Diagnostic Value of Electroencephalogram in Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is an inexorably progressive and consistently fatal transmissible spongiform encephalopathy, characterized by the accumulation of an abnormal isoform of the host-encoded cellular prion protein in the brain, resulting in rapidly progressive dementia, cerebellar and extrapyramidal signs, and myoclonus and visual symptoms.[1] CJD is a rare disease occurring with an incidence rate of 1 to 2 cases per million population per year.[2] Based on the etiopathogenesis, CJD is classified into sporadic (sCJD), familial (fCJD), iatrogenic (iCJD), and variant (vCJD) subtypes; of these, sCJD is the most common subtype accounting for around 85% of CJD cases reported worldwide.[1,3] sCJD typically occurs later in life with a mean age of 67 years with a postdiagnosis survival of around four months; however, there is marked heterogeneity in the clinical presentation.[1,3] Emerging understanding of the molecular mechanisms of sCJD has underscored the influence of methionine (M)/valine (V) polymorphisms involving codon 129 of the prion protein gene *PRNP*, located on the short arm of chromosome 20, on the electroclinical characteristics and course of the disease.[1,3] While M homozygous polymorphism (MM) occurs in more than half of the individuals, heterozygous polymorphism (MV) is encountered in just over one-third and V homozygous polymorphism (VV) is the least common.[1,3] The clinical presentation of sCJD can imitate that of the other dementias, extrapyramidal disorders, metabolic and toxic encephalopathies, autoimmune encephalitis, and nonconvulsive status epilepticus (NCSE).[1,3-5]

A reliable and early diagnosis of CJD is critical in excluding other, potentially treatable, causes of rapidly progressive encephalopathies before disclosing the diagnosis of an incurable disease to the relatives of the patient. Although brain biopsy is necessary to definitely establish the diagnosis of CJD, concerns about the resistance of the transmissible agent to conventional methods of sterilization of the surgical instruments deters this procedure. Noninvasive investigative means such as electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) have become an integral part in substantiating the diagnosis of sCJD. Consequently, diagnostic criteria integrating clinical features, such as EEG and MRI findings, and the presence of protein 14-3-3 in the cerebrospinal fluid (CSF) in various combinations have been designed to provide an early and reliable clinical diagnosis of sCJD. The World Health Organization (WHO) criteria,[6] which did not include the MRI findings, has largely been replaced by the updated clinical diagnostic criteria for sCJD that incorporated the MRI findings.[7] Several recent studies have deduced the sensitivity, specificity, and positive predictive values (PPV) of the individual tests and their combinations in diagnosing sCJD.[3,7-9]

EEG has been the method of choice to corroborate the clinical diagnosis of CJD for decades.[1] Several studies from across the world have reported the EEG findings from a sizeable number of definite and clinically probable cases of sCJD.[1,3,9] Two recent studies[10,11] have followed the EEG terminologies recommended by the latest American Clinical Neurophysiology Society's (ACNS) critical care EEG terminologies in classifying the EEGs findings.[12] The periodic discharges (PDs) of CJD consist of generalized biphasic or triphasic sharp waves recurring (GPDs) every 0.5 to 2 seconds over the low-amplitude slow background.[1,3,9-11] The GPDs of CJD are typically prominent over the anterior head region but can be posterior dominant in the rare Heidenhain variant. In the early stage of sCJD, the PDs can be asymmetric or even lateralized (LPDs). They appear by 3-4 months from the onset of disease, and are encountered in two-thirds of patients with sCJD during the course of the disease. Unlike in subacute sclerosing panencephalitis, the GPDs of CJD tend to disappear during sleep and may get accentuated when the patient is alerted from drowsiness and they bear no relationship with the myoclonus. Among the molecular sCJD subtypes, PDs occur more often in patients with MM and MV genotypes when compared with the VV genotype[1,3] In patients with iCJD, PDs occur as frequently as sCJD, but manifest with a more regional distribution corresponding to the site of inoculation of the transmissible agent.[1] The typical PDs are uncommon in fCJD (about 10% of patients) and do not occur in vCJD.[1] The PDs of CJD resemble those associated with NCSE, metabolic, toxic (lithium, baclofen, ifosfamide, and anesthetic drugs), and anoxic and autoimmune encephalopathies.[1,3-5]

What is the comparative value of EEG in relation to MRI abnormalities and elevated CSF 14-3-3 protein in the diagnosis of sCJD? The most reliable information in this regard has emerged from the multinational study involving 12 countries.[7] Among 214 definite (confirmed by brain pathology) CJD patients and 77 definite non-CJD cases, MRI abnormalities had a sensitivity and specificity of 83% and CSF protein detection had a sensitivity of 86% and specificity of 68%, and EEG had the lowest sensitivity (44%) and highest specificity (92%).[7] Combining the results of these three tests, provided a sensitivity of 92% and specificity of 71%.[7] In general, PDs have a sensitivity of 64%–67% in the diagnosis of sCJD[1,8] and high specificity (up to 91%) in the clinical probability group.[9] The positive predictive value of a combination of PD and CSF protein 14-3-3 in patients with probable or possible CJD has been reported to be as high as 99%.[9]

In this issue of the Journal, Mundlamurri *et al*.[13] have reported from the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a retrospective

analysis of the EEG data of 50 probable CJD patients, which as claimed by the authors, constitute the largest number of cases from a single institution in India. PDs were noted in 66% of patients. While the sensitivity of PDs in those with positive MRI was 68.7%, the sensitivity of positive MRI was 94% in those with PDs in the EEG. Overall, the findings of this study differ a little from those already reported from elsewhere. The younger mean age of the patients and the marked male preponderance are possibly spurious (related to referral/ascertainment biases), inherent to hospital-based studies from developing countries. The use of ACNS EEG terminology, addition of 14-3-3 CSF results (the expertise for this is available at NIMHANS, Bangalore), and molecular genetic analysis could have enhanced the value of this study. While I wish to complement the authors for their effort, I encourage the neurology community in our country to organize a multicenter study to gather a uniform protocol-based data on CJD in India to overcome the limitations listed by the authors of the study.

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