**Viral Infections**

**CASE 24: CREUTZFELDT – JAKOB DISEASE: (Slide 24A, B: H&E, IHC)**

**HISTOLOGY:**
There are two histological sections, one from the frontal cortex and the other from cerebellum. The section from the frontal cortex showed diffuse and fine vacuolation of the neuropil displacing the neurons. Some of the vacuoles are seen abutting the neuronal soma. In addition reactive astrocytosis is noted. No inflammatory component is evident. The white matter is relatively normal though focal pale ischemic zones are noted.

In the cerebellum, the cerebellar folia are thinned out and have variable vacuolation of the molecular layer neuropil. There is patchy loss of Purkinje cells and Bergmann glia and their radial fibres are prominent. No active necrosis, intra neuronal inclusions or inflammation are noted.

The histological features in conjunction with clinical history of rapidly progressive dementia are suggestive of spongiform encephalopathy of Creutzfeldt–Jakob disease, sporadic form (in the absence of family history).

The sections are stained with monoclonal antibody KG-9 to detect abnormal Prion protein (PrP\textsuperscript{sc}). The antibody is specific to the domain lying between amino acid residues 140 and 180 of Prion protein – (BBSRC Resource Centre, National Surveillance Unit, Western Hospital, Edinburgh, UK). The immunostaining of the frontal cortex revealed two patterns of labeling (a) Diffuse synaptic pattern (diffuse stippling of the neuropil), at places along the cell membrane of the neurons and axons (b) Focal perivacuolar dense labeling and round dense globular masses suggestive of multicentric plaques. In the cerebellum small neurons of the granular cell layer and surface of Purkinje cell soma are labeled. In addition in the midst of granular layer dense plaques are found. Both these features are suggestive of CJD.

**DIAGNOSES:** CREUTZFELDT – JAKOB DISEASE

**COMMENT:**
Transmissible spongiform encephalopathies are a complex group of rare but fatal neurodegenerative disorders encompassing multiple clinical syndromes. The disorders are caused by the accumulation of post-translationally modified, insoluble, fibrillary Prion protein (PrP\textsuperscript{sc}) in the brain causing spongiform (vacuolar) degeneration of neuropil in the brain and variable amyloid plaque formation. The global annual incidence of CJD ranges from 0.3 to 1.1 per million population while in India the incidence of 0.085 per million is recorded by the CJD Registry at Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore (unpublished data). Based on Master’s criteria, 52% were categorized as “definite” when there was histopathological confirmation and the remaining as “probable” with rapidly progressive dementia, myoclonus and extrapyramidal symptoms in the absence of histological confirmation. The formation of protease-resistant Prion protein (PrP\textsuperscript{sc}) is considered to be an early event in the pathogenesis of Creutzfeldt-Jakob disease (CJD) and hence its demonstration in brain biopsies by immunohistochemistry is considered diagnostic.

The presence of varied clinical manifestations with cognitive deficits, dementia, ataxia, visual loss often poses a diagnostic dilemma necessitating histopathological confirmation on brain tissue collected by biopsy or at post-mortem. Histopathological features have been the gold standard for diagnosis and the cardinal findings accepted as standard diagnostic criteria include spongiform change in the neuropil,
neuronal loss and reactive astrocytosis. A small proportion of cases of sporadic CJD, familial and iatrogenic CJD can show amyloid plaques. However, the degree and extent of these cardinal findings are notoriously variable and patchy and to an extent depend upon the duration of illness. This makes ante-mortem diagnosis using small brain biopsy samples difficult, particularly if these characteristic histomorphological changes are absent in the biopsy.

Additional techniques have now emerged to circumvent this problem as more information on the pathogenesis of this enigmatic disease is known. It became clear that the formation of protease-resistant Prion protein (PrP\(^{sc}\)) is an early or primary event in the disease pathogenesis. Using immunocytochemistry and Western blot analysis it has now become possible to detect this protein using very small amounts of brain tissue. Therefore, these techniques have assumed an important role not only in early diagnosis of CJD but also in arriving at a definitive diagnosis in the absence of structural lesions, using just a small amount of brain biopsy tissue.

Both the naturally present PrP\(^c\) and the abnormal, disease causing PrP\(^{sc}\) in the brain are encoded from the same sequence of the 16 kb single copy PRNP gene that is positioned on the short (p) arm of human chromosome 20 (20p13). The abnormal PrP\(^{sc}\) isoform differs from the normal PrP\(^c\) isoform in the secondary and tertiary structure, but not in the primary amino acids sequence. PrP\(^c\) is predominantly rich in alpha helical contents, while PrP\(^{sc}\) is predominantly rich in beta sheet conformation. This conformational discrepancy renders the PrP\(^{sc}\) form extremely resistant to proteolysis and degradation by conventional means of chemical and physical decontamination for disinfection. In contrast to PrP\(^{sc}\), PrP\(^c\) is soluble in non-denaturing detergents and is completely degraded by proteases.
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Fig A: Very low power view of the cerebral cortex showing diffuse spongy vacuolation. (H&E Obj X 1.6)

Fig B: Higher magnification shows vacuolation of the neuropil close to neurons. The neurons are fairly well preserved. (H&E Obj X 20)

Fig C: Immunostaining with Prion antibody (clone KG-9) highlights the deposition of Prion protein along the vacuoles. In addition small globular masses (plaques) are seen. (IHC Obj X 20)

Fig D: Molecular layer of the cerebellum has vacuolation of the neuropil, without associated microglial response. Purkinje cell depletion and proliferation of Bergmann glia is evident. (H&E Obj X 10)

Fig E & F: Immunostaining for Prion protein shows a dual pattern. The molecular layer has diffuse and granular deposition. (ii) The Purkinje cells have dense, small nodular deposits along the cell membrane of Purkinje cells. Occasional granular cells are also stained. (IHC; E: Obj X 20, F: Obj X 40)