SHORT REPORT

Clinical range and MRI in Creutzfeldt-Jakob disease with heterozygosity at codon 129 and prion protein type 2

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Abstract

A 68 year old woman with sporadic Creutzfeldt-Jakob disease is described, who neither showed characteristic EEG abnormalities nor a positive test of the neuronal protein 14–3–3 or neuron specific enolase (NSE) in CSF, despite a clinical presentation with ataxia of cerebellar type, rapidly progressive dementia, myoclonus, and marked hyperintense signal abnormalities in the deep cortical layers and the basal ganglia on T2 and diffusion weighted MRI. Moreover she showed atypical clinical features with a syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) and a peripheral sensorimotor polyneuropathy. Whether these disturbances are independent of Creutzfeldt-Jakob disease or a feature of it is discussed. It has recently been shown that in Creutzfeldt-Jakob disease different clinical and pathological phenotypes correlate with the polymorphism at codon 129 of the prion protein gene (PRNP) and the type of the protease resistant fragment that accumulates in the brain. According to the new classification at least six sporadic variants of Creutzfeldt-Jakob disease exist. The molecular genetic analysis showed heterozygosity of PRNP at codon 129 for methionine and valine and the presence of PrP^{CJD} type 2 in the brain of this patient. As a new feature of changes on MRI, striking cortical changes of hyperintense signals are described in diffusion weighted as well as T2 weighted MRI that directly correlate with the histomorphological spongy degeneration of the brain in this region. In cases of rapidly progressive dementia, Creutzfeldt-Jakob disease always needs to be considered even if unusual features are present and current diagnostic criteria are not in favour of this disease.

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Creutzfeldt-Jakob disease occurs worldwide in late middle age and usually manifests as a rapidly progressive dementia. In more than 90% it occurs sporadically, with an annual incidence of one person per million. There are often myoclonic jerks and the disease is typically associated with periodic sharp wave discharges on EEG. Neuropathological changes consist of spongy degeneration, neuronal loss, and astrocytic gliosis. A positive immunoassay of the neuronal protein 14–3–3 and an increase in neuron specific enolase (NSE) in CSF indicate rapidly progressive neuronal degeneration and are supportive of a diagnosis of Creutzfeldt-Jakob disease.[1 2] Parchi *et al* recently showed that in Creutzfeldt-Jakob disease different clinical and pathological phenotypes correlate with the polymorphism at codon 129 of the prion protein gene (PRNP) and the type of the protease resistant fragment that accumulates in the brain.[3] According to the new classification, at least six sporadic Creutzfeldt-Jakob disease variants exist.[3 4] We describe a 68 year old woman with sporadic Creutzfeldt-Jakob disease, who neither showed characteristic EEG abnormalities nor a positive test of 14–3–3 or NSE in CSF, despite a clinical presentation with ataxia of cerebellar type, rapidly progressive dementia, myoclonus, and marked hyperintense signal abnormalities in the deep cortical layers and the basal ganglia on T2 and diffusion weighted MRI. The cortical MRI abnormalities correlated well with histomorphological spongy degeneration in a biopsy of frontal lobe cortex. Moreover, the patient showed atypical clinical features with a syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) and a peripheral sensorimotor polyneuropathy. The molecular genetic analysis showed heterozygosity of PRNP at codon 129 for methionine and valine and the presence of PrP^{CJD} type 2 in the brain.

Case report

The 68 year old female patient was healthy and had no remarkable medical history until August 1996, when she first experienced some movement related dizziness without any further impairment of balance or gait. Emotional lability, hypochondriasis, slight memory diffi-

culties, and inappropriate behaviour led her relatives to assume a depressive reaction to the recent divorce of her daughter. In October 1996, she noted numbness and tingling of her toes and consulted a neurologist, who diagnosed a mild peripheral neuropathy of unknown origin and a mild depression. Neurological examination showed bilateral loss of ankle reflexes, distal hypaesthesia of her feet, and atrophy of the extensor digitorum brevis muscles. In February 1997, she complained of increased dizziness and was noted to have an intermittently unsteady gait. Outpatient neurological and ear, nose, and throat examination could not substantiate any vestibular or cerebellar dysfunction. To exclude a cerebellopontine angle tumour MRI of the brain was performed in March 1997, which showed discrete, diffuse cerebral atrophy and small T2 signal hyperintensities in subcortical cerebral white matter, which were attributed to an early stage of subcortical vascular encephalopathy. Because of unexplained loss of weight, she was referred to a regional district hospital where a neoplastic illness was excluded. However, she continued to lose weight up to 12 kg, so she was admitted to the university department of gastroenterology in July 1997 for further investigations. Here, the clinical course took an unexpected turn, when suddenly self limiting episodes of somnolence and confusion with abrupt onset as well as fluctuating signs of cerebellar ataxia dominated the clinical picture, which offered features strongly suggestive of a psychogenic background. For example, one moment the patient thought she was in an airport and spoke English as a foreign language, and in the next moment she was reoriented, indignantly refusing psychiatric exploration. The psychiatrist diagnosed a histrionic personality disorder and recommended referral to the department of psychiatry. Within 2 weeks, the repeated confusional states developed into a manifest dementia, in the course of which she was alert, but easily frightened and disoriented to time, place, and situation. The first hyperkinetic movements were choreoathetoid and affected mainly the arms and hands. Subsequently superimposed myoclonic jerks were elicited by minor tactile and auditory stimuli. Her speech became dysarthric and she was unable to obey simple commands. At this stage she developed a transient SIADH with hyponatremia, that required restriction of fluids for about 8 weeks. Extensive diagnostic work-up for secondary SIADH was negative. In August 1997 she became akinetic, mute, and bedridden and showed a most pronounced myoclonic startle response. Brain MRI now disclosed severe, generalised cerebral atrophy, especially of the grey matter. Hyperintense signal abnormalities on T2 and diffusion weighted imaging as well as reduced apparent diffusion coefficient (ADC) values in the striatum and thalamus were shown (fig 1 A–C). The T2 weighted images of the

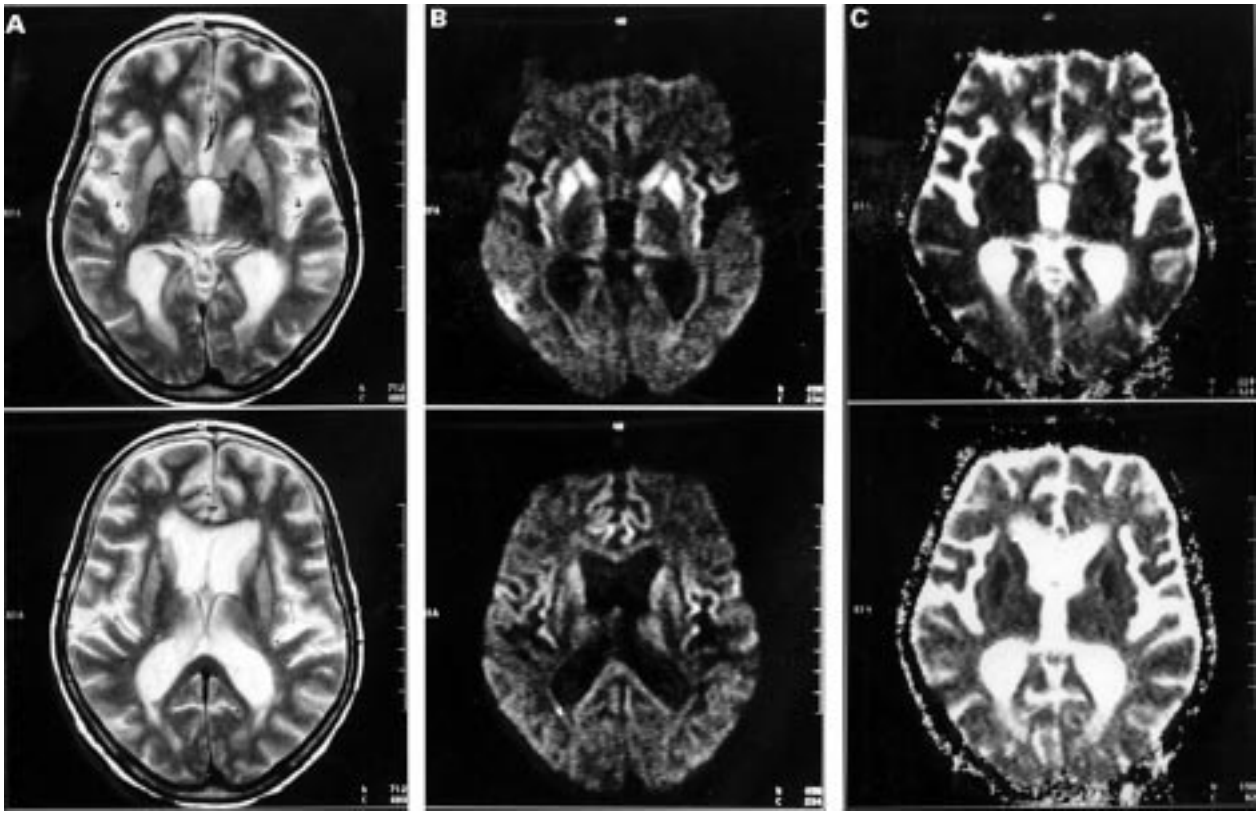

Figure 1 (A) The T2 weighted turbo spin echo axial slice (TR 2620 ms, TE 85 ms, acquisition 1, slice thickness 5 mm, matrix size 190x256 mm) shows increased signal intensity in the striatum and thalamus. (B) The diffusion weighted echo planar image (TR 0.8 ms, TE 123 ms, TA 6.77 s, acquisition 1, slice thickness 5 mm, intersection gap 0.5 mm, matrix size 128x200 mm, b value=1000 s/mm^2) shows a reduced diffusion (high signal intensity) in the striatum, thalamus, and cortical layers. (C) The calculated apparent diffusion coefficient (ADC) values (TR 3000 ms, TE 110 ms, TA 42 s, slice thickness 5 mm, intersection gap 0.5 mm, matrix size 96x200 mm, variable b values 1250/1000/750/500/250/0 s/mm^2) measured in variable regions confirm diffusion abnormalities with reduced signal intensities bilaterally in the putamen and the head of the caudate nucleus. ADC values in different regions of interest: right caudate head: 54.4; left caudate head 58.2; right putamen 42.4; left putamen 43.2; right thalamus 63.9; left thalamus 73.2x10^{-5} cm^2/s.

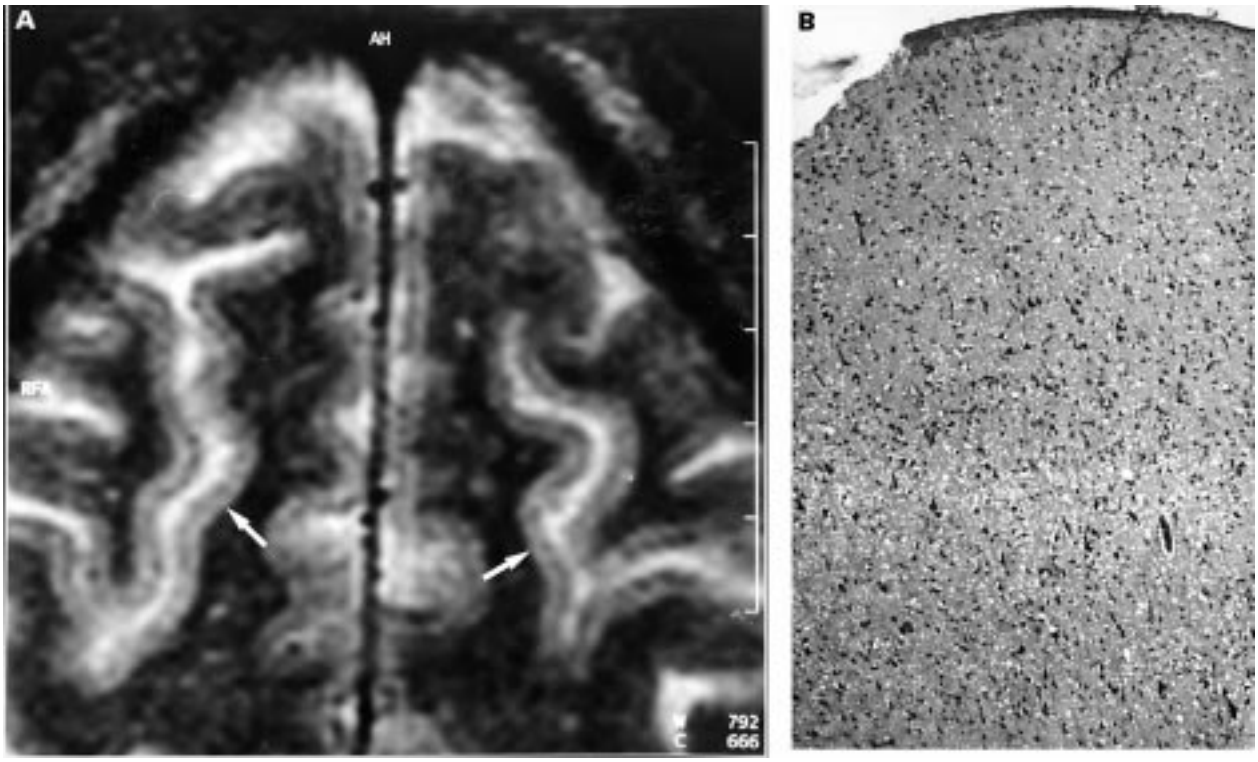

Figure 2 (A) T2 weighted image of the frontoparietal region shows an abnormal hyperintense signal of the deep cortical layers (arrows). (B) Histology of the biopsy taken from the right frontal lobe. Spongiform changes, astrocytic gliosis, and nerve cell loss are seen. Spongiform changes are located predominantly in the deep layers of the cortex corresponding to radiological changes (haematoxylin and eosin, originally×200).

frontoparietal region showed a pronounced, abnormal hyperintense signal of the deep cortical layers (fig 2 A). Nerve conduction studies in September and November 1997 (follow up values) showed in the median nerve a compound muscle action potential amplitude 10.0 mV (3.6), distal latency 3.8 ms (3.9), conduction velocity 54.2 m/s (50.0), in the peroneal nerve an amplitude 0.83 mV (0.03), distal latency 6.1 ms (6.7), conduction velocity 37.9 m/s (41.3), in the tibial nerve amplitude 0.48 mV (0.21), distal latency 5.4 ms (3.5), conduction velocity 41.0 m/s (34.0), and in the sural nerve sensory nerve action potential an amplitude 3.4 μV (3.1), conduction velocity 39.2 m/s (40.7), and thus were consistent with a severe, sensorimotor, axonal polyneuropathy. Diagnostic laboratory investigation was normal, including full blood count and white blood differential, liver, and renal function tests, glucose profiles, serum electrophoresis, thyroid function tests, and vitamin B_1, B_6, B_{12}, and folate concentrations. In the CSF, cells and protein were normal, NSE was not raised and 14–3–3 protein was not detectable in western blot analysis. Twenty four hour EEG monitoring and repeated EEG recordings over several weeks showed background slowing without periodic sharp wave discharges. While the choreoathetoid movements decreased, stimulus induced myoclonus increased and additionally a supranuclear downgaze palsy, oculomotor apraxia, neck rigidity with retrocollis, and variably increased tone of the arm muscles became evident. Deep tendon reflexes were normal in the upper limbs, depressed in the lower limbs, and plantar responses were flexor. A cerebral biopsy was taken from the right frontal lobe and showed spongy degeneration predominantly in the deep layers of the cortex, astrocytic gliosis, and neuronal loss, thus corresponding well to the MRI signal changes (fig 2A and B). With western blot analysis using anti PrP antibody 3F4, the proteinase K resistant isoform of the prion protein (PrP^{CJD}) was detectable, proving the diagnosis of Creutzfeldt-Jakob disease. The unglycosylated PrP^{CJD} migrated at 19 kDa resembling prion protein type 2 according to Parchi *et al*.[3] Over the next 2 months, the patient became stuporous. Twenty nine months after her first symptoms, she died; necropsy was not performed.

Discussion

The physiological polymorphism at codon 129 of PRNP has been implicated in predisposition to prion diseases as well as age at onset and phenotypic appearance of diseases.[5] About 50% of the white population are heterozygous at codon 129 of the PRNP whereas only 15% of patients with sporadic Creutzfeldt-Jakob disease show heterozygosity. The large majority of cases of sporadic Creutzfeldt-Jakob disease occur in persons who are homozygous for either allele. With ongoing epidemiological and neuropathological studies, a new classification of sporadic Creutzfeldt-Jakob disease is becoming evident, using the polymorphic position at codon 129 of the PRNP and the prion protein types 1 and 2 according to Parchi *et al*.[3] It seems that the polymorphism at codon 129 combined with the prion protein type determines the phenotype of sporadic Creutzfeldt-Jakob disease.[4] According to this classification,

cases of heterozygosity in combination with PrP^{CJD} type 2 characteristically lack the typical EEG changes. In the present case, the typical EEG changes were absent, and on western blot analysis protein 14–3–3 was not detectable in CSF. With these negative additional investigations our case did not fulfill the criteria for a clinically probable Creutzfeldt-Jakob disease, according to current diagnostic criteria (modified from[6]).

In establishing the diagnosis of Creutzfeldt-Jakob disease, the hyperintensities of the basal ganglia and frontoparietal cortex in T2 and diffusion weighted MRI were important features. T2 and proton density weighted MRI signal abnormalities of the basal ganglia have been shown previously in a large series of patients with Creutzfeldt-Jakob disease, and in four of 29 changes in the occipital cortex were also seen.[7] These changes in the basal ganglia are not limited to Creutzfeldt-Jakob disease, but are also found in Wilson's disease, HIV infection, and Leigh disease. As recently reported, the specificity of diffusion weighted imaging with high signal intensities in the striatum and thalamus in Creutzfeldt-Jakob disease depends on whether other diseases show the same diffusion weighted imaging signal abnormalities.[8] Nevertheless, the pathological signal intensities in diffusion weighted imaging and measured reduced apparent diffusion coefficient values comparable with the ones found in that recent report, supported our clinical suspicion of Creutzfeldt-Jakob disease. As a new feature of MRI changes we describe striking frontoparietal cortical changes in T2 and diffusion weighted MRI. These hyperintense signals can be directly correlated with the histomorphologically shown spongy degeneration of the frontal lobe biopsy. Apart from spongiform degeneration, gliosis, and cell loss the biopsy did not display Kuru-like plaques, although expected in heterozygous PRNP codon 129 with PrP type 2. This is most likely due to their preferential distribution in cerebellar tissue.[3 4]

The peripheral sensorimotor polyneuropathy, which developed in an early stage of the disease and then progressed rapidly, and the transient SIADH represent two additional aspects worth mentioning. The SIADH could be an independent, transient, endocrine disturbance, as it is described in at least 26% of elderly people without recognisable cause.[9] Nevertheless, the question arises whether the SIADH as a disturbance mediated by the hypothalamus could be attributed to the underlying spongiform changes, which in our case preferentially affected the basal ganglia and the deep cortical layers. In the hypothalamus of scrapie infected hamsters a decrease of ADH immunostained neurons and an increase of corticotropin releasing factor immunostained neurons was described.[10] These changes suggest that the neuroendocrine system can be affected by prion diseases.

Our patient first presented with distal paraesthesia in the feet and showed electrodiagnostic features consistent with a rapidly progressive axonal neuropathy. There was no evidence of another disease causing peripheral neuropathy. Demyelinating peripheral neuropathy is well known in familial Creutzfeldt-Jakob disease with mutation at codon 200 of PRNP.[11 12] Recently, axonal peripheral neuropathy was reported in a patient with sporadic Creutzfeldt-Jakob disease homozygous for valine at PRNP codon 129.[13] Our case also shows that peripheral neuropathy may possibly be a feature of sporadic Creutzfeldt-Jakob disease, and the question is raised if dysaesthesia and pain in the feet—prominent presenting symptoms in the new variant of Creutzfeldt-Jakob disease in the United Kingdom[14]—may not exclusively be a feature of thalamic involvement.

We conclude that in cases of rapidly progressive dementia Creutzfeldt-Jakob disease always should be considered even if unusual features are present and current diagnostic criteria are not exactly fulfilled. As with the finding of cortical hyperintensity in T2 and diffusion weighted MRI in our patient, new features of Creutzfeldt-Jakob disease may become detected. Various phenotypic expressions of Creutzfeldt-Jakob disease may eventually be explained on a molecular level as our understanding of prion protein genetics and pathophysiology improves further.

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