Subtype Specific CSF Biomarkers in Sporadic Creutzfeldt-Jakob Disease

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Abstract

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare but fatal type of spongiform encephalopathy with unidentified origin. The conjoining methionine-valine polymorphism of PRNP gene at codon 129 contributes to the manifestation of six different molecular subtypes (MM1, MM2, MV1, MV2, VV1 and VV2) to differential diagnosis of subtype specific sCJD. Presumptive subtype specific diagnosis showed differential clinical manifestations and levels of CSF 14-3-3 protein. Even with the above mentioned differential diagnostic guidelines, pre-mortem subtype specific diagnosis of sCJD can be unreliable with high rates of misdiagnosis. The need for more reliable biomarkers for improving the diagnosis as well as understanding the pathogenesis of this mysterious ailment is amplified. This review compiles the levels of CSF proteins, i.e., PrPC, PrPSC 14-3-3, tau, phosphorylated tau, S100B, neuron-specific enolase (NSE) alpha-synuclein and beta-amyloid to differential diagnosis subtype specific sCJD cases. The detection of pre-mortem distinction targets might be useful diagnostic tool for sCJD in subtype specific manner and might lead towards differential treatment approaches.

Keywords: Creutzfeldt-Jakob disease; CJD; PrP; Prion; 14-3-3; Tau; NSE; Alpha-synuclein

sCJD Subtype Specific CSF Proteins Signature

Sporadic Creutzfeldt–Jakob disease (sCJD) is an invertebrate disease caused by the misfolding of the cellular prion protein. The two major different PrP conformations (type 1 and type 2) in combination with methionine/valine polymorphic of codon 129 contributes to the manifestation of six different molecular subtypes (MM1, MM2, MV1, MV2, VV1 and VV2) leading to differential clinical pathological phenotypes [1,2].

However, the diagnosis of sCJD can only be made with certainty after a patient has deceased, by histological examination of brain tissue at autopsy or, rarely, following brain biopsy. Histopathology should reveal evidence of the distinctive hallmarks of CJD, which are extracellular accumulations of PrPsc aggregates.

Due to diverse phenotypic heterogeneity of Creutzfeldt-Jakob disease (CJD) and atypical variants [3-5] differential diagnosis of CJD from other neurological diseases (sometimes reversible and treatable) is very challenging. Initially diagnostic criteria of CJD were based on combination of clinical symptoms and biomarkers such as MRI, EEG and classical CSF protein marker 14-3-3 [6-9] protein. 14-3-3, which is released into interstitial fluid on death of neurons, indicates rapid neurodegeneration [6]. But this protein is not only present in CSF of CJD but also in other neurodegenerative diseases including some cases of rapidly progressing Alzheimer disease [10-14]. Later studies reported improved differential diagnosis between typical CJD and AD or between CJD and large clinically unselected dementia populations by using t-tau, t-tau to phosphorylated-tau ratio in combination to advanced MRI [15-20]. Many studies have reported overall high diagnostic accuracy for CSF total-tau as compared to 14-3-3 or S100B [21-24]. Recent study has shown that level of total prion protein (t-PrP) in cerebrospinal fluid (CSF) is very useful marker to differentiate CJD from AD. Further a combination of t-PrP with CSF tau even provides more accuracy as compared to using 14-3-3 alone [25]. This review compiles the levels of CSF proteins i.e. PrPC, PrPSC, tau, phosphorylated tau, S100, NSE and alpha-synuclein to differential diagnosis of subtype specific sCJD cases (Figure 1).

PrPC and PrPSC

Over the current years, total PrP (t-PrP) level in CSF have been pronounced as a novel biomarker [25]. For clinicians the level of t-PrP in CSF might support the differential diagnosis of atypical cases in between the CJD and Alzheimer diseases. Additionally, the t-PrP ratio of CSF with tau proteins (Creutzfeldt-Jakob factor=Total tau/Phospho-tau x Total-PrP) lead to differentiate between CJD and atypical AD cases with 100% sensitivity and 95.7% specificity [25]. Many studies reported differential levels of t-PrP in in CJD (subtypes), Alzheimer disease, Parkinson disease, and dementia with Lewy Bodies disease and found slightly but significant decrease in comparison to age matched controls [26,27]. We also reported CJD subtype (MM1 and MM2) t-PrP level correlation in between CSF and brain at mRNA level [26,28-31]. Recent development and consolidation of innovative techniques lead to improve the detection system with more sensitivity and specificity by using RT-QuIC ultra-sensitive in vitro assay lead to diagnose CJD patients. The diagnostic sensitivity of RT-QuIC is between 82-96% and practically fully specificity. Nonetheless, technique still not that improved to discriminate CJD subtypes in comparison to age matched healthy and non-demented controls [32-36]. However, recent reports also showed lower detection sensitivity in CJD subtypes interrelated to type 2 abnormal prion protein (PrPSc) (VV2, MV2 and MM2) than in typical MM1 subtype of CJD.

Altogether, these studies indicate that the level of PrP in CSF are on average lower level in individuals with prion disease and could be a specific marker in symptomatic prion disease patients than in controls [25-28,37] but not at the subtype levels.

Tau and Phosphorylated Tau

Currently, CSF protein analysis in combination to advanced MRI

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these four biomarkers has considerably improved diagnostic accuracy of t-tau/p-tau and other ratios based on different combinations of Aβ42, p-tau and total-PrP levels with the calculation accurate than 14-3-3 [24,37,46]. For differential diagnosis with AD, current approvals to prioritise t-tau analysis over 14-3-3 although western blot 14-3-3 assay, providing an evidence for a change in the diagnostic markers for sCJD [24]. Altogether, data suggest that 14-3-3 for the sCJD MV2K type [24]. This study has shown moderate superiority of t-tau improved value of CSF biomarkers for the clinical diagnosis of CJD authentic approach for subtype differentiation of the disease [23,45].

The common pathogenic signs such as deposition or aggregation of the proteins, plaque or fibril formation demonstrated in more than twenty degenerative diseases [55]. Alpha-synuclein-related pathology in sCJD brain tissue has been reported. In CJD cases are still not clear, nevertheless so far no underlying mechanisms leading to elevated CSF levels of alpha-synuclein in CJD patients [58-60]. Recently, many reports demonstrate the role of alpha-synuclein in CJD as CSF and serum [56,57]. The differential pathological profile of the particular sCJD subtypes contributed to differential NSE and S100B levels in sCJD homozygous and heterozygous groups. Sensitivities and specificities of CSF S100b with other markers including CSF 14‐3‐3 may improve [21,45,52,53]. Alone it does not have better predictive potential than the already used clinical markers or CSF 14‐3‐3, but the combination of S100b with other markers including CSF 14‐3‐3 may improve diagnostic capability. However, NSE, or S-100 contributed substantially to correctly classify into ‘CJD’ or ‘non-CJD’ but is worth to screen patients with dementia and not as first screening test. Furthermore, the levels of S100B and S-100B contributed substantially elevated being predictive for the VV2 subtype, with elevation being predictive for the VV2 subtype [45,54].

**NSE and S100B**

Neuron-specific enolase (NSE) is reported to be elevated and was one of the first protein with potential for differential diagnosis of Creutzfeldt-Jakob disease from other dementing illnesses [24,47-50]. In our sCJD patient cohort homozygous group (MM and VV) showed elevated levels of NSE as compared to the heterozygous [45]. S100B protein is a glial associated, calcium binding, cytoplasmic neurotrophic factor linked to neuronal survival and brain damage [51]. S100B showed similar trend like NSE levels in sCJD homozygous and heterozygous groups. S100B showed elevated levels of NSE as compared to the heterozygous [45]. S100B protein is a glial associated, calcium binding, cytoplasmic neurotrophic factor linked to neuronal survival and brain damage [51]. S100B showed similar trend like NSE levels in sCJD homozygous and heterozygous groups. S100B showed elevated levels of NSE as compared to the heterozygous [45]. S100B protein is a glial associated, calcium binding, cytoplasmic neurotrophic factor linked to neuronal survival and brain damage [51]. S100B showed similar trend like NSE levels in sCJD homozygous and heterozygous groups. S100B showed elevated levels of NSE as compared to the heterozygous [45]. S100B protein is a glial associated, calcium binding, cytoplasmic neurotrophic factor linked to neuronal survival and brain damage [51].

The differential pathological profile of the particular sCJD subtypes contributed to differential NSE and S100B levels in sCJD. The differential brain region and subtype specific inflammatory response might contribute to the different S100B CSF profile [29].

**Alpha-Synuclein and Beta-Amyloid**

The common pathogenic signs such as deposition or aggregation of the proteins, plaque or fibril formation demonstrated in more than twenty degenerative diseases [55]. Alpha-synuclein is an emerging, well conserved target which has been detected in biological fluids such as CSF and serum [56,57]. Recently, many reports demonstrate the elevated levels of alpha-synuclein in the CSF of CJD patients [58-60]. However, the underline mechanisms leading to elevated CSF levels of alpha-synuclein in CJD cases are still not clear, nevertheless so far no synuclein-related pathology in sCJD brain tissue has been reported. In
advancement of CSF alpha-synuclein based RT-QuIC analysis in Lewy bodies and Parkinson’s disease patients showed overall specificity of 100% in comparison with Alzheimer and control [61,62]. However, the CSF biomarkers of sCJD and dementia with Lew body sometimie concomitant an overlap, with reduced levels of amyloid beta 42 and induced levels of tau [60,63-65]. Therefore, supplementation of alpha synuclein levels may be helpful for the perspective of differential diagnostics.

The expressive levels of beta-amyloid peptide in CSF are an extensive pragmatic diagnostic tool in Alzheimer’s disease [66,67]. A reduced level of Beta-amyloid has also been reported in the CSF of patients with sporadic CJD when compared to control samples [68]. These CSF biomarkers have proven to be an extremely valuable in the confirmatory diagnosis of CJD cases. However, all the known biomarkers are sensitive only when the disease is already at an advanced or terminal stage and there is no data available at preclinical stages of the prion disease.

Conclusion

Three core CSF CJD biomarkers have been evaluated in a great number of studies and may provide valuable information for differential CJD diagnostic from other rapidly progressive dementias. Though, diagnostic potential of CSF biomarkers and imaging techniques is very low for differentiation of CJD subtypes particularly for atypical variants of the disease. Efforts should be made to develop new biomarkers for pre-mortem differentiation of molecular subtypes in an attempt to treat the disease in a particular way depending on the disease subtype and underlying pathology related to that disease subtype.

However, all the known biomarkers are sensitive only when the disease is already at an advanced or terminal stage and there is no data available at preclinical stages of the prion disease.

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