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Zaid Waqar Waqar
Pakistan Institute of Medical Sciences, Islamabad

Amina Sadiqa
Pakistan Institute of Medical Sciences, Islamabad, Pakistan

Soban Khan
Pakistan Institute of Medical Sciences, Islamabad

Muhammad Annas Farooq Farooq
Pakistan Institute of Medical Sciences, Islamabad, Pakistan

Zeeshan Munawar
Pakistan Institute of Medical Sciences, Islamabad, Pakistan

See next page for additional authors

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Zaid Waqar Waqar, Amina Sadiqa, Soban Khan, Muhammad Annas Farooq Farooq, Zeeshan Munawar, Maryam Khalil, and Adil Awan

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CREUTZFELDT-JAKOB DISEASE EXPERIENCE IN PATIENTS PRESENTING TO A TERTIARY CARE HOSPITAL: A CASE SERIES

Zaid Waqar[1], Amina Sadiqa[1], Soban Khan[1], Muhammad Annas Farooq[2], Zeeshan Munawar[1], Maryam Khalil[1], Adil Awan[1]

[1].Department of Neurology, Pakistan Institute of Medical Sciences, Islamabad.
[2].Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad.

Correspondence Author: Zaid Waqar *Department of Neurology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan* ***Email:*** *chikky789@gmail.com*

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a rare cause of rapidly progressive dementia, it is a neurodegenerative disorder caused by the misfolding of prion proteins in the brain, and misfolded proteins further propagate by causing misfolding of other proteins. It presents with insidious onset of neurobehavioral symptoms that rapidly develop into cognitive and motor decline and uncontrolled seizures. The diagnosis is established with help of clinical signs and symptoms, and using imaging and lab investigations to rule out other treatable causes. Some imaging findings point to the diagnosis of CJD that will be viewed in the cases below. Diagnosis can be augmented by CSF studies but due to the risk of biohazard and spread of CJD, special care needs to be taken. Confirmation is only via brain biopsy. In this article we share our experience with four cases of CJD that presented to our hospital.

Keywords: Dementia, Prion, Myoclonus, CJD, Creutzfeldt-Jakob disease

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare disease overall, but the most common prion disease, affecting 1–1.5 people/million/year. Spongiform Encephalopathy is caused by the transformation of the normal neuronal prion protein, resulting in its abnormal accumulation within the neurons.[1] Various forms have been recognized so far but the sporadic form is the most common form of all, accounting for approximately 85 % of cases.[2,3] The mean onset of the disease is in 6th decade but cases in young adults have been recognized recently. Multiple risk factors have been identified; these patients mostly have a medical history of psychosis. CJD can be clinically heterogeneous but the most common feature in these patients is neuropsychiatric decline with death usually occurring within one year of symptoms onset. Neuropsychiatric symptoms manifest as rapidly progressive dementia, behavioural abnormalities, impaired concentration, and deficits involving higher cortical functions.[4] Myoclonus, especially provoked by startle, is present in mostly 90 percent of cases at some point during their disease course. In this case series, we will discuss various presentations of suspected CJD presentations that presented to us.

CASE PRESENTATION

Case 1:

A patient 13 years of age, female, student of class eight, had a history of febrile convulsions at two years of age. She was started on antiepileptic sodium valproate (oral formulation) till seven years of age and was then discontinued. She presented to ER of Pakistan Institute of Medical Sciences with a history of aggressive behaviour from six months and abnormal jerky movements of the body with posturing from two months, and history of fever for five days. Her EPI vaccination schedule was completely followed. There was no history of any psychiatric medication or cognitive impairment. There was no history of headaches associated with vomiting, photophobia, loss of consciousness, neck stiffness, seizures, weakness of limbs, balance issues, or visual symptoms. There was no history of abdominal pain, diarrhoea, vomiting, or constipation. There was no history of oral ulcers, hair loss, fatigue, or rashes on the body. There was also no history of bleeding from the gums, nasal cavities, blood in any vomiting, blood in stools, melena, petechial rash anywhere on the body, or a blanching rash.

The patient presented to ER and was evaluated by the Neurology department; vital signs at the time were BP 80/50 mm Hg, pulse 115 bpm. Oxygen saturation was 97% at room air, and blood glucose was 100 mg/dl. The neurological examination noted was GCS 11/15 (E4M5V2), pupils bilaterally equally reactive, and plantars were bilaterally downgoing. The tone was increased more in the left upper and lower limbs as compared to the right upper and lower limbs. During

the examination, she was noted to have persistent left arm myoclonic jerks; she was administered Inj. Sodium Valproate 500 mg over 30 minutes to abort the seizures. Arterial blood gases obtained showed metabolic alkalosis, so a bolus of Inj. 0.9% saline 1000 ml was administered. Based on the history and clinical examination in ER, a differential diagnosis of autoimmune encephalitis, Creutzfeldt-Jakob disease CJD, subacute sclerosing panencephalitis (SSPE), and Wilson Disease were made. The patient was admitted to ward, under the care of the Department of Neurology, for a work-up of her symptoms and signs.

During her stay in the ward, she was started on pulse steroid therapy with Inj. Methylprednisolone 1.0 g IV once daily for a total of five days to empirically cover autoimmune encephalitis, and Inj. Levetiracetam 1.0 g IV TDS for myoclonic seizures. Before initiating therapy, blood samples were withdrawn and were sent for blood CP, liver function tests, renal function tests, serum sodium, potassium, and calcium, and blood cultures. A lumbar puncture was also performed, and samples were sent for CSF DR, autoimmune profile, and IgG (measles). All baseline labs returned normal, with normal TLC, hemoglobin, hematocrit, platelet, and neutrophil count, as well as entirely normal liver function tests. Moreover, an EEG was done which showed diffuse encephalopathy with localized spike and wave activity in bilateral temporal areas, although it should be mentioned that the patient was highly uncooperative and fidgety during the procedure. CSF DR report came normal. No Kayser-Fleischer rings could be appreciated.

Previous records dating 1-3 months were obtained which further revealed another hospital admission; her work-up at the hospital included 24-hour urinary copper that was normal, as well as a detailed ultrasound abdomen showing normal hepatobiliary system, along with normal values of baseline labs, except mild hypokalemia of 3.2 mg/dl.

In the ward, the patient had multiple fever spikes, accompanied by repeated episodes of myoclonic jerks of the left arm. Inj. Sodium Valproate as a second antiepileptic was added to the treatment; however, myoclonic jerks persisted. For refractory seizures, Inj. Piracetam 1.0 g was added as the third antiepileptic, resulting in the successful abortion of myoclonic seizures.

A contrast-enhanced MRI brain was significant for bilaterally symmetrical and non-enhancing signal intensity areas affecting lentiform nuclei and head of caudate nuclei (Figure 1).

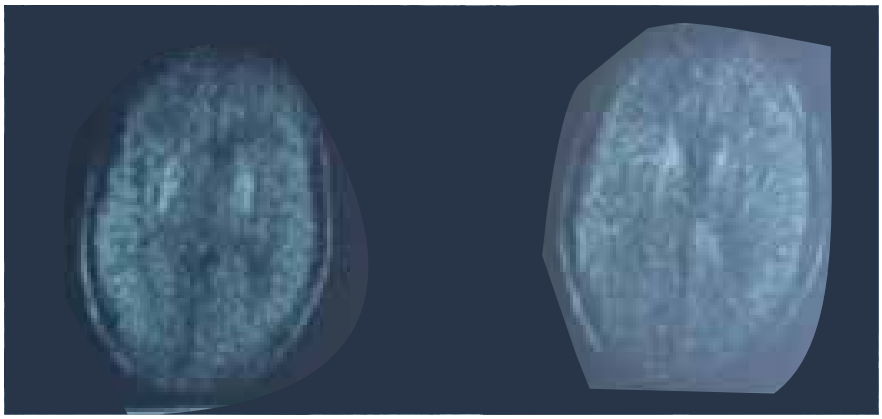

Figure 1: DWI/ADC view showing bilateral symmetrical and non-enhancing areas affecting lentiform nuclei and head of caudate nuclei

She remained admitted to neurology ward for about three weeks . For suspicion of CJD, brain biopsy, and repeat MRI Brain with contrast were in the plan but could not be done due to the critical condition of the patient, which ultimately led to mortality.

Case 2:

The patient 52 years old female, married, a resident of Lahore, having diabetes and hypertension for three months, presented to PIMS Hospital emergency with complaints of behavioral and cognitive changes for two months, history of drowsiness and abnormal jerky movement of limbs for one week. Her family noticed that she developed gradual behavioral and cognitive changes over the last two months This involved being convinced that she was suffering from a life-threatening illness despite having no obvious signs and symptoms and becoming overly concerned about her health. Initially, her family reassured her, and occasionally she would agree but later would become convinced again.

This was later complicated by mistrust towards her family, especially her husband whom she would frequently accuse of being unfaithful. This gradually affected her interpersonal relationship with her family. Apart from this, she developed sleep disturbances in which she would fall asleep at irregular hours. Moreover, her family noticed that she was becoming increasingly vague and unconcerned in maintaining personal hygiene, so much so that she often needed help in dressing and washing.

One week before the presentation, the patient began to get increasingly vague and would be in a trance-like state. Often, she would cease communicating and would stare off-space. This was gradually complicated by getting drowsy; initially, she would wake by voice, but later would need to be shaken to awake. In addition to this, her family noticed that her legs and arms would sometimes abruptly jerk on their own. There was no fever or any other signs or symptoms.

There was no history of headaches associated with vomiting, photophobia, loss of consciousness, neck stiffness, seizures, weakness of limbs, balance issues, or visual symptoms. There was no history of abdominal pain, diarrhea, vomiting, or constipation. There was no history of any significant chest pain, palpitations or orthopnoea, paroxysmal nocturnal dyspnea, or shortness of breath associated with chest pain. There was no history of oral ulcers, hair loss, fatigue, or rashes on the body. There was also no history of bleeding from the gums, nasal cavities, blood in any vomiting, blood in stools, melena, coffee ground vomitus, easy bruising, petechial rash anywhere on the body, or a blanching rash.

On examination, her vitals were BP 120/65 mm Hg and pulse 108 b/min. Blood glucose was 98mg/dl. GCS was 8/15, unresponsive, pupils bilateral equal and reactive to light, no signs of meningeal irritation, motor power was at least 3/5 in all limbs at every joint, tone increased with brisk reflexes in both upper and lower limbs, plantars bilateral withdrawing, sensations could not be assessed.

Following this, the patient was admitted to the Neurology ward, and a workup for possible rapidly progressive dementia was done. Baseline investigations were done, in which all parameters of the blood complete profile, liver function tests, renal function tests, and serum electrolytes were normal. CT angiography was done for a work-up of chest pain which was a normal study. ECG showed normal sinus rhythm, Echocardiography showed no regional wall motion abnormality and ejection fraction 60% with normal contractility and no pericardial effusion.

A CT scan brain revealed no remarkable findings. EEG showed generalized periodic epileptiform discharges with triphasic sharp waves. Following this, an MRI brain with contrast was performed which revealed altered signal areas in bilateral basal ganglia, including the caudate and lentiform nuclei, with low to iso-intense on T1 and high on T2 and FLAIR with no contrast enhancement. Furthermore, the DW1 and ADC imaging showed areas of restricted diffusion symmetrically in bilateral basal ganglia, the caudate, and lentiform nuclei. Importantly, a cortical ribbon was appreciated on the scan (Figure 2 and 3).

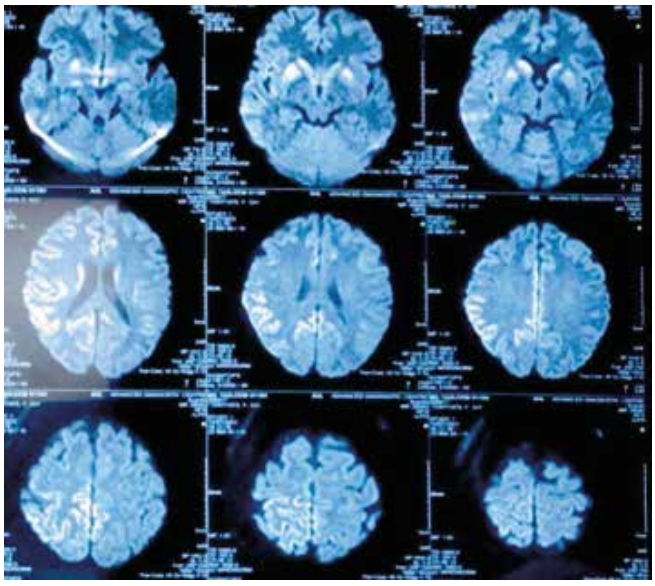

Figure 2: DWI/ADC view showed the area of restricted diffusion symmetrically in bilateral basal ganglia including caudate and lentiform nuclei and cortical ribbon sign which is an increased signal delineating the cortex.

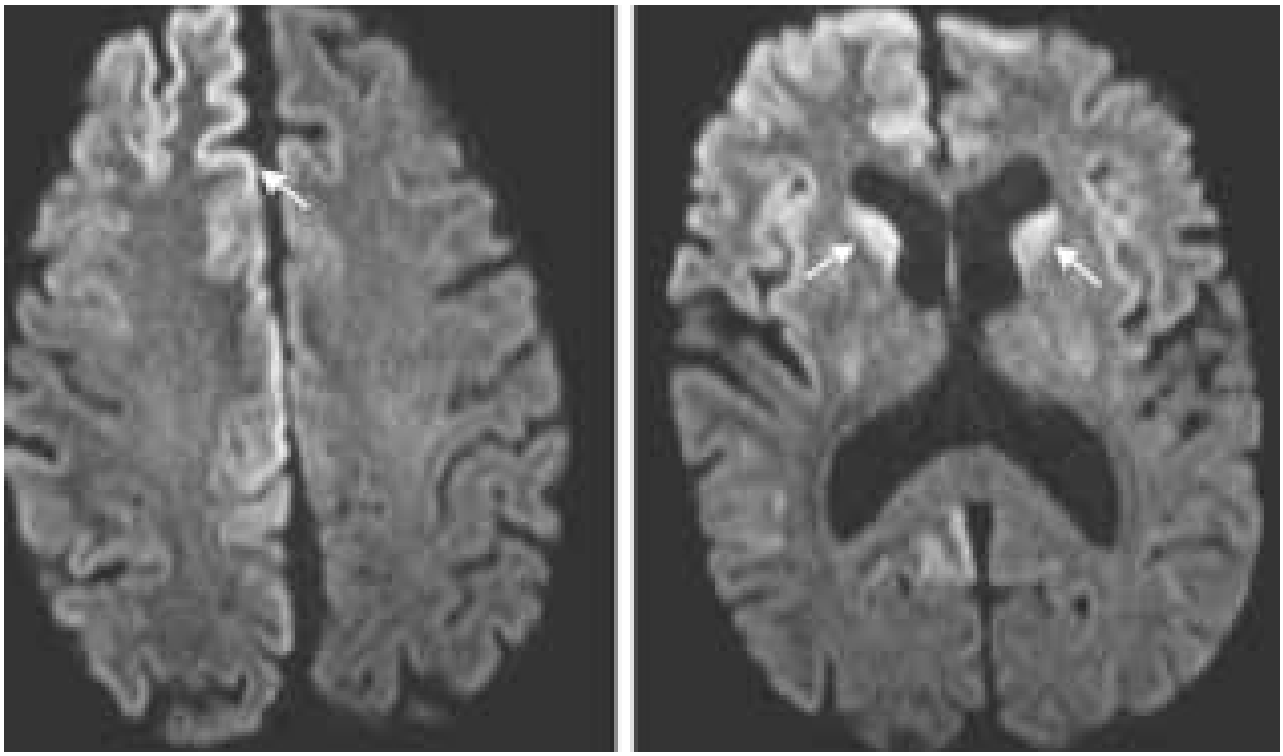

Figure 3: MRI Brain Axial diffusion-weighted slices show restricted diffusion within the cortical ribbon and caudate heads.

Case 3:

The patient 43 years of age, female, previously diagnosed case of hypertension, had a history of ischemic stroke 20 days back which involved left-sided weakness, presented with complaints of abnormal movements of the body and altered conscious state from eight days, along with mood changes. There was a history of generalized body weakness, vertigo, altered talk, hallucinations, decreased oral intake, and abnormal body movements for the last few months. There was also a history of multiple visits to a psychiatrist and she was on antipsychotic medication previously.

On examination GCS of 11/15 (E4 V2 M5), abnormal movements of the left hand and neck dystonic posturing, pupils bilateral equal and reactive to light, no signs of meningeal irritation, plantar bilateral down going, myoclonic jerks, tone slightly increased bilaterally, and sensations could not be assessed.

The patient was admitted to the neurology ward and extensive workup was done. Baseline investigations of blood complete picture, liver function tests, renal function tests, serum electrolytes, ESR, CPK, and CKMB turned out to be normal. Lumbar puncture was done; CSF DR showed cell count 2 cells per mm3, protein 50.5 mg/dl, glucose 93.3 mg.dl. CSF culture showed no bacterial growth, MTB Gene xpert not detected, ANA was negative, brucella serology was negative, serum uric acid and fasting lipid profile were normal.

Ultrasound abdomen pelvis was unremarkable, carotid doppler ultrasound was normal. Echocardiography showed no regional wall motion abnormality and ejection fraction 60%. EEG was abnormal because of sharp slow theta waves and the background was slow generalized theta waves, suggestive of diffuse cortical dysfunction MRI Brain with contrast was done which showed hyperintense bilateral basal ganglia and pulvinar nuclei depicting restricted diffusion in association with cortical gyriform and focal midbrain signal abnormalitie.

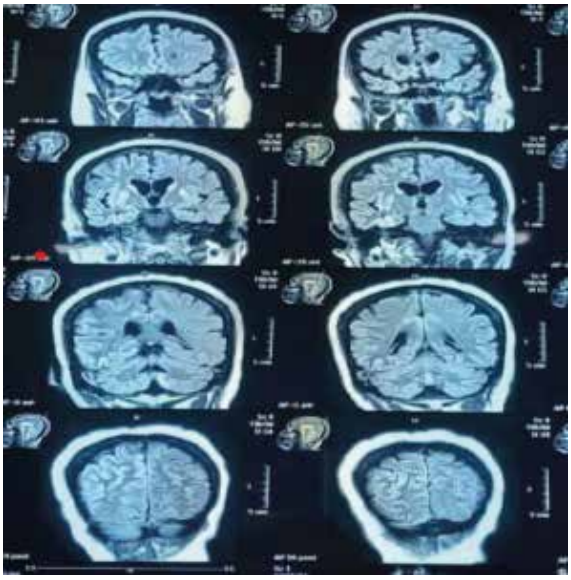

Figure 4: T2 FLAIR showed hyperintensity in bilateral basal ganglia particularly evident in caudate and putamen nuclei along with dorsomedial thalami (pulvinar nucleus), multifocal hyperintense cortical patches with more generalized involvement in the right cerebrum.

She remained admitted to the neurology ward for four weeks and palliative treatment was started. Brain biopsy was in the plan, but couldn't be done due to the non-availability of resources.

Case 4:

A 19-year-old male patient, with no previous comorbid presented with a history of progressive psychomotor deterioration, altered sensorium, and myoclonic jerks for six months. He was a student of class 12 when he initially complained of difficulty in walking which started six months back and was gradually progressive. He became bed-bound within six months. There was a history of behavioural changes, mood disorder, and decrease responsiveness. He started experiencing abnormal jerky movements involving upper limbs more as compared to lower limbs from five months. About one month back he developed shortness of breath, and a productive cough, and remained admitted to a local hospital and managed as a case of lower respiratory tract infection. There was no history of headaches associated with vomiting, photophobia, loss of consciousness, neck stiffness, seizures, weakness of limbs, balance issues, or visual symptoms. There was no history of abdominal pain, diarrhea, vomiting, or constipation There was no history of oral ulcers, hair loss, fatigue, or rashes on the body. There was also no history of bleeding from the gums, nasal cavities, blood in any vomiting, blood in stools, melena, coffee ground vomitus, or easy bruising.

On examination, his vitals at presentation in ER were BP 140/80 mm hg, and pulse 121/min. Blood glucose was 95 mg/dl. GCS was 8/10, i.e. E4 V (ETT) M4 (patient was intubated). Pupils were bilateral equal and reactive to light, no signs of meningeal irritation, tone slightly increased in both upper and lower limbs, plantars bilateral equivocal, and sensations could not be assessed The patient was shifted to the neurology ward. Baseline investigations were done, in which all parameters of the blood complete profile, liver function tests, renal function tests, and serum electrolytes were normal. Special investigations serum copper, serum ceruloplasmin were within normal limits. A lumbar puncture was done. CSF DR showed cell count normal, RBC 150 per mm3, protein 84.9 mg/dl, and glucose 115 mg/dl. CSF culture was negative, and serum autoimmune encephalitis profile was negative. A fundoscopic examination was done which was normal. No KF rings were seen on the slit lamp examination. Neuroimaging was done, CT brain plan showed marked cerebral atrophy more prominent on left, MRI Brain with contrast was done which showed mild cortical atrophy with lacunar infarcts, subtle T2 hyperintense lesions, blurring of grey and white matter junction, and cerebral atrophy (Figure 5). He was on multiple antiepileptic drugs and antipsychotics but his condition deteriorated and with time he developed grade 3 bedsores (due to bedbound status, poor nursing care), and his condition further worsened due to lower respiratory tract infections. He remained admitted in neurology ward for eigjt days but couldn't survive.

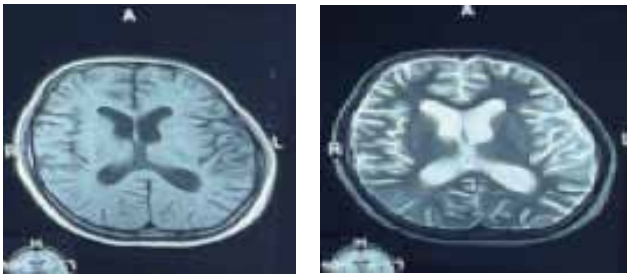

Figure 5: MRI Brain showed mild cortical atrophy with lacunar infarcts, subtle T2 hyperintense lesions, blurring of grey and white matter junctions.

DISCUSSION

CJD is one of the causes of rapid onset dementia. It is the most frequent prion disease although it is still rare; it has been distinguished from more common causes of dementia because of its rapidly progressive course and presence of myoclonus. Table 1 shown below lists the causes of rapidly progressive dementia.

Table 1: Differential diagnoses of rapidly progressive dementia with abnormal movements.

DIFFERENTIAL DIAGNOSES OF RAPIDLY PROGRESSIVE DEMENTIA WITH ABNORMAL MOVEMENTS	
1.	Prion Disease
2.	Lewy body dementia
3.	Voltage-gated potassium cell antibody encephalitis
4.	Limbic encephalitis
5.	Hashimoto encephalitis
6.	Herpes and viral encephalitis
7.	Toxic encephalitis (hyperammonaemia, lithium intoxication)
8.	Sub-acute sclerosing panencephalitis
9.	Carcinomatous meningitis
10.	Intravascular lymphomatosis

The sporadic form is the most common variant of CJD; other forms include variant and genetic forms. Early in the disease course, FLAIR and DWI sequences demonstrate hyper-signal in the striatum (caudate and putamen) and thalamus as well as 'cortical ribboning' (hyper-signal delineating the cortex) in the parietal, temporal, and frontal cortices. MRI with these sequences (DWI being more sensitive than FLAIR) is highly sensitive and specific (92 and 94 %, respectively) for the diagnosis of CJD. The above characteristic findings can be seen well before the EEG periodic abnormalities and the positivity of the 14-3-3 protein test. Recently, the development of a highly sensitive and specific test, the real-time quaking-induced conversion (RT-QuIC) assay has improved the diagnostic accuracy of CSF testing. CSF testing in CJD is difficult because of the possibility of transmission of prion disease from living organism tissue and body fluid makes CSF of such patients a biohazard. And since these tests mentioned above are not available in Pakistan, diagnosis is made with help of neuroimaging and clinical criteria mentioned below in Table 2.

Table 2: Diagnostic Criteria for Creutzfeldt-Jacob Disease

Definite CJD	Hyperintense signal on DWI > FLAIR with: Typical presentation: cingulate gyrus, striatum and >1 gyrus of neocortex (often precuneus, angular gyrus, superior or middle frontal gyrus) Additional criteria of subcortical structure involvement: Striatum with antero-posterior gradient Subcortical hyperintensity on ADC map Additional criteria of cortical involvement: Asymmetric involvement of neocortex in midline or of cingulate gyrus Spared precentral gyrus Cortical hypointense edging on ADC map Only from cortex (>3 gyri). See additional criteria as above
Probable CJD	Unilateral involvement of striatum or cortex (< or =3 gyri). See additional criteria above Bilateral involvement of striatum or postero-lateral thalami. See additional criteria above.
Probably not CJD	Increased signal on FLAIR/DWI in limbic areas, appearing physiologically (e.g. insula, anterior part of cingulate gyrus, hyppocampus), no changes on ADC map Hyperintense signal on DWI due to artifacts. See below. Abnormalities on FLAIR>DWI. See below
Definitely not CJD	Normal MRI Abnormalities of different type than in CJD
Other MRI features	Long courses of sCJD (>1 year) – MRI may reveal significant brain atrophy with loss of hyperintense signal on DWI.

A literature review of published studies has shown only sporadic case reports and a series of two cases. Our series has collected more patients than any single published work from Pakistan. In this case series we discussed four patients who presented to us with a history of neuropsychiatric symptoms, rapidly progressive dementia, and the presence of myoclonus. An extensive workup was done to rule out treatable causes like autoimmune encephalitis, Wilson's disease, and all other metabolic, infective causes. All patients showed positive MRI findings suggestive of suspected probable CJD. Case 2 showed a cortical ribbon sign typical of MRI finding with symmetrical involvement of bilateral caudate nuclei. EEG of Case 3 showed diffuse cortical dysfunction. All these patients had a history of myoclonus, It is the most characteristic and constant sign in CJD.[5] According to CDC diagnostic criteria for sCJD our four cases showed signs and symptoms of probable CJD.[5] Diagnostic criteria of CJD include MRI findings with detection of hyperintensity in basal ganglia and at least two cortical regions.[6] All four cases showed hyperintense signals in bilateral basal ganglia.

Conclusion:

This series of cases demonstrates various presentations of probable CJD in the different age groups of people. Neuroimaging helped in the early detection of CJD cases, especially visualized in FLAIR and DWI images. Sporadic CJD is a rapidly developing neurodegenerative disease, though a definitive diagnosis requires a histopathological basis. Currently, no definitive treatment options are available but early diagnosis help in the earlier initiation of palliative care and emotional support to patient's families and caregivers and reduces risks of iatrogenic transmission and the spread of disease.[8]

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Author's contribution:

Zaid Waqar; concept, case management, data collection, data analysis, manuscript writing
Amina Sadiqa; case management, data collection, data analysis, manuscript writing,
Soban Khan; case management, data analysis, manuscript revision
Muhammad Annas Farooq; case management, data analysis, manuscript revision
Zeeshan Munawar; case management, data analysis, manuscript revision
Maryam Khalil; case management, data analysis, manuscript revision
Adil Awan; case management, data analysis, manuscript revision
All the authors have approved the final version of the article, and agree to be accountable for all aspects of the work.