Case Series

Clinical and magnetic resonance imaging features in sporadic Creutzfeldt–Jakob disease: A case series of four patients

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ABSTRACT

Creutzfeldt–Jakob disease (CJD) is one of the subtypes of prion diseases, classified as hereditary, infectious, and sporadic disorders. Magnetic resonance imaging (MRI), particularly diffusion-weighted imaging, has become an important tool for the diagnosis of CJD due to its peculiar findings of cortical ribboning and hyperintense basal ganglia structures. In our case series, we described clinical details and MRI findings of four patients admitted to a tertiary center of North India, diagnosed as sporadic sCJD. Among these, three patients were female and one was male. The age ranged from 42 to 65 years, with a mean age of 55.5 years. Investigations, including MRI, electroencephalogram, and viral markers, were done for all four patients. The clinical features, neuroimaging characteristics, and outcomes were discussed with a review of the literature. The patients were treated with anti-epileptics and supportive drugs, but despite it, all the four patients died within one year of onset of illness. Our report may impress the treating physicians about the role of MRI as even now, it is underdiagnosed due to rare occurrence.

Key words: Cortical ribboning, Creutzfeldt–Jakob disease, Human prion disorders

Creutzfeldt–Jakob disease (CJD) is a rare fatal neurodegenerative disorder, a spongiform transmissible encephalopathy, characterized by rapidly progressive dementia, myoclonus, ataxia, pyramidal, extrapyramidal, and visual abnormalities [1]. Neuroimaging techniques, particularly diffusion-weighted imaging (DWI), apparent diffusion coefficient, and T2 fluid-attenuated inversion recovery (FLAIR) images, have simplified the diagnosis in CJD [2]. The classical magnetic resonance imaging (MRI) abnormalities are restricted to the cortical mantle and basal ganglia structures. It is underdiagnosed as the antemortem biopsy is not frequently done. We described a case series of four patients, diagnosed as probable CJD, and admitted to a tertiary center of North India. The clinical features, neuroimaging characteristics, and outcomes were discussed with a review of the literature.

CASE SERIES

Case 1

A 65-year-old female presented with complaints of rapid cognitive decline, changes in personality and behavior, diffuse myoclonic jerks, and difficulty in walking for the past 6 months. She gradually became bed-bound and developed bladder and bowel incontinence. The attendant also noticed the complaint of visual hallucinations. There was no history of prolonged fever, cough with, or without expectoration, arthralgia, and cutaneous manifestations. The patient denied a history of beef consumption or previous surgery.

On examination, there was a loss of interest in the conversation, reduced verbal output, and incomprehensible speech. Motor system examination revealed rigidity in all limbs. Deep tendon jerks were brisk with plantar flexor response. The hematological parameters, including hemogram, renal function test, liver function parameters, thyroid function test, thyroid peroxidase, antithyroglobulin antibody, serum electrolytes, serum lactate, and blood sugar, did not suggest any abnormality. The autoantibodies for antinuclear antibody, anti-neutrophilic cytoplasmic antibody, and antiphospholipid reactants were none reactive in sera. The cerebrospinal fluid routine assessment revealed normal findings and reactivity to the herpes virus, Japanese encephalitis virus, Epstein–Barr virus, and dengue virus showed negative results. The panel for the autoimmune receptors antibody was negative. Neurosyphilis was ruled out with appropriate serological investigations.

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The serum lactate level was normal and Kayser–Fleischer ring was not visible on the slit-lamp examination. The computed tomography brain was normal. MRI brain showed T2 hyperintensity in caudate, putamen region on both sides, and at multiple areas along the cortical gyri (suggestive of hockey stick sign and cortical ribbon sign). Both these findings were best appreciated on the DWI image (Fig. 1). An electroencephalogram (EEG) showed periodic spike and wave complexes at an interval of 1 s (Fig. 2). The diagnosis of probable CJD was entertained. The patient received valproate 500 mg twice daily and flupirtine 100 mg thrice daily along with supportive management. The patient succumbed to illness after 2 weeks of hospitalization.

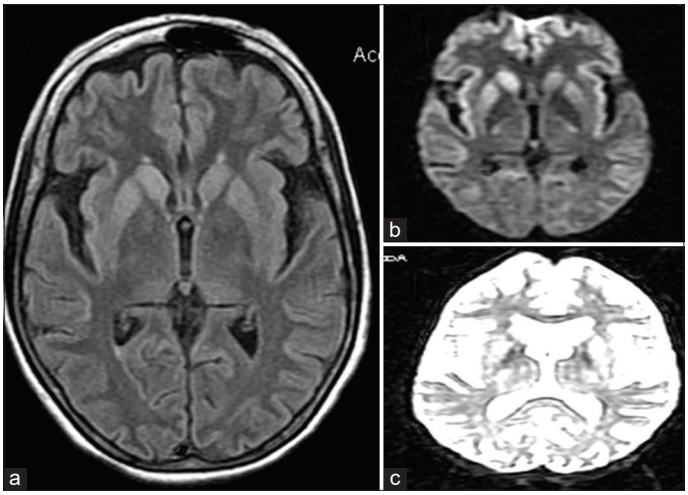

Figure 1: Magnetic resonance imaging (Cranium) on T2 fluid-attenuated inversion recovery. (a) Demonstrated hyperintense signals in the bilateral caudate nucleus and putamen, (b) diffusion-weighted imaging showing restricted diffusion (hyperintense signals) in bilateral caudate nucleus and putamen with gyral hyperintensity in the left frontal region (cortical ribboning), and (c) axial apparent diffusion coefficient displayed reduced signals in bilateral caudate nucleus and putamen (case 1)

Case 2

A 42-year-old male manifested with a progressive cognitive decline for the past 8 months. Initially, he noticed forgetfulness. He felt difficulty in picking up placed objects. He started forgetting the names and faces of his relatives. He developed difficulty in a speech in the form of reduced verbal output and not getting appropriate words for conversation. He had intentional tremors and sometimes manifested with spillage of fluids on his clothes. There was a positive history of widespread myoclonic jerks. The patient denied a history of prolonged fever, joint pains, jaundice, and skin rashes. There was no history of beef intake, organ transplantation, or previous surgery.

Examination disclosed memory dysfunction, language abnormalities, and behavioral disorder on higher mental status evaluation. Motor system assessment revealed generalized rigidity. Sudden arrhythmic myoclonic jerks were present. There was the presence of bilateral symmetrical cerebellar signs. The routine laboratory parameters comprising hemogram, renal function test, liver biochemistry, thyroid function test (T3, T4, and thyroid-stimulating hormone), serum electrolytes, and blood sugar did not reveal an abnormality. Anti-thyroid peroxidase and antithyroglobulin antibodies were not raised. Enzyme-linked immunosorbent assay for human immunodeficiency virus was non-reactive. The cerebrospinal fluid examination displayed total cells 40 (lymphocytes – 80%), protein 54 mg/dl, and sugar value of 86 mg/dl (corresponding blood sugar 119 mg%).

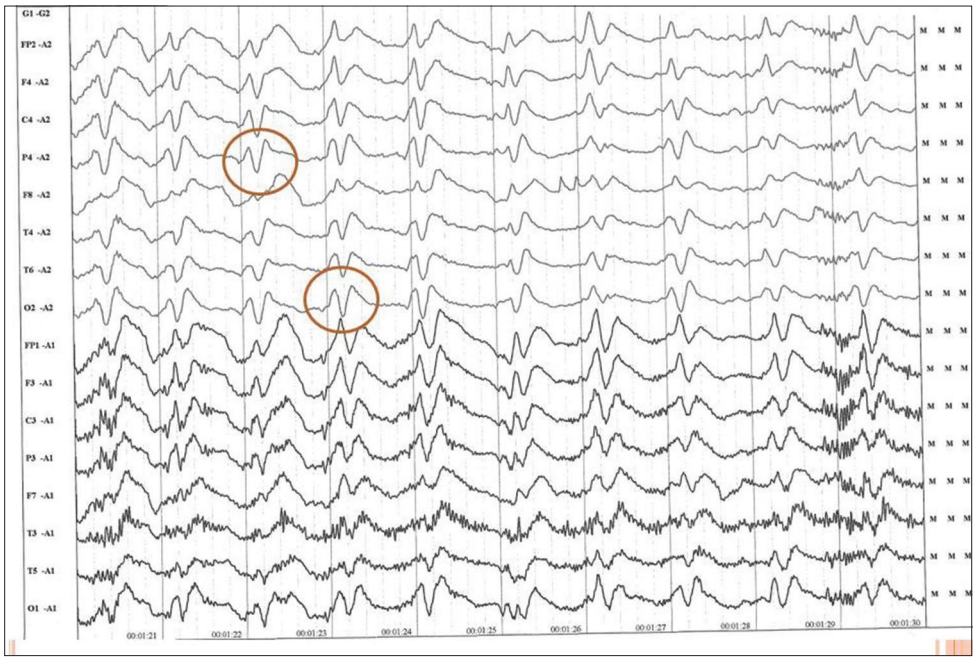

Figure 2: Electroencephalography of the patient revealed periodic triphasic sharp waves (350 ms) discharges at an interval of 1 second (Red circle) (case 1)

The viral markers in sera for herpes simplex virus, Japanese encephalitis virus, hepatitis virus, Epstein–Barr virus, and dengue virus revealed negative results. The vasculitic antibodies, including antinuclear antibody, antineutrophilic cytoplasmic antibody, and antiphospholipid antibodies, were non-reactive. Investigations were negative for mitochondrial and Wilson disease. EEG exhibited periodic triphasic wave discharges. MRI, including T2 FLAIR and DWI, demonstrated cortical ribboning effect (Fig. 3). The clinical and investigative workup favors the diagnosis of probable CJD. The patient has been prescribed valproate 500 mg twice a day, flupirtine 100 mg thrice daily and levetiracetam 500 mg twice daily along with supportive measures in the intensive care unit. The patient died after 4 weeks of hospital stay.

Case 3

A 55-year-old female presented with gait difficulty, diminution in memory, visual hallucinations, abnormal jerky movements, and speech difficulty in quick succession in the past 4 months. The patient also manifested with ataxia and incoordination in both upper and lower limbs.

Examination revealed memory impairment, language dysfunction, intermittent myoclonic jerks, generalized rigidity, and bilateral cerebellar signs. Investigations were negative for metabolic encephalopathies, viral markers, and vasculitic studies. The electroencephalographic study demonstrated periodic triphasic waves. MRI, including T2 FLAIR and DWI, exhibited hyperintense signals in the bilateral caudate nucleus and putamen with apparent diffusion coefficient hypointense signals and cortical ribboning of the cortical mantle (Fig. 4).

Probable CJD was diagnosed and antiepileptic and flupirtine have been prescribed. The patient survived for around 5 months from the onset of illness.

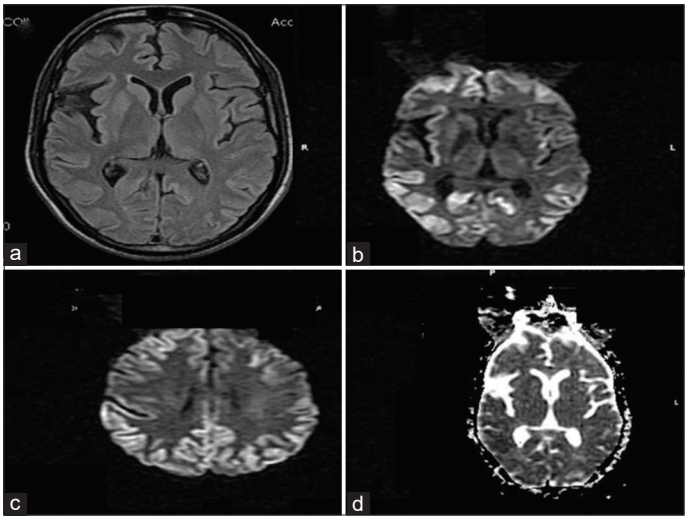

Figure 3: (a) Magnetic resonance imaging (Cranium) on T2 fluid-attenuated inversion recovery displayed hyperintensities in bilateral basal ganglia, (b) and (c) diffusion-weighted imaging revealed gyral hyperintensities in the bilateral frontal and parietal region(cortical ribboning), and (d) apparent diffusion coefficient exhibited reduced signals in gyriform cortex (case 2)

Case 4

A 60-year-old female presented with gait impairment, change in personality and behavior, cognitive decline, myoclonic jerks, and imbalance for the past 10 months. The patient became bedridden when she was hospitalized 15 days ago. The examination findings were generalized rigidity, language dysfunction, and asynchronous myoclonic jerks. The viral encephalitis, thyroid-related encephalopathy, and metabolic dementia were excluded by appropriate investigations. EEG revealed periodic triphasic waves. MRI demonstrated bilateral hyperintense signals in the caudate nucleus, putamen along with the cortical ribboning effect on T2-weighted FLAIR and DWI (Fig. 5). We diagnosed

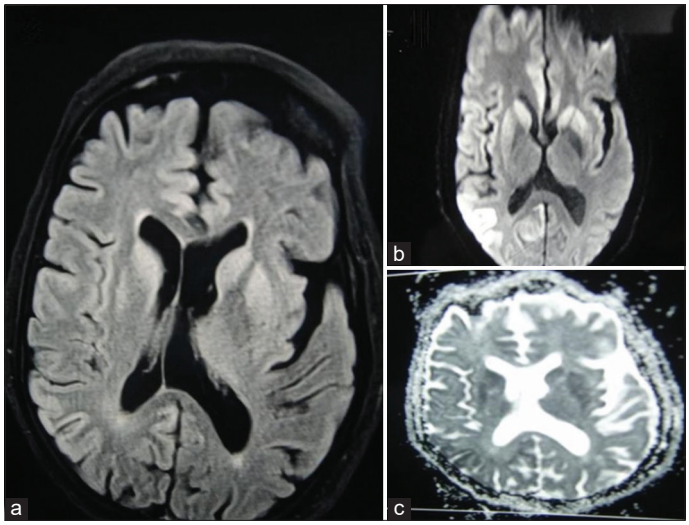

Figure 4: Magnetic resonance imaging (Cranium) revealing (a) hyperintense caudate nucleus and putamen with, (b) minimal cortical ribboning, and (c) corresponding hypointense areas on apparent diffusion coefficient (case 3)

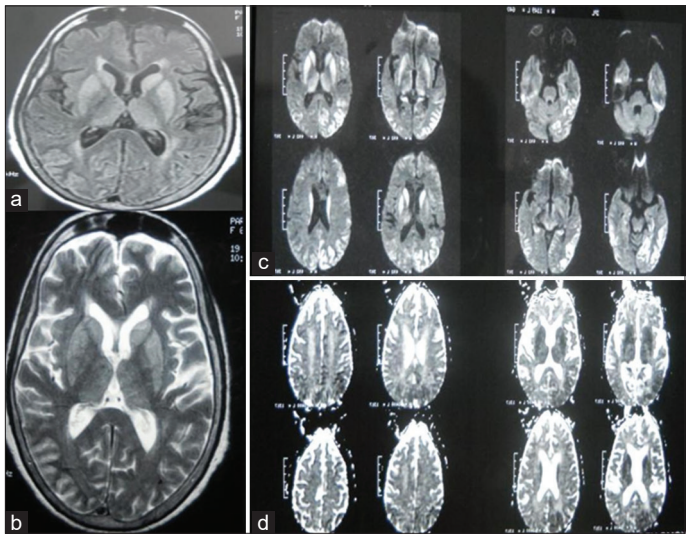

Figure 5: Magnetic resonance imaging (Cranium) on T2 fluid-attenuated inversion recovery (a) T2-weighted image, (b) exhibiting hyperintense signals in bilateral caudate nucleus and putamen, (c) diffusion-weighted imaging demonstrated marked cortical ribboning due to the involvement of cortical mantle, and (d) apparent diffusion coefficient disclosed hypointense signals in corresponding areas (case 4)

the patient as probable CJD and treated with anti-epileptics and supportive drugs. The patient succumbed to illness after 2 months of discharge from the hospital.

DISCUSSION

The human prion disorders represent various clinical conditions, including CJD, Gerstmann Straussler–Scheinker syndrome, and fatal familial insomnia [3]. CJD is classified as familial, sporadic, or acquired. The commonly encountered human prion disease is sporadic Creutzfeldt–Jakob disease (sCJD) which is not mutational and non-iatrogenic. The sCJD has been classified on the basis of the molecular mass of the protease-resistant scrapie prion protein (PrPSc), which can be type 1 or type 2, and the genotype at the methionine (M)/valine (V) polymorphic codon 129, which can be MM, MV, or VV [4]. The sCJD is clinically characterized by rapidly progressive dementia, myoclonic jerks, changes in personality and behavior, ataxia, pyramidal, extrapyramidal, and visual abnormalities. The human prion disorders are progressive, universally fatal, and untreatable clinical conditions. The worldwide incidence of CJD approximates 1 per million populations per year [5]. The neuropathology of sCJD is characterized by prion (PrP^{Sc}) accumulation, vacuolation, intense reactive astrocytosis, and neuronal cell loss. Although the progression of the disease is not well understood, current evidence from humans and animal models indicate that pathologically PrP^{Sc} accumulates first, followed by vacuolar degeneration of neuritic processes and reactive astrocytic gliosis and finally by neuronal loss [6,7].

In our case series, three patients were female and one was male. The age ranged from 42-65 years, with a mean age of 55.5 years. The epidemiological studies on CJDare limited and the literature consist mainly of case reports and case series. The previous studies indicated that it was more common in females. Mehndiratta *et al*. reported equal sex distribution in ten patients described in their study [8]. The mean age of onset in our study is compatible with the previous literature [8]. All four patients in our study died within 1 year of onset of illness. The outcome of sCJD is extremely dismal; more than 90% of patients lost their lives within 1 year of diagnosis [9].

Due to the rare occurrence, and to simplify ascertaining the diagnosis for treating physicians and research purposes, various operational criteria have been formulated. The World Health Organization evolved diagnostic criteria for probable sCJD, which comprises at least two findings among pyramidal or extrapyramidal features, myoclonic jerks, visual or cerebellar symptoms, akinetic mutism with rapidly progressive dementia, and one out of typical EEG positive or 14-3-3 protein in cerebrospinal fluid [10].

It is important to rule out the main differential diagnoses of sCJD with the help of MRI to avoid misdiagnosis. The radiological differential diagnoses are severe hypoxic-ischemic encephalopathy, autoimmune-mediated encephalopathy, Epstein–Barr virus encephalitis, infectious disease encephalitis, postictal state, hyperammonemia, mitochondrial disorders, posterior cortical atrophy, extrapontine osmotic demyelination, autosomal-dominant striatal degeneration, Wernicke encephalopathy, Wilson's disease, spectacular shrinking deficit, hyperglycemia-hemichorea-hemiballism syndrome, manganese deposition, granule cell neuronopathy, and Gerstmann–Sträussler–Scheinker disease [11].

In the last few years of research of MRI, findings, mainly on T2-weighted FLAIR and DWI have reduced difficulty in establishing the diagnosis of sCJD due to its non-invasiveness and wider accessibility. The MRI in all our four patients demonstrated hyperintense signals in the bilateral caudate nucleus, putamen, and cortical ribboning. In a recently published paper, the authors described clinical and MRI findings in three patients of sCJD confirmed by brain biopsy. They found the involvement of basal ganglia and neocortex. The DWI findings in sCJD of decreased diffusion in the cerebral cortex known as cortical ribboning with restriction in basal ganglia have high sensitivity (91%) and specificity (95%) [12]. The cause for restricted diffusion is attributed to the accumulation of abnormal vacuoles in the cytoplasm and microvacuolation of neuritic process heralding spongiform degeneration [13]. This diagnostic modality has great significance as typical electroencephalography findings of periodic sharp wave complexes were found in only 60% of patients of sCJD. In the purview of MRI characteristics, Zerr *et al*. updated the diagnostic criteria for sCJD, including detection of either hyperintense signals in basal ganglia (caudate nucleus and putamen) or minimal two cortical regions (temporal, parietal, or occipital cortex).

The most recent MRI-CJD consortium criteria for sporadic CJD (2009) include at least two findings out of dementia, cerebellar or visual, pyramidal or extrapyramidal, akinetic mutism and one out of Periodic sharp wave pattern on EEG, 14-3-3 protein detection in the cerebrospinal fluid, or hyperintense signals in caudate nucleus and putamen or at least two cortical regions (temporal, parietal, or occipital) either in DWI or FLAIR MRI [14]. Limitations of our report were that we were unable to subject patients for 14-3-3 protein assay in cerebrospinal fluid. None of our patients underwent a brain biopsy.

CONCLUSION

Creutzfeldt–Jakob disease is an underdiagnosed, fatal neurodegenerative disorder. The awareness of this lethal neurological disorder among physicians is essential to differentiate from other causes of dementia, which could be treatable. MRI should be used as an additive tool for the diagnosis of CJD.

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