LETTERS TO THE EDITOR

Codon 200 mutation in a new family of Chilean origin with Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a fatal progressive transmissible dementia, with a worldwide incidence of 0.5–1.0 cases per million. In some populations, such as Libyan Jews and Slovaks from the Orava region, there is a high incidence of Creutzfeldt-Jakob disease which is associated with a mutation at codon 200 of the prion protein gene (PRNP). The same mutation was identified in six families with Creutzfeldt-Jakob disease from Chile, where the disease has a high frequency and is familial in about half of the cases. We describe an additional Chilean family carrying this mutation.

The figure shows the pedigree of the family. The proband (V-1) was a 56 year old Chilean woman who, in the early 1990s, became seriously depressed. Five months later, she showed progressive mental deterioration, cortical blindness, ataxia, tremor, dysmetria, hypotonia, and sporadic bursts of myoclonic jerks. She had repeated generalised tonic-clonic seizures and the EEG recorded slow background activity with periodic discharges. The patient died nine months after the onset of symptoms. At neuropathological examination, the cerebral cortex, basal ganglia, and thalamus showed diffuse spongiform changes with severe neuronal loss and astrogliosis. PrP27−30 was detected by western blotting from a frozen brain sample. Small virus-like particles were isolated and identified by electron microscopy (referred to as CJD200 in Ozel et al.).

The proband’s 53 year old cousin (V-4) died from a typical Creutzfeldt-Jakob illness in the late 1970s after a total duration of three and a half months. The disease started with an insidious and progressive course consisting of childish behaviour, emotive frailty, and absurd fears. The patient deteriorated mentally and had bilateral cerebellar ataxia with cerebellar dysarthria, generalised myoclonus, and distal fasciculations. Repeated EEGs showed diffuse periodic activity without normal basal rhythms. Finally, the patient showed a progressive stuporous condition with convulsive seizures. Necropsy was not done.

A niece of V-4 (VI-1) was 43 years old when, in the 1980s, the disease started with rapid mental deterioration, depressive mood, and severe memory disturbances. She deteriorated mentally and became blind but with normal pupillary reactions and fundus oculi. She also showed an unstable gait, bilateral palomomental reflexes, absence of plantar responses, and hyperactive deep reflexes. Finally, she was bedridden with generalised muscle rigidity and generalised myoclonic jerks. Serial EEG examinations showed typical and diffuse high voltage triphasic complexes with short periodicity. The patient died seven months after the onset of symptoms. Necropsy was not done.

Another cousin (V-5) developed Heidenhain’s syndrome (the visual variant of Creutzfeldt-Jakob disease) at the age of 70, with periodic EEG complexes. He died in the early 1990s after a duration of four months. Necropsy was not done.

The proband had the heterozygous mutation at codon 200 and was homozygous for methionine and glutamic acid at the codon 129 and 219 polymorphic sites respectively. Other PRNP point (at codons 102, 105, 210, 117, 198, 199, 179, 185, 217) and other mutations were not detected. The proband was homozygous for the non-informative apolipoprotein E3 isoform. It is likely that, similar to other Chilean Creutzfeldt-Jakob disease families, all the other affected members of the family carried the same mutation at codon 200 of PRNP.

No other family member is known to have had a similar consanguineous marriage between diseases. The proband’s mother died very young from breast cancer. Her father (IV-1), who died at the age of 88, was an obligate carrier as two of his nieces (V-4 and VI-1) died from probable Creutzfeldt-Jakob disease. Subject IV-3 is also an obligate carrier and died at the age of 24. The other eight brothers and sisters of IV-1 (IV-2) died aged between 55 and 81 years without showing neurological symptoms. Subjects IV-4 and V-3 are two other obligate carriers. Subject IV-4 died at the age of 57 without showing neurological symptoms; V-3 is still alive at the age of 75. In generation III, subject III-5 is most likely a mutation carrier (age at death 75) but we cannot infer that subjects III-1 (age at death 66) or III-2 (age at death 74) were carriers as they were first degree relatives.

Members of family R8 are long time residents of Chile. Their ancestors came from Galicia (Spain) in the 17th century and during the centuries mixed with the local population. A consanguineous marriage between two cousins (III-1 and III-2) was present in generation III (figure). As in the Creutzfeldt-Jakob disease cluster in Libyan Jews, the mutation in our patient is carried by an allele with methionine at codon 129. The mutation may likewise be coupled to a methionine allele at codon 129 in the other six Chilean families with codon 200 mutation as none of the patients carrying the mutation was homozygous for valine (Brown P., unpublished data). These data, and the fact that the other six previously studied Chilean families with codon 200 mutation have Spanish ancestries, support the suggestion that this mutation first arose in central Europe and the Mediterranean and then spread to other countries by migration. However, the finding of the codon 200 mutation with methionine at codon 129 in a Japanese family without known racial mixing sustains the alternative hypothesis that this mutation has arisen independently in different world regions.

The clinical presentation among the affected members is similar to sporadic Creutzfeldt-Jakob disease. Typical periodic activity of the EEG recording was present in all of them. It is noteworthy that, in three of the affected members, the disease began with cortical blindness. Visual symptoms were also described in five of 14 Jewish patients with Creutzfeldt-Jakob disease with the codon 200 mutation.

The R8 family has four affected members in two generations and is one of the largest.
Brain CT and MRI showing bilateral calcification of substantia nigra, visible as high signal on CT and low attenuation on MRI.

Calcification of the substantia nigra in a patient with anakinetic rigid syndrome

Calcification of the caudate and lentiform nuclei of the basal ganglia are a recognised feature of apparently normal subjects as well as of patients with neurological disease. There have been previous reports of calcification of the substantia nigra, and we describe a patient with mental retardation, epilepsy, and an akinetic rigid syndrome, with neuroimaging features of heavy calcification of the substantia nigra.

A 59 year old man presented with an unsteady gait and general slowing up of his motor abilities for two years. His birth was normal and development had been normal until he was 18 months old, when he developed frequent tonic clonic seizures. These were treated with barbiturates and the seizures eventually went into remission from the age of 24. He never achieved full intellectual development but his full scale IQ was stable at 55-60 between 1944 and 1995. There was no family history of note and no history of carbon monoxide exposure. On examination he was short (height 1.5 metres) but otherwise phenotypically normal. There was poverty of facial expression, a stooped, unsteady gait with axial rigidity, and poor postural reflexes. His eye movements were normal and ophthalmological examination was normal. He had limb rigidity and akinesia, but no tremor. There were no cerebellar or pyramidal signs.

Investigations included normal calcium blood levels, normal thyroid hormone concentrations, normal copper studies, negative venereal disease research laboratory test, normal serum and CSF lactate studies, and normal CSF protein and cell analysis. Hand radiography was normal. A muscle biopsy showed type 2 fibre atrophy with abnormal mitochondria on electron microscopy. Serum DNA mitochondrial analysis was normal. Brain CT and MRI showed pronounced deposition of calcium in both substantia nigra (figure). The course of the condition was static and the patient showed a modest but definite response to levodopa.

Bilateral calcification of the basal ganglia is not an uncommon finding in apparently normal people and may be identified on plain skull radiography, CT, or postmortem examination. There are specific neurological diseases associated with basal ganglia calcification, and these can be divided into those that cause calcification—such as birth anoxia, disorders of calcium metabolism (such as hypoparathyroidism), or carbon monoxide poisoning—and patients with calcification of the basal ganglia, in whom no cause is identified but in whom it may be familial. When symptomatic the patients may have parkinsonism, dementia, dystonia, or chorea, suggesting that the calcification of the basal ganglia is causing or is at least a marker of underlying neuronal damage. The calcification may occur in the globus pallidus, caudate, or putamen, and often in all three regions.Calcification may also occur in the cerebellar macules. However, despite an extensive medical literature on intracerebral calcification, there have been no previous reports of calcification affecting the substantia nigra. The site of the calcification in our patient is likely to be a marker of damage to the substantia nigra and the response to levodopa suggests destruction of the nigrostriatal inputs with relative preservation of the striatum itself. The patient’s low IQ and epilepsy indicate that there is involvement outside the basal ganglia, although there was no obvious calcium deposition in the cortex or neuroimaging, and this is similar to patients with idiopathic calcification of the striatopallidal denervation system, as these patients may also have dementia or epilepsy, or both. The cause of the calcification in our patient is not clear. We excluded all the described causes including pseudohypoparathyroidism. Some patients with idiopathic calcification have been taking antiepileptic drugs and a causal role for this has been suggested. Deposition of calcium was proposed but seems unlikely. The constellation of features and abnormal muscle biopsy suggests that a disorder of mitochondrial metabolism was probably responsible although the common mitochondrial deletions in blood (8344, 8356, 4343, 8193, and multiple and single large mutations) were negative. Mitochondrial disease has been associated with basal ganglia calcification, but no patients have been described with calcium in the substantia nigra. The mechanism underlying calcium deposition in the substantia nigra is likely to be as obscure as that underlying calcification of other parts of the basal ganglia.