Review Article

Cerebrospinal Fluid Biomarkers in Familial Forms of Alzheimer's Disease and Frontotemporal Dementia

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Key Words

Biomarkers · Cerebrospinal fluid · Alzheimer's disease · Frontotemporal dementia · Tau protein · Amyloid- β · Diagnosis · Familial dementia

Abstract

As dementia is a fast-growing health care problem, it is becoming an increasingly urgent need to provide an early diagnosis in order to offer patients the best medical treatment and care. Validated biomarkers which reflect the pathology and disease progression are essential for diagnosis and are important when developing new therapies. Today, the core protein biomarkers amyloid- β_{42} , total tau and phosphorylated tau in the cerebrospinal fluid (CSF) are used to diagnose Alzheimer's disease (AD), because these biomarkers have shown to reflect the underlying amyloid and tau pathology. However, the biomarkers have proved insufficient predictors of dementias with a different pathology, e.g. frontotemporal dementia (FTD); furthermore, the biomarkers are not useful for early AD diagnosis. Familial dementias with a known disease-causing mutation can be extremely valuable to study; yet the biomarker profiles in patients with familial dementias are not clear. This review summarizes CSF biomarker findings from studies on symptomatic and presymptomatic individuals carrying a mutation in one of the genes known to cause early-onset familial AD or FTD. In conclusion, the biomarker profile of inherited AD is quite similar between carriers of different mutations as well as similar to the profile found in sporadic AD, whereas familial FTD does not seem to have a clear biomarker profile. Hence, new biomarkers are needed for FTD.

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Introduction

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are neurodegenerative disorders characterized by decline in memory and other cognitive abilities. Nearly 40 million people worldwide are affected by dementia, and this number is estimated to double every 20 years, thus giving rise to a growing global socioeconomic and medical problem [1]. AD is the most common form of dementia in elderly people (>65 years) and arises sporadically in most cases. Familial dementias are rare, and autosomal dominantly inherited AD only comprises 1–3% of all AD cases, whereas between 20–40% of FTD cases are familial [2, 3].

Familial AD is caused by autosomal dominant mutations in one of the three identified risk genes amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and *PSEN2*. These mutations are autosomal dominantly inherited, with an age-dependent complete penetrance resulting in alterations of amyloid- β ($A\beta$) processing and development of early-onset AD (EOAD) with clinical symptoms before 65 years of age.

The clinical presentation of FTD differs from that of AD in various behavioural symptoms and language functional deficits, which are the most common symptoms [4]. Mutations in *MAPT*, *GRN*, *TARDBP*, *VCP*, *FUS* and *CHMP2B* and a recently identified *C9ORF72* hexanucleotide repeat expansion all cause early-onset familial FTD with similar clinical presentations, whereas the underlying protein pathology, although leading to neurodegeneration, is different between the genetic subtypes.

In typical cases, the clinical diagnosis of AD, FTD and other types of dementia is based on medical history, physical and neurological examination, structural neuroimaging, neuropsychological tests and blood biochemistry. The core cerebrospinal fluid (CSF) biomarkers used for AD diagnosis [$A\beta_{42}$, total tau (t-tau) and phosphorylated tau (p-tau)] may be applied in parallel with imaging markers using MRI, fluorodeoxyglucose or amyloid PET scans for early and more accurate diagnosis [5, 6]. In sporadic AD, the CSF profile is normally characterized by decreased levels of $A\beta_{42}$, reflecting the aggregation of $A\beta$ into insoluble plaques, and increased levels of both t-tau and p-tau as a result of neuronal damage. A large subset of FTD cases has pathological tau changes, with robust increases in CSF t-tau and p-tau levels but normal levels of $A\beta_{42}$ [4]. However, the biomarkers lack specificity, and a vast clinical overlap between normal aging, AD, FTD and other neurodegenerative diseases makes it difficult to distinguish these diseases and other forms of dementia disorders from one another. Patients may be misdiagnosed and consequently left without access to appropriate treatment and care; therefore, a new battery of biomarkers is highly needed.

A majority of biomarker discovery and validation studies have been performed on CSF from patients with sporadic AD and FTD, and although familial forms of dementia are rare in the population compared to the sporadic forms, knowledge of biomarkers within these disorders may help elucidate the disease pathology of the sporadic diseases. Furthermore, familial forms of dementia can be studied in a presymptomatic state, which affords a unique opportunity to assess biomarker profiles before symptom onset. Biomarker profiles reflecting early disease pathogenesis would be valuable in the attempt to provide an early diagnosis for individuals presenting to the clinic with mild cognitive problems. This systematic review summarizes published reports on CSF biomarker findings in patients with familial AD and FTD.

Methods

Search Strategy and Selection Criteria

A PubMed and Google Scholar search up to September 2014 was performed, using the search term 'CSF AND biomarker AND xx mutation carriers', xx being one of the following genes: *PS1/PSEN1*, *PS2/PSEN2*, *APP*,

MAPT, *GRN*, *TARDBP*, *VCP*, *CHMP2B*, *FUS* and *C9ORF72*; subsequently, the results were reviewed for relevance. Only publications in the English language were evaluated. Articles were selected if (a) they were on human subjects, (b) they contained biomarker data on CSF and (c) individuals with mutations in one of the above-mentioned genes were included in the study, both symptomatic and presymptomatic cases. Case studies were included.

Results

In total, 44 research papers were of relevance for this review (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381828); 27 described familial AD and 17 described familial FTD. Several studies included more than one gene/mutation. Only papers on patients with disease-causing mutations in the genes, with described changes in CSF biomarkers, were reviewed.

Eighteen of the 40 papers were case studies with 1 or 2 mutation carriers included. In 6 studies, 20 or more mutation carriers were included. In the majority of studies, immune-based assays were used to assess biomarker levels. In 3 studies, mass spectrometry was used.

Biomarker Profiles in Familial AD

In both symptomatic and presymptomatic *APP*, *PSEN1* and *PSEN2* mutation carriers, the majority of the studies found a decrease in $A\beta_{42}$ and an increase in both t-tau and p-tau levels when compared with healthy control individuals, consistent with a typical AD profile [7–26] (table 1). In some cases, 1 or more markers were found to be unchanged compared to controls [27–30]. In 1 study, symptomatic carriers of *PSEN1* mutations had significantly lower mean levels of CSF $A\beta_{42}$ compared to patients with sporadic EOAD, sporadic late-onset AD and healthy controls, but no difference in respect to both t-tau and p-tau levels was found between the symptomatic mutation carriers and the patients with the sporadic forms of the disease. Interestingly, levels of grey matter loss as assessed by structural MRI were equal between mutation carriers and sporadic EOAD patients, thus revealing a lack of correlation between total brain amyloid load and the degree of cerebral atrophy [19]. In addition to the standard CSF biomarkers, a few studies have analysed other proteins as potential biomarkers. In individuals carrying *APP* or *PSEN1* mutations, levels of F2-isoprostanes, which are markers of lipid peroxidation, were found to be elevated compared with controls [20]. In another study, a marker of neuronal death, VILIP-1, was found to be increased in carriers of *APP*, *PSEN1* and *PSEN2* mutations [13]. In 3 studies, mass spectrometry was used to assess $A\beta$ isoforms and the proteome in familial AD [9, 31, 32].

Biomarker Profiles in Familial FTD

Individuals with *MAPT* G272V, P301L and R406W mutations were found to have normal levels of $A\beta_{42}$, and in one study elevated levels of tau and p-tau [33–35] (table 1). Some individuals with familial FTD caused by *GRN* mutations had a biomarker profile typical of AD, with decreased $A\beta_{42}$ and increased p-tau and t-tau CSF levels [36, 37]. However, in other cases, p-tau and t-tau levels were within normal range [38, 39]. *C9ORF72* repeat expansion carriers were found to have either CSF profiles within a normal range or profiles similar to those of AD patients, with decreased $A\beta_{42}$ and increased p-tau and t-tau levels [39–43]. Another biomarker candidate, phosphorylated TDP-43, was measured in patients with *GRN* or *C9ORF72* mutations and was found to be higher in these individuals when compared to sporadic FTD patients [39].

Table 1. Main biomarker findings in familial AD and FTD

Gene	CSF findings					References
	A β ₄₀	A β ₄₂	t-tau	p-tau	other proteins	
<i>APP</i>	= (2) = (1)	↓ (9) ↓ (1)	↑ (8) = (1)	↑ (7) = (1)	↑ F2-isoprostanes (1), ↑ VILIP-1 (1) NA	7–13, 20, 26 30
<i>PSEN1</i>	= (3)/↑ (1) = (1)	↓ (22)/= (2) ↓ (3)/↑ (1)	↑ (21) = (4)	↑ (15) = (4)	↑ albumin (1), ↑ F2-isoprostanes (1), ↑ VILIP-1 (1), 14-3-3 protein positivity (1) NA	8–23, 26 27–30
<i>PSEN2</i>	= (1)	↓ (5)	↑ (3)	↑ (4)	↑ VILIP-1 (1)	8, 11, 13, 24, 25
<i>MAPT</i>	NA NA	= (5) = (3)	= (3)/↑ (4) = (3)	= (3)/↑ (2) = (3)	NA ↓ progranulin (1), ↑ pTDP-43 (1)	26, 33–35, 58–60 38, 39, 61
<i>GRN</i>	NA NA	↓ (3) NA	↑ (3) NA	↑ (2) NA	NA = progranulin (1)/↓ progranulin (1)	26, 36, 37 62, 63
<i>C9ORF72</i>	NA = (1)	↓ (2) ↓ (1)/= (2)	↑ (2) = (3)	↑ (2) = (3)	NA ↑ pTDP-43 (1)	40, 42 39, 41, 43

The table summarizes the CSF biomarker profiles found in mutation carriers of *APP*, *PSEN1*, *PSEN2*, *MAPT*, *GRN* or *C9ORF72*. Numbers in parentheses denote the number of publications with the given biomarker finding. ↑ Levels increased in mutation carriers when compared with controls; ↓ levels decreased in mutation carriers when compared with controls; = levels unchanged in mutation carriers when compared with controls; NA = not assessed; pTDP-43 = phosphorylated TDP-43.

Discussion

The scientific community Alzforum (www.alzforum.org) has listed 223 reported mutations in *PSEN1*, 40 in *APP* and 37 in *PSEN2*, both pathogenic and non-pathogenic [44]. *PSEN1* and *PSEN2* are part of the γ -secretase complex, responsible for the generation of A β from cleavage of APP to fragments of 39–42 amino acids, with A β ₄₀ as the most common fragment. Mutations in *PSEN1* or *PSEN2* result in an increased production of A β ₄₂ peptides, which are considered the more pathogenic and aggregation-prone form of A β . A β ₄₂ peptides form toxic oligomers and aggregate into neuritic plaques, whereas soluble A β ₄₂ harms synapses and causes inflammation, leading to synaptic injury and additional pathological events such as hyperphosphorylation of MAPT [45, 46]. The hypothesis of an APP imbalance being involved in disease pathogenesis is supported by the observation that individuals born with Down's syndrome (trisomy 21) – thus having an extra copy of chromosome 21, on which the APP gene is located – develop AD pathology with severe amyloid plaques [47, 48]. Although there is a well-established triplet of CSF biomarkers used for AD diagnosis, there is a lack of biomarkers that reflect disease progression, early prediction and specificity against other dementias. The findings reviewed here show a similar biomarker profile amongst patients with inherited AD, with decreased CSF levels of A β ₄₂ and increased p-tau and t-tau. This observation is not surprising, since these three biomarkers have specifically been developed for AD diagnosis and have shown to be specific for plaque and tangle pathology.

As for the familial FTD cases, the biomarker findings are more varied and do not reveal a clear picture of the underlying pathology (table 1). The differences in the CSF findings cannot be explained by the different mutations, since patients harbouring identical *MAPT* mutations are found to have opposing tau measurements in two unrelated studies [33, 35]. There are several possible explanations for the different observations. One reason might be age differences among study subjects; also differences in sample handling in the clinics and labora-

Table 2. A β isoform findings in familial AD

Gene	Other A β isoforms															Ref.
	A β_{13}	A β_{14}	A β_{15}	A β_{16}	A β_{17}	A β_{18}	A β_{19}	A β_{20}	A β_{30}	A β_{33}	A β_{34}	A β_{37}	A β_{38}	A β_{39}	α -sAPP	
<i>APP</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	↓	64
<i>PSEN1</i>	=	=	=/↑	=/↑	=	=	=	↑	=	=	=	↓	↓	↓	NA	31, 32

↑ Levels increased in mutation carriers when compared with controls; ↓ levels decreased in mutation carriers when compared with controls; = levels unchanged in mutation carriers when compared with controls; α -sAPP = α -soluble APP; NA = not assessed.

tories could affect outcome measurements, since a number of preanalytical factors have shown to influence the stability of CSF proteins [49]. Also, it was not possible to find a distinct biomarker profile which separates FTD cases with *GRN* mutations from sporadic cases based on A β , tau and p-tau levels [37]. This suggests that the underlying pathology of FTD is unrelated to the tau and A β pathology observed in AD.

A specific and sensitive FTD marker has yet to be discovered. The literature reviewed here does not provide FTD markers as the findings are not consistent between the different studies, although some of the studies deal with individuals with the same mutation, especially among *GRN* mutation carriers. In sporadic FTD patients, TDP-43, progranulin and tau have been suggested as CSF biomarkers, but none of them has proven to be specific for differentiating FTD patients from AD or other dementia patients [4].

A weakness of the studies reviewed here is the very limited number of individuals included, with some of the studies being case studies. Biomarker findings in case reports on a single individual may not reflect overall or average changes found in patients with inherited AD or FTD, and this might also explain some of the opposing CSF findings in the reviewed studies shown in table 1. The case reports have been included in this review due to the very limited number of large CSF biomarker studies on individuals with inherited AD or FTD, and we find it important to shed light on all CSF findings on the inherited AD/FTD dementias to date.

The strategy for developing AD biomarkers for clinical diagnostic use has been to assess whether the A β and tau pathology observed in postmortem AD brains as plaques and tangles is reflected in the CSF. Using a new approach, Ringman et al. [9] applied unbiased proteomics to study overall protein changes in presymptomatic and symptomatic individuals with familial AD carrying either *PSEN1* or *APP* mutations. When compared, the proteomic profile of the mutation carriers showed 56 proteins significantly changed compared to non-carriers, including several markers of inflammation and synaptic loss. Forty-six proteins were found to be upregulated and 10 proteins were downregulated in familial AD mutation carriers compared to non-carriers. Interestingly, most of the participants in the study were presymptomatic, and changes in A β , tau and p-tau were detected 10 years or more before the age at onset. Further, several of the 56 proteins shown to be changed have been found to be altered in AD patients before, including APP, transferrin, $\alpha_1\beta$ -glycoprotein, complement components, afamin precursor, spondin 1 and plasminogen. Additionally, Portelius and colleagues [31, 32] used immunoprecipitation mass spectrometry to investigate A β isoforms in individuals with *PSEN1* mutations and found that certain isoforms (A β_{1-37} , A β_{1-38} and A β_{1-39}) were decreased while A β_{1-20} was increased in the CSF of both presymptomatic and symptomatic mutations carriers when compared to non-carriers (table 2). The data suggest that these proteins might be useful as biomarkers in presymptomatic and symptomatic individuals with *APP* and *PSEN1* mutations. Further, the findings from Ringman et al. [9] indicate that other molecular mecha-

nisms than A β and tau pathology are involved in development and progression of AD and point towards other possible treatment targets and strategies. The proteomic approach is interesting as a range of new potential biomarkers have been discovered which have not previously been under investigation. The method could be used when assessing changes in CSF proteins as the disease progresses; however, the results from both studies need to be replicated in a new and larger sample set.

Regarding FTD, only a few studies have investigated CSF with proteomics in sporadic FTD [50–52], and to our knowledge no studies on familial FTD have been published. Some of the proteins found to be changed comparing sporadic FTD patients and control individuals in the studies were albumin and transthyretin (upregulated) and truncated cystatin C, granin-like neuroendocrine precursor, retinol-binding protein and apolipoprotein E (downregulated). It would be interesting to assess if the same proteins are changed in individuals with familial FTD and whether proteomic changes can be detected decades before the onset of symptoms, as it seems to be the case in familial AD.

Yet another approach has been to assess the levels of inflammatory markers in the CSF using immunoassays. AD is characterized by upregulation of the brain's innate immune responses, resulting in inflammatory processes that orchestrate cytokine and cellular responses and culminate in neuronal injury and destruction [6]. In one of the reviewed studies, the levels of F2-isoprostanes, a marker of lipid peroxidation which is associated with inflammation, were increased in the CSF of both asymptomatic and symptomatic young *APP* or *PSEN1* mutation carriers [20]. It remains unclear to what extent the inflammatory proteins are specifically linked to AD pathology, but these data suggest that inflammatory markers might have a potential role as early biomarkers in AD.

The ultimate goal would be to discover biomarkers reflecting early disease pathogenesis or predictors of disease development. Interestingly, Bateman et al. [11] and Fagan et al. [13] observed CSF biomarker abnormalities in autosomal dominant AD caused by mutations in *PSEN1*, *PSEN2* or *APP* (the DIAN cohort) as early as 10–20 years before the estimated onset of symptoms, and mutation carriers developed a classic AD CSF profile the closer they were to the onset of symptoms. Further, Fagan et al. [13] found that VILIP-1, a marker of neuronal injury and cell death, was increased in mutation carriers up to 15 years before the estimated onset of symptoms. These studies and others [10, 28] demonstrate that disease pathogenesis in dementia most likely starts many years before the onset of dementia symptoms in individuals with autosomal dominant AD. It is therefore of great importance to discover specific biomarkers which can detect early disease pathogenesis and enable patients to begin medical evaluation and treatment in an attempt at potentially delaying the onset of symptoms.

Conclusion

In general, levels of A β_{42} , t-tau and p-tau are comparable between familial and sporadic AD patients and between familial and sporadic FTD patients, as shown in the biomarker findings reviewed here. These results as well as strong similarities in imaging markers and disease progression profiles suggest that some or most of the pathophysiology is shared between familial and sporadic forms of AD and FTD, respectively. The DIAN consortium has been established with the aim to study pathological changes in mutation carriers years before the onset of symptoms and to thereby determine how the AD process develops.

Individuals from the DIAN cohort are currently enrolled in a clinical drug trial with the anti-A β antibodies gantenerumab (phase II trial) and solanezumab (phase III trial). The CSF markers which will be monitored in the solanezumab trial are A β species, free A β_{42} and A β_{40} compared to total A β_{42} and A β_{40} , as the antibody recognizes soluble A β . Gantenerumab is an

antibody directed against aggregated A β , and in this trial changes in A β peptide concentrations will be measured. Also changes in tau and p-tau₁₈₁, compared between subjects on the active drug and mutation carriers in the placebo group, will be measured in both trials [53–55]. Despite clinical trials in sporadic AD individuals being cancelled prior to the end date as they failed to meet clinical endpoints, the two trials in the DIAN cohort are ongoing [56, 57]. An initiative like DIAN is necessary for understanding the AD disease course and will contribute to clarifying a strategy for early diagnosis.

A similar consortium for studying familial FTDs caused by *GRN*, *MAPT* and *C9ORF79* mutations, the GENFI consortium, has recently been established and is currently enrolling mutation carriers. It will be interesting to follow the work of GENFI and to see the impending results of their studies.

In view of the literature on biomarker research on familial AD and FTD presented here, further investigation of specific proteins and the overall protein content of the CSF is recommended, since this will provide a better understanding of the disease mechanisms causing neurodegeneration in AD and FTD and allow the discovery of new biomarkers for diagnosis.

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Disclosure Statement

The authors declare that there are no conflicts of interest regarding the publication of this review.

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