in clinical trials and accelerate the drug development process through the design of new drug molecules that can be targeted on the right individuals at the right stage. The complex nature of AD definitely directs us toward a strong rationale to use multiple biomarkers for understanding disease pathogenesis, and for a successful and accurate preclinical diagnosis, prognosis and treatment.

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Compliance with ethical standards

Conflict of interest KB has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Merck, Novartis, Pfizer, and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. HZ has served at scientific advisory boards of Eli Lilly, Roche Diagnostics, Samumed, CogRx and Wave, has received travel support from Teva and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

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