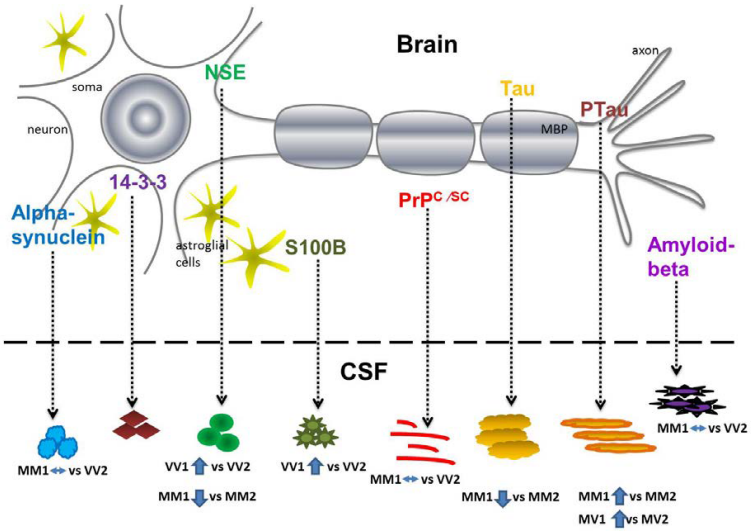


**Figure 1:** Schematic representation of subtype CJD specific diagnostic CSF markers. The CSF biomarkers exhibit the pathological modifications in the neurons of the brain with and demonstrate the potential cellular origin of the biomarkers that are associated with CJD subtype specific pathology. The cascade of events starts by an alteration of alpha synuclein, $PrP^{C/SC}$ AND amyloid beta expression in CSF, nevertheless, with no significance (↔) alterations in between CJD-MM1 and VV2 subtypes. NSE and S100B demonstrate increased levels (↑) in CSF of CJD-VV1 verses (vs.) CJD-VV2, however, CJD-MM1 vs. CJD-MM2 showed decreased levels (↓) in CSF. The expression levels of Tau in CJD-MM1 vs. CJD-MM2 showed decreased levels (↓) in CSF. In addition, P-tau levels in CSF showed increased in CJD-MM1 vs. CJD-MM2 and CJD-MV1 vs. CJD-MV2 subtypes.

techniques such as DWI and FLAIR are the most prominent in vivo diagnostic markers for sCJD [24,38]. Most widely used surrogate protein markers are brain derived CSF proteins (14-3-3, t-PrP, total (t)-tau and t-tau/phosphorylated (p)-tau ratio) with different level of specificity and sensitivity for differential diagnosis of CJD from other rapidly progressive dementias [8,18,20,39-43]. While many studies have analysed utility of these biomarkers for differential diagnosis, only few studies have particularly analysed the effect of the disease-subtypes on the specificity and sensitivity of the biomarkers [23,24,44]. Recently, we showed that CSF protein analysis (14-3-3, tau protein, phosphorylated tau (181P) (p-tau) protein, amyloid β1-42, S100B and NSE can be used as a marker for pre-mortem diagnosis of sCJD subtypes when genotype of codon 129 is known [44,45]. Authors have reported significantly high tau levels in PrP type 1 patient with MM and MV genotype but lower in VV cases. Authors claim that a combination of genotyping and CSF tau assay can be authentic approach for subtype differentiation of the disease [23,45]. A very recent study has provided novel evidence for a significantly improved value of CSF biomarkers for the clinical diagnosis of CJD subtypes [24]. This study has shown moderate superiority of t-tau levels in terms of both specificity and sensitivity for all sCJD subtypes as compared to conventional CJD marker 14-3-3-protein. More precisely authors have shown that t-tau resulted in a lesser number of false positive results, particularly in cases having inflammatory related disorders and sub–acute dementias; and it has higher sensitivity than 14-3-3 for the sCJD MV2K type [24]. Altogether, data suggest that the t-tau assay has technical advantages as compared to the standard western blot 14-3-3 assay, providing an evidence for a change in the current approvals to prioritise t-tau analysis over 14-3-3 although in case of differential diagnosis with Alzheimer disease, t-tau is less accurate than 14-3-3 [24,37,46]. For differential diagnosis with AD, combination of Aβ42, p-tau and total-PrP levels with the calculation of t-tau/p-tau and other ratios based on different combinations of these four biomarkers has considerably improved diagnostic accuracy [25,27,42].

## 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. Sensitivities and specificities of CSF S100b range from 65 to 98% and from 29 to 90%, with an area under the ROC of 0.98% [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 NSE and S100B enabled differentiation between VV1 and VV2 subtypes, with elevation being predictive for the VV2 subtype [45,54].

The differential pathological profile of the particular sCJD subtypes contributed to differential NSE and S100B levels in CSF. 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 sometime 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 expressional 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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