Familial CJD- A Brief Commentary

Prion disease, a transmissible spongiform encephalopathy, is characterized by prominent heterogeneity in pathology unlike relative homogeneity of Alzheimer's disease, Huntington disease, Parkinson's disease and other so called neurodegenerative diseases. Based on mode of acquisition, prion disease could be sporadic, familial or acquired (infectious).The heterogeneity of the prion disease is modulated by PRNP polymorphism at Codon 129 involving methionine (Met) or valine (Val) (Met/Met, Met/Val, or Val/Val) and physicochemical properties of prion protein strain (type 1 PrP^{Sc} or type 2).[1,2]

Among the Caucasians, 32% of subjects are methionine homozygous (MM), 36% heterozygous (MV), and only 12% are VV homozygous. In Japan, 91.6% of normal population are MM, 8.4% MV and 0% VV.[1] Among sporadic CJD patients, 95% of the MM homozygous belong to PrP^{sc} type I and 86% with VV or MV have PrP^{sc} Type 2 proteins.[3] Similar data is not available among Indian population due to limited availability of genetic testing.

The inherited forms are autosomal dominant with high penetrance and include genetic CJD, FFI, GSS and newly described prion protein cerebral amyloid angiopathy. Not all have a family history, and in its absence, only PRNP mutation provides diagnosis. Over 40 mutations in PRNP gene are identified and polymorphism at Codon 129 and 219 influence the wide range of clinicopathologic phenotypes.[2] E200K-129M is the most common form of familial CJD with clinical phenotype of sporadic CJD.

The D178N-129M haplotype is associated with FFI and the most prevalent form of familial CJD. The duration of illness is variable. The insomnia, myoclonus and autonomic malfunctions are often more severe in 129 MM subjects and ataxia in 129 MV subtypes.[3] The EEG may not show classic PSW. In CSF, 14-3-3 maybe absent. Spongiform change and astrogliosis resent invariably present in cerebral cortex, milder in striatum, diencephalon and cerebellum.[2]

From India, reports of CJD are scarce, with few suspected familial CJD cases from Mumbai and Hyderabad reported to the CJD Registry (personal communication), but no genetic studies could be carried out. Because of infectious nature of CJD the clinicians and pathologists shun autopsy studies and hence cases remain uncharacterized as sporadic or familial; though consanguinity is common in India.[4,5]

In a previous report, Sehwal *et al*., 2019 reported an Indian kindred with haplo type of the index case being D178N-129VV.[5] The clinical phenotype was sCJD with insomnia in one member. PRNPD178N is usually associated with FFI phenotype but MM at codon 129, reinforcing disease modulating effect of Codon 129 polymorphism. The unaffected family members revealed a MV polymorphism at codon 129 despite harboring the D128N mutation. Lack of classic triphasic waves on EEG and absence of 14-3-3 in CSF add to the diagnostic dilemma. In the current report, PRNP gene mutation was similar.[6]

Histopathological features are also influenced by the PRNP gene and show florid spongiform change with scant prion plaques in cases with D128N mutation. In the report by Sawal from Delhi, the pathological features are not described as biopsy/autopsy was not conducted.[6] In the current case report, the pathological features described was typical of D128N mutation.[7]

With increasing awareness, CJD is being increasingly suspected by neurologists and need for availability of genetic testing for confirmation is increasing.

To conclude, it is essential to develop scientific collaboration and establish genetic testing facility in India. It is time to establish a referral laboratory for the country to augment the CJD registry to gain realistic epidemiological data for the country.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Satish Chandra, Anita Mahadevan[1], S.K. Shankar[1]

Departments of Neurology and [1]Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

Address for correspondence: Prof. Satish Chandra, Department of Neurology, National Institute of Mental Health and

Neurosciences (NIMHANS), Bangalore, Karnataka, India.
E-mail: drsatishchandra@yahoo.com

References

1. Iwasaki Y. Creutzfeldt-Jakob disease. Neuropathology 2017;37:174-88.
2. Ritchie DL, Ironside JW. Neuropathology of human prion diseases. Prog Mol Biol Transl Sci 2017;150:319-39.
3. Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. Sporadic familial CJD Classification and characterization. Br Bull 2003;86:213-39.
4. Kher M, Rao MY, Acharya PT, Mahadevan A, Shankar SK. Heidenhain variant of *Creutzfeldt-Jakob disease*: An autopsy study from India. Ann Indian Acad Neurol 2009;12:48-51.
5. Mahadevan A, Shankar SK, Yasha TC, Santosh V, Sarkar C, Desai AP, *et al*. Brain biopsy in Creutzfeldt-Jakob disease: evolution of pathological changes by prion protein immune histochemistry. Neuropathol Appl Neurobiol 200228:314-24.
6. Sawal N, Chakravarty K, Puri I, Goyal V, Garga A, Shi Qi, *et al*. Familial CreutzfeldtJakob disease is first reported from South East Asia. Ann. Indian Acad Neurol 2019;22:225-27.
7. Katrak SM, Pauranik A, Desai SB, Mead S, Beck J, Brandner S, *et al*. Familial Creutzfeldt-Jakob Disease in an Indian Kindred. Ann Indian Acad Neurol 2019;22:458-61.

Received: 09.10.2019 **Accepted:** 09.10.2019
Published: 25.10.2019

DOI: 10.4103/aian.AIAN_508_19