

Case series of probable sporadic Creutzfeldt-Jakob disease from Eastern India

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Abstract

Background: Creutzfeldt-Jakob disease is a rapidly progressive, fatal, transmissible neurodegenerative disorder caused by prion protein. It is still considered rare in countries like India. This is probably due to nonavailability of autopsy studies in majority of the center. The recent European diagnostic criterion for sporadic CJD (sCJD) is useful for making an early diagnosis. **Objective:** To report a series of patients of probable sCJD from a neurology institute of eastern India. **Materials and Methods:** Patients of rapidly developing dementia fulfilling the diagnostic criteria for sCJD were included. All were investigated in detail to find out any possible treatable cause including electroencephalography (EEG), magnetic resonance imaging (MRI) of brain, and cerebrospinal fluid analysis. **Results:** A total 10 patients of probable sCJD diagnosed using the European diagnostic criterion between December 2011 and January 2013. The clinical features are consistent with other reported series. While 60% of patients had the classical EEG findings, 100% had typical MRI features. Eight patients died within a mean duration of 4.56 months from the disease onset. **Conclusions:** The clinical features are similar to other reported series. Our observation raises question about the prevalence of this disease in India which needs more elaborate studies.

Key Words

Creutzfeldt-Jakob disease, electroencephalography, magnetic resonance imaging

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Introduction

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive, fatal transmissible neurodegenerative disorder caused by accumulation of an abnormally shaped membrane-bound protein, the prion protein, in neurons.^[1] In about 85% of cases classified as sporadic CJD (sCJD), no etiology can be identified. The incidence of disease is 0.5-1.5 per million per year with little annual, seasonal or geographic variation.^[2] Mean survival of CJD patients reported in the literature is 5 months with over 80% of patients succumbing to the disease by 12 months of onset.^[3,4] In India, the disease is still underreported. According to the national CJD registry at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, there were only 85 recorded cases of CJD till September 2005.^[5] Thirty

cases including 20 definite and 10 probable cases were reported between 1971 and 1990. Demographic analysis has shown similarities to the previously published reports from other parts of the world. Another series of 10 cases was published by Mehndiratta *et al.*, in 2001 from New Delhi.^[6]

Here we report a series of 10 cases from eastern India diagnosed in year 2011-2012 of sCJD on the basis of current European diagnostic criteria.^[7]

Materials and Methods

Patients of rapidly developing dementia admitted in the institute between December 2011 and January 2013 were included in this study. The patients were diagnosed on the basis of criteria proposed by magnetic resonance imaging (MRI)-CJD consortium criteria for sCJD. Details of place of residence, occupation, dietary habits, age at onset, duration of symptoms, history of any surgical procedure or head trauma, hypertension, exposure to drugs like lithium, toxins like bismuth, hormone replacement therapy, and any relevant family history were recorded. History of dog bite and vaccination with Semple's vaccine for the same was not known in any of the cases. All patients underwent investigations including complete hemogram, erythrocyte sedimentation rate (ESR), blood sugar, kidney function tests,

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liver function tests, urinalysis, serum Venereal Disease Research Laboratory (VDRL), human immunodeficiency virus (HIV), serum anti-thyroid peroxidase (anti-TPO) antibodies test, antinuclear antibody (ANA). Cerebrospinal fluid (CSF) studies for cell count, cell type, protein and sugar, bacteriological and virological studies, electrocardiogram (ECG), and chest X-rays, and ultrasonography (USG) abdomen were carried out in all the patients. All patients were subjected to a 1.5 Tesla MRI scan including diffusion weighted and fluid-attenuated inversion recovery (FLAIR) images. Electroencephalography (EEG) was recorded using the international 10-20 System. The periodic polyspike-wave complexes (PSWCs) were defined as diffuse biphasic or triphasic sharp wave complexes with duration between 100 and 600 ms and an intercomplex interval between 500 and 2,000 ms. None of the patients underwent brain biopsy.

Results

A total 10 cases of probable sCJD were admitted at our center during December 2011 to January 2013 (M:F = 4:6). Table 1 gives details of demographic profile of patients, their clinical, EEG, and MRI findings. All of them were the residents of West Bengal, but came from various districts suggesting no geographical clustering. The mean age of patients at the time of diagnosis was 56.1 (SD = 8.26, range 39-70) years. While six patients presented with behavioral abnormalities, four had ataxia, five had extrapyramidal features, four had visual hallucination, and one with cortical blindness as their presenting symptoms. All of our patients had spontaneous myoclonus during some stage of the disease and of them 5 had stimulus-sensitive myoclonus. All of them became bedbound within 3-4 months from their illness and developed akinetic mutism. One of our patients had known history of surgical procedure (cataract surgery) done 2 years before onset of illness. None of our patients had history of head trauma, intake of lithium, or any hormone replacement therapy. No history suggestive of exposure to toxins like bismuth was noted in any of the cases. Eight patients died with mean duration of illness of 4.56 months from disease onset. We do not have information about two patients. Six patients (60%) had periodic spike wave complexes, while all patients had diffuse slowing of background on EEG [Figure 1]. We could not perform repeat EEG in our patients as they were either discharged or taken away from hospital once a diagnosis was disclosed to

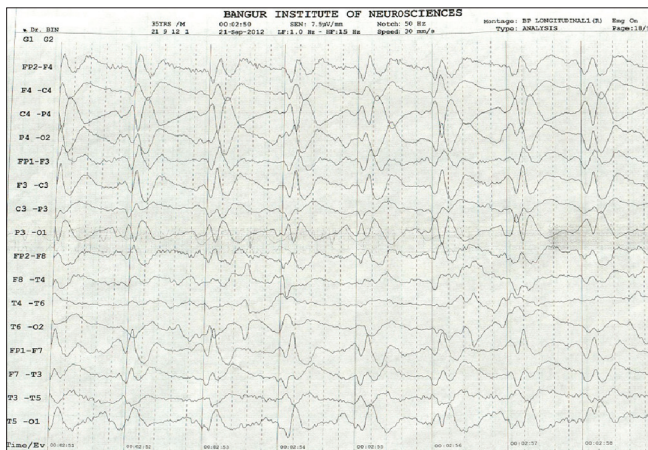


Figure 1: Electroencephalography showing periodic spike and wave discharges

their relatives. CSF showed normal to mildly elevated protein in all our patients and only one patient had raised cell count in CSF (20 cells/mm³). The CSF of all patients was negative for viral/bacterial infection. The serum anti-TPO antibodies were positive in three patients with very high titer in one. MRI was performed in all 10 patients including diffusion weighted imaging (DWI) sequence. All patients (100%) had MRI features suggestive for CJD that include bilateral symmetrical hyperintensities in caudate and putamen in T2 and FLAIR sequences with gyral pattern diffusion restriction in bilateral parieto-occipital and temporal regions [Figure 2]. In addition, the “hockey stick sign” was detected in one patient [Figure 3] and “pulvinar sign” in another one. Three patients received high dose methylprednisolone for 5 days with the suspicion of autoimmune encephalitis, but none of them showed improvement.

Discussion

This case series consists of 10 cases (M:F = 4:6) of probable sCJD diagnosed on the basis of current European diagnostic criteria. All of our patients had clinical features of rapidly developing dementia with myoclonus. The other clinical features include behavioral abnormalities, ataxia, extrapyramidal features, cortical blindness, etc., All of them were evaluated with detailed investigations to exclude other treatable causes; like metabolic, infective, and autoimmune diseases. Three patients were given high dose methylprednisolone for 5 days with the suspicion of autoimmune encephalitis, without any improvement. All patients showed a positive MRI finding fulfilling the criteria. The EEG was positive for PSWCs in six patients, while all patients showed diffuse slowing of background. Thus, all of our patients fulfilled the diagnosis of probable sCJD according to the criteria.

The mean age of patients at the time of diagnosis was 56.1 years. In the 10 cases of Mehndiratta *et al.*,^[6] the mean age was 53.80 (SD = 7.32) years with M:F of 1:1. All of our patients had myoclonus and similar finding was also reported by Mehndiratta *et al.*^[6] Myoclonus is considered as the most characteristic and constant sign in CJD. Our observation about various presenting symptoms, for example, abnormal behavior, ataxia, and extrapyramidal features are similar to the case series of Mehndiratta *et al.*^[6] All of our patients became bedbound and developed akinetic mute state and eight patients died within a mean period of 4.56 months from the disease onset. This is consistent with other reported series.

While six of our patients had classical EEG changes like PSWCs, all patients had diffuse slowing of background. PSWCs in EEG give a sensitivity of 67% and specificity of 86% for detection of CJD.^[8] More than 90% of patients may show periodic complexes if repeated EEG records are taken.^[9] We could not perform repeat EEG in our patients, and thus it was not possible to document changes.

The PSWCs on EEG have been used as one of the central diagnostic tests for CJD.^[10] PSWCs are recorded usually in middle and late stages of the disease.^[11] PSWCs, either lateralized (in earlier stages) or generalized, occur in about two-thirds of patients with sCJD, with a positive predictive value of 95%.^[11] However, PSWCs are not always specific for CJD.^[11] PSWCs are therefore of limited use for the early diagnosis of CJD.

Table 1: Demographic profile including disease duration and total duration illness before death, clinical features, EEG, and MRI findings

Case no.	Age/ sex	Duration of illness (months)	Duration of illness at time of death	Symptoms at onset	Subsequent symptoms	EEG	MRI brain
1.	56/F	3	5	Cortical blindness, abnormal behavior, memory loss, cognitive decline, apathy	Visual hallucination, Parkinsonism, stimulus sensitive myoclonus, akinetic rigid state	Periodic spike and slow waves	Bilateral basal ganglia hyperintensities in FLAIR and DWI, gyral pattern diffusion restriction in parieto-occipital, frontal region
2.	50/M	2	6	Broad based gait, tremulousness of all four limbs, loss of jocular, cognitive decline	Myoclonus, akinetic rigid state, parkinsonism	Diffuse slowing of background activity	T2 and FLAIR hyperintensities in bilateral caudate, lentiform nuclei and posteromedial part of thalami. Diffusion weighted images restriction in same areas
3.	53/F	2	5	Behavioral disturbances, right hemiparesis	Quadriparesis, myoclonus akinetic rigid state	Diffuse slowing of background activity	Diffusion restriction in bilateral basal ganglia and periventricular regions along with gyral pattern diffusion restriction in left temporoparietal cortex
4.	58/M	1	3	Tremulousness of left upper limb later whole body	Cognitive decline behavioral changes, myoclonus, cognitive decline	Diffuse slowing of background activity with periodic spike and slow wave discharges	MRI showed diffusion restriction in parieto-occipital region in a gyral pattern
5.	60/F	4	5	Bilateral symmetric Parkinsonism, behavioral problems, memory impairment	Stimulus sensitive myoclonus, akinetic rigid state	Diffuse slowing of background activity	T2 hyperintensities symmetrically involving bilateral basal ganglia and thalami (hockey stick sign) with diffusion restriction in these areas and bilateral frontal gyri
6.	39/M	2	Lost in follow-up	Visual hallucination, rapidly developing cognitive decline	Seizure, myoclonus	Diffuse slowing of background activity with occasional pseudo-periodic discharges	T2 hyperintensities symmetrically involving bilateral basal ganglia with diffusion restriction in parieto-occipital areas
7.	70/F	2	3	Ataxia, incoordination, memory impairment	Stimulus sensitive myoclonus, choreoathetoid movement	Diffuse slowing of background activity	Hyperintensities in T2 and FLAIR in pons, bilateral capsuloganglionic region, thalamus and bilateral hippocampus along with diffusion restriction in bilateral hippocampus, thalamus (pulvinar) and caudate nuclei
8.	64/M	12	4.5	Topographical memory loss, recent memory loss	Episodic memory and visuospatial dysfunction, Gait ataxia, myoclonus	Diffuse slowing of background activity with periodic spike and slow wave discharges	Gyriform hyperintensity in T2 weighted sequences in bilateral cerebral hemispheres more in the parieto-occipito-temporal lobes with diffusion restriction in DWI, along with patchy hyperintensities noted scattered in both cerebral hemispheres
9.	55/F	5	No information	Behavioral abnormalities, visual hallucination, decrease speech output, tremor	Extrapyramidal features, Stimulus sensitive myoclonus, mutism	Diffuse slowing of background activity with periodic spike and slow wave discharges	T2 and FLAIR hyperintensities in basal ganglionic region forming a hockey stick with diffusion restriction and cortical ribbon sign in bilateral occipital areas
10.	56/F	2	5	Behavioral abnormalities, visual hallucination, Parkinsonian features	Akinetic rigid state, mutism, Stimulus sensitive myoclonus	Diffuse slowing of background with generalized periodic spike and wave discharges	Bilateral symmetrical T2 and FLAIR hyperintensities in both basal ganglia. Mild diffusion restricted nonenhancing hyperintensities seen in T2 and FLAIR in both basal ganglia and frontal and perisylvian area

EEG=Electroencephalography, MRI=Magnetic resonance imaging, DWI=Diffusion weighted imaging, FLAIR=Fluid-attenuated inversion recovery

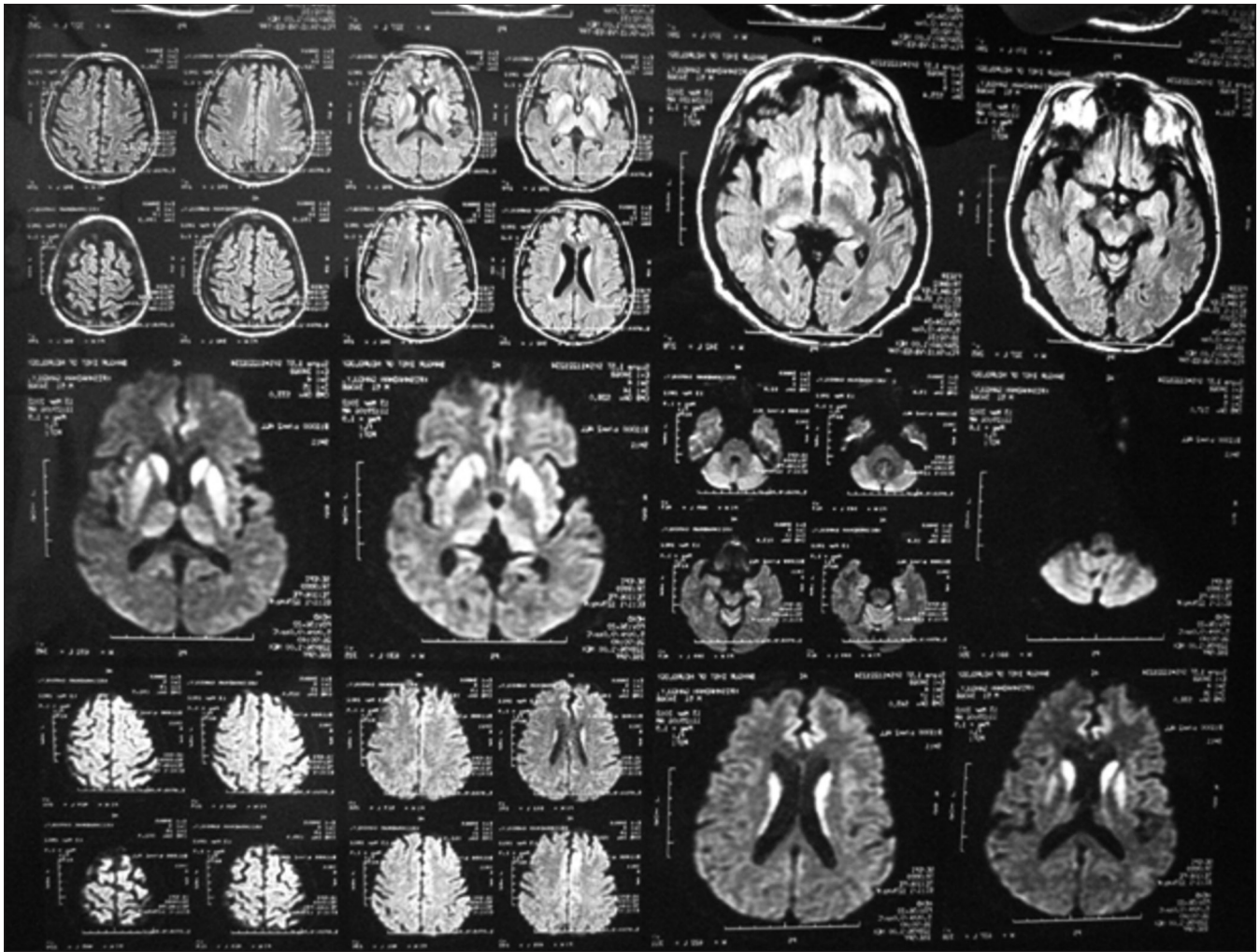


Figure 2: Magnetic resonance imaging diffusion weighted sequence showing restriction in bilateral basal ganglia and gyral pattern of diffusion restriction in bilateral parieto-occipital cortex and bilateral frontoparietal cortex

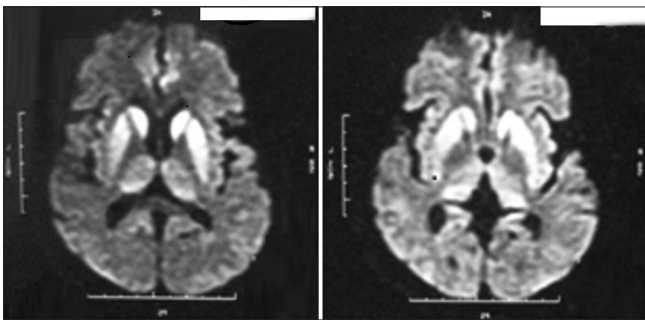


Figure 3: MRI showing “hockey stick sign”

MRI with DWI and FLAIR sequences is an invaluable modality in supporting the diagnosis of CJD. The detection of the specified high signal abnormalities in FLAIR or DWI MRI is considered to have similar diagnostic importance as PSWCs on the EEG or 14-3-3 protein detection in the CSF.^[8] Shiga *et al.*, in their study concluded that diffusion-weighted MRI had higher sensitivity (92%) in the detection of CJD than FLAIR (41-59%), T2 sequences (36-50%), EEG (50-78%), CSF protein 14-3-3 (84%), or neuron-specific enolase (73%).^[13] Matoba *et al.*, noted that the hyperintensity in the basal ganglia and cortex during the early

stages was more extensive and conspicuous while in the later stages there was disappearance of the abnormal signals in the cortex.^[14]

Zerr *et al.*,^[12] modified the clinical diagnostic criteria for sCJD and included MRI findings with detection of either hyperintensity in the basal ganglia (both caudate nucleus and putamen) or in at least two cortical regions (from either the temporal, parietal, or occipital cerebral cortices). This implies that the detection of the specified high signal abnormalities in FLAIR or diffusion weighted MRI is considered at the same level of diagnostic importance as PSWCs on the EEG or 14-3-3 protein detection in the CSF.

The combination of FLAIR and DWI has a sensitivity, specificity, and accuracy of over 90% in differentiating CJD from other dementias.^[15] It is argued that the multifocal cortical and subcortical hyperintensities in the grey matter showing restricted diffusion on MRI may be more useful than the CSF protein 14-3-3 analysis.^[16] Zerr *et al.*,^[12] proposed that high signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital lobes) either in DWI or FLAIR together with typical clinical signs can be diagnostic

for probable sCJD. Based partly upon their report, 'high signal in caudate/putamen on MRI brain scan' has been used as one of the laboratory findings in the diagnostic criteria for probable sCJD in the European CJD Surveillance System (EUROCD) since January 2010.^[7] However, their criteria did not distinguish DWI and FLAIR, thereby maintaining ambiguity about the diagnostic values of MRI in situations where DWI is not available. More recently, Vitali *et al.*, reported that hyperintensity greater on DWI than FLAIR is diagnostic for sCJD, whereas hyperintensity greater on FLAIR than DWI is characteristic for nonprion rapidly progressive dementia.^[17] Furthermore, reduction of apparent diffusion coefficient in subcortical (striatum) hyperintensity regions on DWI is supportive for sCJD.^[17] In another recent study, Fujita *et al.*, argued that FLAIR without DWI is unreliable for the diagnosis of sCJD.^[18] On the other hand, high signals in the cerebral cortex have not been regarded as diagnostic in the EUROCD criteria, probably because cortical abnormalities are less reliable on conventional MRI. They suggest that, using standardized or variable DWI but not FLAIR, cortical signals can also be used as a diagnostic marker.^[18] All of our patients had bilateral symmetrical hyperintensities in caudate and putamen in T2 and FLAIR sequences with gyral pattern diffusion restriction in bilateral parieto-occipital and temporal regions. One of them also had the "hockey stick sign" and another one had the "pulvinar sign".

This case series is single center experience over a period of 1 year. The disease is still considered a rare entity in India. Barring NIMHANS registry and case series from New Delhi, there are few case reports from various parts of India. Mehndiratta *et al.*, reported 10 cases from a tertiary care center in north India, gathered over 9 years (1990-1998). While their patients came from four different states of north India, all our patients are resident of West Bengal. However, we did not find any geographical clustering. The observation of so many patients within 1 year period is an important observation. This demands rethinking about the disease prevalence in our country. However, it may also be because of availability of new diagnostic criteria and easier availability of MRI in recent years, that helped us to make a diagnosis even without autopsy and availability of sophisticated test like estimation of CSF protein 14-3-3.

Conclusion

CJD is a fatal spongiform encephalopathy. Diagnosis is usually suspected in a patient with rapidly progressive dementia with myoclonus. Additional signs include visual hallucination, cerebellar or extrapyramidal features, akinetic rigid state, and mutism. These clinical features with a typical EEG finding of periodic PSWCs and MRI features of T2 and FLAIR hyperintensities in cortical or subcortical grey matters and diffusion restriction are almost diagnostic of this disease. Early diagnosis may be possible on basis of MRI brain scan and this has been used as one of the laboratory findings in the diagnostic criteria for probable sCJD in the EUROCD since January 2010. Our study highlights the increasing prevalence of the disease in India, which needs to be validated by studies from other parts of the country.

Limitations of the study

We could not perform the CSF 14-3-3 protein analysis because of the lack of the availability of the test at our institute. Diagnosis can only be confirmed by histological examination of brain tissue

obtained either by the brain biopsy or after autopsy which was not performed at our center.

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