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Unusual presentations in patients with E200K familial Creutzfeldt-Jakob Disease

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Abstract

Background and propose—Familial Creutzfeldt-Jakob disease (fCJD) in Jews of Libyan ancestry is caused by an E200K mutation in the *PRNP* gene. The typical presenting symptoms include cognitive decline, behavioral changes and gait disturbances, however some patients may have an unusual presentation such as a stroke-like presentation, alien hand syndrome or visual disturbances. The aim of this manuscript is to describe uncommon presentations in our series of consecutive patients with E200K fCJD.

Methods—The study group included consecutive fCJD patients followed up as part of a longitudinal prospective study ongoing since 2003 or hospitalized since 2005. The clinical diagnosis of probable CJD was based on accepted diagnostic criteria and supported by typical MRI, electroencephalographic findings, elevated CSF tau protein levels, and by genetic testing for the E200K mutation. Disease symptoms and signs were retrieved from the medical files.

Results—The study population included 77 patients (42 men) with a mean age of disease onset of 60.6 ± 7.2 years. The most prevalent presenting symptoms were cognitive decline followed by gait impairment and behavioral changes. However six patients had an unusual presentation

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including auditory agnosia, monoparesis, stroke like presentation, facial nerve palsy, pseudobulbar syndrome and alien hand syndrome.

Discussion—Our case series illustrate the wide phenotypic variability of the clinical presentation of patients with fCJD and widens the clinical spectrum of the disease. A high level of clinical suspicion may prove useful in obtaining early diagnosis and therefore avoiding costly and inefficient diagnostic and therapeutic strategies.

Keywords

Creutzfeldt-Jakob disease; Neuroimaging; E200K mutation

Introduction

Creutzfeldt-Jakob disease (CJD) is the most common prion disease in humans, resulting from a conformational change of the normal prion protein (PrP^C) into a pathological conformation (PrP^{Sc}) which aggregates in the central nervous system [1]. The disease is invariably fatal with survival that rarely exceeds a few months to one year [2]. CJD can be etiologically classified into transmitted, sporadic and familial forms [2]. The largest cluster of familial CJD (fCJD) exists in Jews of Libyan or Tunisian ancestry carrying an E200K mutation (Glu to Lys substitution) in the gene encoding for the prion protein (*PRNP*) [3], many of whom live in Israel. Carriers of the E200K mutation are born with this dominant mutation in the *PRNP* gene, but remain asymptomatic until middle age and some only develop disease at the eighth decade of life [4]. Although early symptoms of the disease may be non-specific the typical presenting symptoms include cognitive decline, behavioral changes and gait disturbances [5-7]. Some patients however may have an unusual or atypical presentation including a stroke-like presentation [8], alien hand syndrome [9], supranuclear gaze palsy [10,11], insomnia [11,12], and demyelinating peripheral neuropathy [11,13]. The aim of this manuscript is to describe unusual or uncommon presentations in our series of consecutive patients with E200K familial CJD and hence to widen the clinical spectrum of the disease.

Methods

The study group included consecutive fCJD patients followed up at the Sheba Medical Center (SMC), as part of a longitudinal prospective study ongoing since 2003 and patients hospitalized in the neurological department at Assaf Harofeh Medical Center (AHMC) since 2005. The SMC study was approved by the Institutional Review Board and all patients signed an informed consent prior to inclusion in the study. The clinical diagnosis of probable CJD was based on accepted diagnostic criteria [14] requiring a progressive dementia with at least two of the following features: myoclonus, visual or cerebellar symptoms, pyramidal or extrapyramidal dysfunction or akinetic mutism. Diagnoses were supported by typical MRI [15], electroencephalographic findings [16], elevated CSF tau protein levels [17, 18] and by genetic testing for the E200K mutation. All patients were followed clinically until death to confirm the diagnosis.

Upon admission to the study each patient and family members were interviewed for the type and date of onset of the various disease symptoms and the information was documented in the medical records. Patients were then examined by a neurologist and the signs were documented in their medical files. Files were retrospectively reviewed for the preparation of this report.

Results

The study population included 77 patients; Forty-two men and 35 women with a mean age of disease onset of 60.6 ± 7.2 years (range 45-77 years).

The most prevalent presenting symptoms were cognitive decline followed by gait impairment and behavioral changes (Table 1). About one fifth of our patients reported that sleep disturbances were among their initial symptoms. Three patients reported a severe and torturing headache and 2 patients had pruritus.

Case reports

Six patients had an unusual or atypical presentation as reported below:

Case 1: Presentation as auditory agnosia (pure word deafness)

This 54 years old woman had a family history of a paternal aunt who died of CJD (presented as dementia and gait disturbance). Her past medical history was remarkable for ventricular tachycardia and congestive heart failure. Four months prior to her admission she started complaining of hearing decline, tinnitus, insomnia and general fatigue. She underwent two audiogram examinations, the first of which was interpreted as normal. In the second examination, 6 weeks later, pure tone level was normal however speech audiometry was interpreted as “unreliable” since “the patient claimed that she could not understand words “. Two brain stem evoked response (BERA) examinations (2 months apart) were normal. Over the following months she complained of dizziness and disequilibrium and had a few falls as well as severe anxiety and confusion events. Examination of the external auditory meati and tympanic membranes revealed no apparent abnormality. On neurological examination she was alert and oriented, could hear and respond to sounds and voices but had severe difficulty to understand spoken language. Reading comprehension and writing were intact and communication was possible only by writing. Speech was dysarthric and she had a staring gaze, end point nystagmus on lateral gaze to the right and a positive glabellar sign. She had dystonic posture of both hands with myoclonic jerks. Deep tendon reflexes were brisk and plantar responses were flexor. Sensation was intact and the gait was ataxic. She scored 27/30 on minimal status examination (MMSE) [19] (communicated in writing) and her score of the CJD neurological status scale (CJD-NS) [20] was 10 (range 0-52).

Lumbar puncture revealed elevated tau level (986 pg/ml). She was positive for the E200K mutation in the *PRNP* gene. MRI revealed hyperintense non enhancing lesions in the subcortical white matter without brainstem involvement. EEG revealed non-specific generalized slowing. Polysomnography revealed severe insomnia with very short sleep periods and irregular breathing. In the following weeks she continued to deteriorate and

developed severe dysarthria and ataxia and eventually stupor. She died from aspiration pneumonia five months after the onset of her symptoms.

Case 2: Presentation as progressive monoparesis

This man had a family history of 5 (out of 7) siblings who have died from CJD (4 presented with cognitive decline and one ataxia and insomnia). He was followed up in our prospective study since 2005 as a healthy subject. His last routine examination, at age 64, was entirely normal, but soon afterward he noticed right leg limping. Neurological examination revealed proximal and distal weakness (3/5 MRC scale) with reduced deep tendon reflexes on the right leg, reduced pain sensation in the form of low stocking in the left lower extremity and high stocking in the right lower extremity. Nerve conduction study revealed a sensory-motor axonal polyneuropathy and needle electromyography was normal.

Over the next couple of weeks he gradually developed imbalance and marked walking difficulty, but no memory or cognitive problems were noted. On examination his MMSE was normal (30/30) but he had rigidity and weakness of the right leg, bilateral hyperreflexia. A work-up including cervical MRI and EEG were normal. CSF tau protein levels on two consecutive examinations (four weeks apart) were 137 pg/ml and 193 pg/ml respectively. The E200K mutation was positive. Two serial MRI scans (one month apart) after the symptomatic onset exhibited DWI hyperintensities in superior frontal, middle frontal and anterior cingulate compatible with the diagnosis of CJD.

During the following weeks the patient developed progressive upper and lower limbs weakness and ataxia and became wheelchair bound. His cognitive performance was relatively preserved (MMSE 27/30) and he had no affective, behavioral or psychiatric symptoms. He died 4 months after the onset of his symptoms.

Case 3: Presentation as stroke

This 62 year-old male of Libyan Jewish origin, whose father died of CJD (presented with behavioral changes and cognitive decline) was admitted due to acute onset of vertigo, diplopia, left hemiparesis, and gait instability. The neurological findings on admission included bilateral internuclear ophthalmoplegia, left hemiparesis and limb ataxia. MMSE was 27/30. Brain CT and MRI (DWI) images showed a lesion at the left pontine-midbrain border compatible with an acute ischemic stroke, but was otherwise normal. A diagnosis of vertebrobasilar stroke was made and the patient was treated by aspirin with subsequent marked clinical improvement and a good remission of his gait and weakness, and was discharged to rehabilitation. However during the following weeks his gait and balance again deteriorated and he was readmitted. On examination he had bilateral internuclear ophthalmoplegia, dysarthric speech, hyporeflexia and ataxia. MMSE was 17/30, and CJD-NS was 7. CSF analysis 3 months following the initial presentation showed elevated tau protein level (789 pg/ml) and a positive E200K mutation. EEG showed generalized dysrhythmia grade II with occasional periodic activity. The patient had 3 additional serial MRI scans (3,5, and 8 months following the first MRI) that revealed gradual shrinkage and finally disappearance of the brainstem lesion but the appearance on DWI of hyperintense lesions in the thalamus, basal ganglia and anterior cingulate, which were typical of CJD. He

continued to deteriorate and eventually became bedridden with gradually decreased level of consciousness. He died due to aspiration pneumonia, 9 months following the clinical presentation.

Case 4: Presentation as pseudobulbar palsy

This 67 year-old male, a retired music teacher of Tunisian Jewish origin, had a positive family history of a paternal uncle who died of CJD (presenting symptoms unknown). Three months prior to his admission to the neurology department he started to suffer from a difficulty to articulate and pronounce words and the speech became effortful and illegible. In addition the family noted that he sometimes choked while eating and also became “emotional” with a tendency to cry inappropriately. His gait became “heavy”. He was hospitalized in another hospital for evaluation approximately one month after the onset of his symptoms. The neurological exam was normal, other than the dysarthric speech. Head CT scan and EEG were interpreted as normal. One month later, he was hospitalized again elsewhere. The neurological examination was normal other than dysarthric “spastic” speech. A second CT scan revealed periventricular white matter changes. EEG showed bilateral frontal slowing. LP revealed elevated tau protein (1200 pg/ml). During the next month the patient continued to deteriorate and became almost completely anarthric and could communicate only by writing. Pathological laughing and crying emerged and he developed gait instability and recurrent falls. He was admitted to SMC about 3 months after the onset of his symptoms. On exam he was alert and oriented. He had a staring gaze with right lateral gaze limitation. Speech was very dysarthric and illegible and he had emotional instability with pathological laughter and crying. He had spasticity and mild weakness of the right limbs with brisk tendon reflexes and an equivocal plantar response on the right, mild dysidiadochokinesis and unsteady stance and gait.

Detailed neuropsychological evaluation was impossible due to the anarthria. The CJD-NS score was 14. CSF tau was elevated (1567 pg/ml) and the E200K mutation was positive. EEG showed generalized slowing with periodic sharp waves activity mainly over the left hemisphere. MRI scan revealed hyperintense lesions and abnormal diffusion values in the basal ganglia bilaterally and in the left frontal cortex compatible with the diagnosis of CJD.

He continued to deteriorate with gradual decline of the level of consciousness until he became unresponsive with multiple myoclonic jerks. He was transferred to a nursing home where he succumbed 3 weeks later, four months following the onset of his symptoms.

Case 5: presentation as peripheral facial nerve palsy

This 55 year-old woman, of Tunisian Jewish origin, without a family history suggestive for CJD and with past medical history of essential tremor, was admitted to the neurology department in AHMC due to sudden onset of facial weakness that started several days after a face-lifting operation. When first examined she had a left peripheral facial nerve palsy with an otherwise normal neurological examination. Diagnostic workup included CT scan, carotid ultrasound, and 24 hours ECG recording that were all normal. She was discharged after several days of hospitalization but readmitted 3 weeks later due to new complaints of gait instability, left hand weakness and general deterioration. She now revealed impaired

upward gaze, left facial nerve palsy, bilateral hand dysmetria and intention tremor and ataxia. CSF tau was elevated (>1200 pg/ml) and the E200K mutation was positive. EEG showed generalized slowing with periodic discharges mainly over the right hemisphere. MRI scan revealed hyperintense lesions and abnormal diffusion values in the head of both caudate nuclei and right basal ganglia, in both pulvinar nuclei and right frontal cortex, compatible with the diagnosis of CJD. During her hospitalization she continued to deteriorate and became comatose with frequent myoclonic jerks. The patient was transferred to a nursing home where she died a few weeks later.

Case 6: presentation with upper limb dystonia and the alien hand sign

This 65 year-old man, of Libyan Jewish origin, with a negative family history of CJD, was admitted to the neurology department in AHMC due to two weeks duration of involuntary movements of the right hand accompanied with a feeling that he cannot control his hand and that “it has its own life”. On examination he was alert and oriented with mildly dysarthric speech and mild weakness and dystonic movements (mainly hand elevation) of the right upper limb, to most of which he was unaware and could not suppress. He had right hand apraxia and brisk tendon reflexes with bilateral extensor plantar responses. The patient refused to have a lumbar puncture but the E200K mutation was positive. EEG showed periodic triphasic waves. MRI scan revealed hyperintense lesions and abnormal diffusion in the basal ganglia bilaterally as well as the left frontoparietal cortex, compatible with CJD diagnosis.

During his hospitalization he developed rapid cognitive decline, myoclonic jerks and severe ataxia and became bedridden. He was transferred to a nursing home where he expired four months later.

Discussion

In this study we documented the presenting symptoms in a unique population of E200K fCJD patients. The common denominator of all these cases is the presentation with a relatively isolated symptom which is unusual for CJD, with a relatively rapid development of the common or “classical” signs of the disease thereafter.

The presentation of CJD may be non-specific or even misleading. In the study of Appleby et al. [21] the authors found that 83% of the patients with prion disease are initially diagnosed with a non-prion disease related dementia including Parkinson's disease, normal pressure hydrocephalus, and other unspecific neurological disorders. This ambiguity is not limited to the sporadic disease and Chapman et al. [6] not only drew attention to the clinical heterogeneity in familial disease but also described a non-specific prodromal syndrome consisting of generalized weakness and malaise in some patients. Since then patients with an unusual or atypical presentation like a stroke-like presentation [8] alien hand syndrome [9] or supranuclear gaze palsy [10] have been described.

The most prevalent presenting symptoms in our cohort were cognitive decline and gait disturbance. This is compatible with the report of the central European cohort [12] in which ataxia and dementia were the most prevalent symptoms.

In our series of consecutive patients with E200K fCJD, unusual or atypical presentation was documented in six of the patients (~ 8 %,) (Table 1). One of our patients presented as auditory agnosia or pure word deafness. Hearing impairment is an unusual manifestation of CJD at the time of onset or during the course of the disease; in a large series of 137 pathologically confirmed sporadic CJD (sCJD) cases none of whom had auditory symptoms [22] and only a few cases were described in the literature up-to-date. The first patient described [23] presented with hearing loss and vague symptoms of imbalance. Another patient [24] presented with auditory agnosia as an initial manifestation and later developed cerebellar signs, dementia and myoclonus. Tobias et al [25] described a patient presenting with word deafness.

All these patients described above were sporadic. Only two cases were described for E200K familial patients both of whom had sensorineural hearing loss. The first patient had neurosensorial hypoacusis [26]. In this case marked neuronal loss, gliosis and PrP deposits were observed in the vestibular and cochlear nuclei. Another patient [27] presented with rapidly progressive bilateral sensorineural hearing loss and accumulation of PrP in the brainstem.

A lesion responsible for auditory agnosia should involve both temporal cortices including the primary auditory cortex. In our patient the MRI did not reveal such involvement as was for other reported cases [24,25]. This finding of normal MRI may reflect the early stage of the disease or the insensitivity of the MRI to posterior fossa structures involvement [28].

Case 2 presented as monoparesis probably due to asymmetric neuropathy. Although neuropathy is not rare in patients with fCJD [6] it is symmetrical and sensory.

Two studies [29,30] documented amyotrophy mainly at terminal stages of the disease of prion diseases (sCJD, fCJD and Gerstmann-Sträussler-Scheinker disease) . For these patients it was believed that prion protein propagation appeared to descend through the corticospinal tract to lower motor neurons and beyond.

There are two reports of pathologically confirmed sCJD cases who presented with lower limb weakness, atrophy and fasciculations [31,32]. One of whom had evidence of demyelinating polyneuropathy mimicking CIDP [31]. The mechanism of neuropathy in CJD is not well identified. In one study [33] neuropathology examination of the spinal cord of sCJD patients with amyotrophy revealed severe loss of spinal motor neurons in one patient and shrinkage and pyknotic appearance of the motor cells in four patients. In another study on E200K fCJD cases with polyneuropathy, [34] PrP deposits were found in the brain but not in the spinal cord. The authors noted some vacuoles in spinal gray matter, varying demyelination and remyelination in the ventral and dorsal roots, as well as Wallerian degeneration; the distal part of the sciatic nerve suggesting a dying-back process. The axonal degeneration of the dying-back type begins in the most distal ramification of axons, but it is believed that the body of motor neurons and neurons of sensory ganglia may be the original site of damage with secondary demyelination.

Two of our patients presented with pseudobulbar or cranial nerve palsy. Pseudobulbar symptoms mimicking motor neuron disease or the Miller-Fisher variant of Guillain-Barre

syndrome are rare in CJD, documented in only one of 278 patients with CJD (234 sporadic, 36 familial, and 8 iatrogenic disease) [35]. It is unclear, however from this description whether these symptoms appeared isolated. Other than this study there are only few case reports of CJD patients who presented with bulbar or pseudobulbar symptoms. One report [36] described a patient with pseudobulbar signs relatively early in the disease course but the patient also had cognitive decline and cerebellar dysfunction. Another patient [37] with pathologically proven CJD presented with isolated dysarthria and dysphagia. Although in case 5 the facial palsy developed several days following face-lifting operation it is unlikely to be considered as a complication of the procedure which typically occurs immediately after the procedure and affects individual branches of the facial nerve [38]. Heye et al. [39] reported a patient who presented with facial nerve palsy. As in our case MRI did not reveal brainstem lesions probably due to the atrophic changes that cause elevated diffusivity reflected in the DWI images as reduced, rather than enhanced, signal. Since standard DWI scans are optimized for detection of restricted diffusion, they may miss brainstem and posterior fossa changes [28].

Several familial and sporadic CJD patients have been described with a sudden stroke-like presentation [40- 47]. Like our patient some cases presented with ataxia directing to vertebrobasilar origin [46] but some presented with hemiparesis [42] mimicking hemispheric stroke. Unlike our patient, in all cases there was no improvement but rather rapid deterioration with a progressive course. However in our patient (case 3) subsequent imaging demonstrated improvement of the brainstem lesion rather than progression as would be expected if the lesion was due to prion disease. Thus this case may represent a co-occurrence. Perhaps that the vascular lesion triggered the appearance of CJD. Initial imaging can be interpreted as normal [46] or as in our case may be interpreted to be compatible with ischemic changes [47]. Population at risk, lack of cerebrovascular risk factors and development of symptoms within days and not minutes or hours as well as progressive disorder should draw attention of the clinician to the possibility of CJD.

Only a few cases of the alien hand syndrome have been described in familial and sporadic CJD [9, 48,49] but in one retrospective study of systematic medical files review revealed 13 CJD patients who had the alien hand sign. In four of whom this was the presenting symptom. The neuroanatomical correlate of this phenomenon in eight patients was the contralateral parietal lobe as seen in our patient.

One limitation of our study is the lack of autopsy confirmation of the disease. Beyond the reluctance of having autopsies in Israel by the general population, pathology personnel are also unwilling to do autopsies. However we feel that the existence of a pathogenic mutation, the CSF findings and the clinical evaluation make the diagnosis of the disease certain. Autopsy is occasionally helpful in identifying the anatomical lesion responsible, but in the case of CJD by the time the patient dies the pathology is so severe that an anatomic clinical correlation is unlikely.

The clinical heterogeneity of sporadic CJD is well known. Our cohort is unique in demonstrating a similar spectrum also in a population with an identical point mutation in the *PRNP* gene. The reasons why the disease starts in a given place are unknown and are worthy

of study, since if such precipitants can be identified this may perhaps pave the way to prevention.

In conclusion: The unusual presentations in our patients demonstrate the clinical variability in the presentation of fCJD. A high level of clinical suspicion may be useful in obtaining early diagnosis and therefore avoiding costly and inefficient therapeutic strategies.

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References

1. Prusiner SB. Molecular biology of prion diseases. *Science*. 1991; 252:1515–1522. [PubMed: 1675487]
2. Knight RS, Will RG. Prion diseases. *Journal of Neurology Neurosurgery and Psychiatry*. 2004; 75(Suppl. 1):i36–42.
3. Goldfarb LG, Korczyn AD, Brown P, Chapman J, Gajdusek DC. Mutation in codon 200 of scrapie amyloid precursor gene linked to Creutzfeldt-Jakob disease in Sephardic Jews of Libyan and non-Libyan origin. *Lancet*. 1990; 336:637–638. [PubMed: 1975415]
4. Chapman J, Ben-Israel J, Goldhammer Y, Korczyn AD. The risk of developing Creutzfeldt-Jakob disease in subjects with the PRNP gene codon 200 point mutation. *Neurology*. 1994; 44:1683–1686. [PubMed: 7936296]
5. Korczyn AD. Creutzfeldt-Jakob disease among Libyan Jews. *European Journal of Epidemiology*. 1991; 7:490–493. [PubMed: 1761106]
6. Chapman J, Brown P, Goldfarb LG, Arlazoroff A, Gajdusek DC, Korczyn AD. Clinical heterogeneity and unusual presentations of Creutzfeldt-Jakob disease in Jewish patients with the PRNP codon 200 mutation. *Journal of Neurology Neurosurgery and Psychiatry*. 1993; 56:1109–1112.
7. Meiner Z, Gabizon R, Prusiner SB. Familial Creutzfeldt-Jakob disease, codon 200 prion disease in Libyan Jews. *Medicine*. 1997; 76:227–237. [PubMed: 9279329]
8. Hohler AD, Flynn FG. Onset of Creutzfeldt-Jakob disease mimicking an acute cerebrovascular event. *Neurology*. 2006; 67(3):538–539. [PubMed: 16894130]
9. Inzelberg R, Nisipeanu P, Blumen SC, Carasso RL. Alien hand sign in Creutzfeldt-Jakob disease. *Journal of Neurology Neurosurgery and Psychiatry*. 2000; 68(1):103–104.
10. Bertoni JM, Brown P, Goldfarb LG, Rubenstein R, Gajdusek DC. Familial Creutzfeldt-Jakob disease (codon 200 mutation) with supranuclear palsy. *JAMA*. 1992; 268:2413–2415. [PubMed: 1404799]
11. Kovacs GG, et al. Genetic Creutzfeldt-Jakob disease associated with the E200K mutation: characterization of a complex proteinopathy. *Acta Neuropathologica*. 2011; 121(1):39–57.
12. Taratuto AL, et al. Insomnia associated with thalamic involvement in E200K Creutzfeldt-Jakob disease. *Neurology*. 2002; 58:362–367. [PubMed: 11839833]
13. Neufeld MY, Josiphov J, Korczyn AD. Demyelinating peripheral neuropathy in Creutzfeldt-Jakob disease. *Muscle and Nerve*. 1992; 15:1234–1239. [PubMed: 1362595]
14. World health organization: emerging and other communicable diseases, surveillance and control. Vol. 1998. Geneva: WHO Global Surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of the WHO consultation; p. 9–11.
15. Fulbright RK, Hoffmann C, Lee H, Pozamantir A, Chapman J, Prohovnik I. MR imaging of familial Creutzfeldt-Jakob disease: a blinded and controlled study *AJNR American Journal of Neuroradiology*. 2008; 29:1638–1643. [PubMed: 18635614]
16. Cyngiser TA. Creutzfeldt-Jakob disease: a disease overview. *American Journal of Electroneurodiagnostic and Technology*. 2008; 48:199–208.

17. Skinningsrud A, Stenset V, Gundersen AS, Fladby T. Cerebrospinal fluid markers in Creutzfeldt-Jakob disease. *Cerebrospinal Fluid Research*. 2008; 5:14. [PubMed: 18727840]
18. Meiner Z, Kahana E, Baitcher F, et al. Tau and 14-3-3 of genetic and sporadic Creutzfeldt-Jakob disease patients in Israel. *Journal of Neurology*. 2011; 258:255–262. [PubMed: 20827556]
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975; 12(3):189–198. [PubMed: 1202204]
20. Cohen OS, Prohovnik I, Korczyn AD, et al. The Creutzfeldt-Jakob disease (CJD) neurological status scale: a new tool for evaluation of disease severity and progression in CJD. *Acta Neurologica Scandinavica*. 124:368–374.
21. Appleby BS, Rincon-Beardsley TD, Appleby KK, Crain BJ, Wallin MT. Initial Diagnoses of Patients Ultimately Diagnosed with Prion Disease. *Journal of Alzheimer's Disease*. 2014; 42:833–839.
22. Will RG, Mathews WB. A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970-1979 I clinical features. *Journal of Neurology Neurosurgery and Psychiatry*. 1994; 47:134–140.
23. Bigelow DC, Eisen MD, Yen DM, Saull SC, Solomon D, Schmidt DE. Otolaryngological manifestations of Creutzfeldt-Jakob disease. *Archives of Otolaryngology–Head & Neck Surgery*. 1998; 124(6):707–710. [PubMed: 9639484]
24. Orimo S, Ozawa E, Uematsu M, et al. 2000). A case of Creutzfeldt-Jakob disease presenting with auditory agnosia as an initial manifestation. *European Neurology*. 2000; 44(4):256–258. . [PubMed: 11096231]
25. Tobias E, Mann C, Bone I, De Silva R, Ironside J. A case of Creutzfeldt-Jakob disease presenting with cortical deafness. *Journal of Neurology Neurosurgery and Psychiatry*. 1994; 57(7):872.
26. Campdelacreu RR, Ferrer J, Escrig I, Povedano A, Gascón-Bayarri M, Moral, E. Familial Creutzfeldt–Jakob disease with E200K mutation presenting with neurosensory hypoacusis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2007; 78(1):103–104.
27. Cataldi ML, Revisto O, Reggio, et al. Deafness an unusual onset of genetic Creutzfeldt–Jakob disease. *Neurological Sciences*. 2000; 21:53–55. [PubMed: 10938203]
28. Cohen OS, Hoffmann C, Lee H, Chapman J, Fulbright RK, Prohovnik I. MRI detection of the cerebellar syndrome in Creutzfeldt-Jakob Disease. *The Cerebellum*. 2009; 8:373–381. [PubMed: 19408064]
29. Worrall BB, Rowland LP, Chin SS, Mastrianni JA. Amyotrophy in prion diseases. *Archives in Neurology*. 2000; 57(1):33–38.
30. Esteban JCG, Atares B, Zarranz JJ, Velasco F, Lambarri I. Dementia, amyotrophy, and periodic complexes on electroencephalogram: a diagnostic challenge. *Archives in Neurology*. 2001; 58:1669–1672.
31. Kovács T, Arányi Z, Szirmai I, Lantos PL. Creutzfeldt-Jakob disease with amyotrophy and demyelinating polyneuropathy. *Archives in Neurology*. 2002; 59(11):1811–1814.
32. Panegyres, Peter K, Armari E, Shelly R. "A patient with Creutzfeldt-Jakob disease presenting with amyotrophy: a case report." *Journal of Medical Case Reports*. 2013; 7(1):218. [PubMed: 23971649]
33. Niewiadomska M, Kulczycki J, Wochnik-Dyjas D, et al. Impairment of the peripheral nervous system in Creutzfeldt-Jakob disease. *Archives in Neurology*. 2002; 59:1430–1436.
34. Antoine JC, Laplanche JL, Mosnier JF, Beaudry P, Chatelain J, Michel D. Demyelinating peripheral neuropathy with Creutzfeldt-Jakob Disease and mutation at codon 200 of the prion protein gene. *Neurology*. 1996(46):1123–1127. [PubMed: 8780103]
35. Brown P, Gibbs CJ, Rodgers-Johnson P, et al. Human spongiform encephalopathy: The National Institutes of Health series of 300 cases of experimentally transmitted disease. *Annals of Neurology*. 1994; 35:513–529. [PubMed: 8179297]
36. Brunet P, Viader F, Hein D. Encephalopathy of rapid development with supranuclear ophtalmoplegia and peripheral neuropathy. *Revue Neurologique (Paris)*. 1986; 142:159–166.

37. Frank HG, Schnorf H, Genoud D, Pizzolato P, Glatzel M, Landis T. Creutzfeldt-Jakob disease presenting as isolated dysarthria and dysphagia due to pseudobulbar palsy. *European Neurology*. 2000; 44(2):126–127. [PubMed: 10965170]
38. Hohman MH, Bhama PK, Hadlock TA. Epidemiology of iatrogenic facial nerve injury: A decade of experience. *The Laryngoscope*. 2014; 124(1):260–265.8. [PubMed: 23606475]
39. Heye N, Cervos-Navaro J. Focal involvement and lateralization in CJD: Correlation of clinical, electroencephalographic and neuropathological findings. *European Neurology*. 1992; 32:289–292. [PubMed: 1521553]
40. Kamogawa K, Toi T, Okamoto K, Okuda B. A case of Creutzfeldt-Jakob disease with stroke-like episode as an initial symptom. *Nihon Ronen Igakkai Zasshi*. 2009 Sep; 46(5):458–461. [PubMed: 19920375]
41. Hirst CL. Sporadic Creutzfeldt-Jakob disease presenting as a stroke mimic590. *British Journal of Hospital Medicine*. 2011; 72(10):590–591. [PubMed: 22041731]
42. Ko KF, Lau WY, Cheng WK, Kwan MC, Yip LK. Creutzfeldt-Jakob disease with initial right hemiparesis masquerading as a stroke. *Hong Kong Medical Journal*. 2010; 16(6):487–488. [PubMed: 21135428]
43. Mehndiratta MM, Chowdhury D, Gupta M. Stroke like presentation of Creutzfeldt-Jakob disease. *Journal of Association of Physicians India*. 2000; 48(6):658–659.
44. Sinha KK. Stroke like presentation of Creutzfeldt Jakob disease: an unusual variant. *Journal of Association of Physicians India*. 2000; 48(5):551.
45. Mantokoudis G, Saber Tehrani AS, Newman-Toker DE. An unusual stroke-like clinical presentation of Creutzfeldt-Jakob disease: acute vestibular syndrome. *Neurologist*. 2015; 19:96–98. [PubMed: 25888195]
46. Damato V, Cuccagna C, Costantini EM, et al. Creutzfeldt-Jakob disease manifesting as stroke mimic in a 78-year-old patient: pitfalls and tips in the diagnosis. *Journal of the Neurological Sciences*. 2014; 346(1-2):343–344. [PubMed: 25201717]
47. Lyytinen J, Sairanen T, Valanne L, Salmi T, Paetau A, Pekkonen E. Progressive Stroke-Like Symptoms in a Patient with Sporadic Creutzfeldt-Jakob Disease. *Case Reports in Neurology*. 2010; 2(1):12–18. [PubMed: 20689629]
48. Oberndorfer S, Urbanits S, Lahrmann H, Jarius C, Albrecht G, Grisold W. Familial Creutzfeldt-Jakob disease initially presenting with alien hand syndrome. *Journal of Neurology*. 2002; 249(5): 631–632. [PubMed: 12021958]
49. Moreaud O, Monavon A, Brutti-Mairesse MP, Grand S, Lebas JF. Creutzfeldt-Jakob disease mimicking corticobasal degeneration. *Journal of Neurology*. 2005; 252(10):1283–1284. [PubMed: 15795791]

Table 1
The prevalence of different presenting symptoms in our population of E200K fCJD”

Symptom	No of patients	Percentage
Cognitive impairment	57	74%
Gait or balance impairment	25	33%
Behavioral changes	18	23%
Sleep disturbances	15	19%
Abnormal movements (tremor or myoclonus)	6	8%
Impairment of dexterity or fine movements	5	7%
General deterioration	4	5%
Headache	3	4%
Sensory disturbances/paresthesias	3	4%
Pruritus/Itch	2	3%
Visual disturbances	2	3%
Other	6	8%