Chilean families for which a genealogy is available. The low degree of penetrance of this mutation is confirmed by the presence of mutation carriers that did not develop the disease up to the age of 88 (IV-1). The accurate study of the degree of penetrance of the codon 200 mutation among different cluster populations with high incidence Creutzfeldt-Jakob disease could clarify the role of other genetic or environmental factors in the development of the disease.

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Calcification of the substantia nigra in a patient with an akinetic 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 and magnesium, and no antihormone concentration, normal copper concentrations, normal copper studies, normal 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.1 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 hypophosphatasidrosis), 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.2 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 calculation may occur in the global pellidus, caudate, or putamen, and often in all the three regions. Calcification may also occur in the cerebellar nuclei.3 However, despite an extensive medical literature on intracerebral calcification, there have never been 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 denatate 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.4 Some patients with idiopathic calcification have been taking antiepileptic drugs and a causal relationship with calcium depositing calcium was proposed but seems unlikely.5 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.

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A sporadic case of dentatorubral pallidolusy atrophy (DRPLA) with CAG repeat expansion but no clinical abnormalities in the father

Dentatorubral pallidolusy atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterised by various combinations of myoclonus, epilepsy, ataxia, choreoathetosis, and dementia. The clinical presentation consists of degeneration of the dentatorubral and pallidolusy systems of the brain. The disease predominantly occurs as an inherited condition and is more common in Japan than in other countries. 

A unique expansion of a CAG trinucleotide repeat in a gene on the short arm of chromosome 12 was recently identified as the pathogenic mutation in DRPLA. There is a good correlation between the clinical signs of DRPLA and CAG repeat size. Patients with earlier onset tend to have a phenotype of progressive myoclonus epilepsy and larger expansions. Whereas the penetrance of DRPLA in Japan is estimated to be high (90%), sporadic patients with expanded alleles have been known. However, to the best of our knowledge, DNA analysis of the DRPLA gene of both parents of a sporadic patient has never been documented. In the present paper, we report a sporadic case of DRPLA and the results of analysis of the DRPLA gene in the patient and her parents.

A 39-year-old woman had been well until the age of 27, when she started to experience generalised epileptic seizures, slurred speech, unsteady gait, and intellectual disturbances. All these symptoms were slowly progressive. At the age of 39 she complained of increased frequency of the epileptic attacks and progressive intellectual and motor dysfunction. Her medical history was unremarkable, and her hospital记录 showed no members with ataxia, epilepsy, involuntary movements, psychosis, or other neurodegenerative diseases (figure). Neither her 66-year-old father nor her 63-year-old mother had any neurological abnormalities or epilepsy. Her three children and her 35-year-old sister were also free of neurological symptoms.

The examination of the patient showed that she was awake and had pronounced dementia. Her IQ on the Tanaka-Binet scale was 16, which corresponds to the intelligence of a child aged 2 years 11 months. Her speech was slurred and explosive. External ocular movements were full in range, and there was no nystagmus. Other cranial nerves were intact. The patient exhibited facial grimacing and choreoathetoid-like movements of her hands and feet. No myoclonus or tremors were noted. There was no motor weakness or atrophy. All four limbs were hypotonic. The patient exhibited ataxia in all four limbs and the trunk. Her gait was wide-based and very ataxic. Babinski’s sign was present bilaterally, but deep tendon reflexes were normal. There were no abnormalities of the sensory or autonomic nervous system. Biomagnetic (MEG) showed moderate atrophy of the cerebellar vermis and hemispheres, the brainstem, more prominently in the tegmentum, and the cerebrum. An EEG showed diffuse, slow basic activity, a few 2-3 Hz waves, single spikes, and polyspikes. High frequency photic stimulation induced photomyoclonus. The patient’s symptoms progressed and she became bedridden and mute over the next few months.

DNA analysis of the DRPLA gene of leukocytes was performed after informed consent had been obtained. The method of polymerase chain reaction (PCR) amplification and method of analysing the CAG repeat in the DRPLA gene have been described previously. The CAG repeat numbers were 64/15 in the patient, 59/18 in her 66-year-old father, and 17/18 in her 63-year-old mother.

The present patient apparently represents a sporadic case of hereditary DRPLA. This report is, to the best of our knowledge, the first documentation of DNA analysis of the DRPLA gene in parents and a child in a sporadic case. Although an asymptomatic father aged 54 years with an expanded CAG repeat was reported by Komure et al., there is no mention of DNA analysis of the mother. This family is interesting and important with regard to how DRPLA may arise.

The number of CAG repeats on the DRPLA gene ranges from 45 to 88 in patients with DRPLA and from 7 to 35 in normal subjects. There is no overlap between the distribution of the number of CAG repeats in normal subjects and patients. The age of onset of DRPLA diagnosed by both clinical features and DNA analysis is reported to range from 4 to 62 years, and an inverse correlation between numbers of CAG repeat units and age at onset has been shown. This inverse correlation seemed to be less strong in an adult onset case than an early onset case. Thus persons who have a mild expansion of CAG repeats may not develop clinical symptoms by their 60s, as in the father of this patient. Those with 59 CAG repeat would be expected to experience the onset of clinical symptoms in their 50s based on the results of a correlation analysis. The age of onset is beyond the range of ages of onset of DRPLA hitherto documented. Nevertheless, all evidence would indicate that the father is at high risk.

There are three possible mechanisms to explain how the trinucleotide repeat length expanded: firstly, expansion via intermediate size alleles, secondly, via asymmetric fully expanded alleles, and thirdly, de novo mutation from normal alleles. Our case is thought to represent the second mechanism. The distribution of repeat numbers in the DRPLA gene in the normal Japanese population has been reported, and 7-4% of the alleles in Japan have greater than 19 repeats. By contrast, none of the alleles in white people and only 1% of the alleles in Afro-Americans are of this size. In addition, no intermediate size alleles with 32 and 34 repeats have been reported in normal Japanese. Thus Burke et al suspect the expansion via intermediate size alleles to fully expanded alleles in succeeding generations for Japanese DRPLA. However, the first mechanism, expansion via intermediate size alleles, has never been found in a sporadic case of DRPLA, although it has been shown in sporadic cases of Huntington’s disease.

Thus a person who shows clinical features resembling those of hereditary diseases without family history, represents the first family member to cross the phenotypic threshold, which is a product of CAG repeat length, time, and other unknown features that govern its onset. The number of CAG repeats in this family increased from 59 to 64 as a result of paternal transmission. In triplet repeat disease caused by expanded CAG repeats, it should be noted that intergenerational increases in CAG repeats in paternal transmission are the major source of the larger expansions.

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