Inherited prion disease (PrP lysine 200) in Britain: two case reports

John Collinge, Mark S Palmer, Tracy Campbell, Katie C L Sidle, Desmond Carroll, Anita Harding

Abstract

***Objective*—To identify cases of inherited prion diseases in Britain and to assess their phenotypic features.**

***Design*—Screening study of patients suspected clinically to have Creutzfeldt-Jakob disease and other neurodegenerative diseases by prion protein gene analysis.**

***Setting*—Biochemical research department.**

***Subjects*—Patients suspected to have Creutzfeldt-Jakob disease and other neurodegenerative diseases.**

***Results*—Two patients with symptoms characteristic of sporadic Creutzfeldt-Jakob disease were found to have inherited prion protein disease (PrP lysine 200), with a mutation at codon 200 of the prion protein gene. Both were homozygous at codon 129 of the gene. One patient was a man aged 58 of British descent while the other was of Libyan Jewish origin.**

***Conclusion*—Two foci of inherited prion disease are known, among Libyan Jews and in Slovakia. A separate British focus of the disease may also exist. Heterozygosity at codon 129 may lead to reduced penetrance of the mutation.**

Introduction

The human transmissible spongiform encephalopathies have been traditionally classified as Creutzfeldt-Jakob disease, Gerstmann-Sträussler syndrome, and kuru. Although these disorders are transmissible, 15% of cases of Creutzfeldt-Jakob disease are familial and Gerstmann-Sträussler syndrome is usually familial.[1] Studies of genetic linkage have shown that familial Creutzfeldt-Jakob disease and Gerstmann-Sträussler syndrome are autosomal dominant conditions,[2] and several mutations in the prion protein gene on chromosome 20p have now been identified in both conditions.[3] DNA diagnosis has shown that these conditions have a larger phenotypic range than previously realised.[4] They form part of a range of diseases now more logically termed inherited prion diseases, and a new nomenclature has been proposed.[5]

A 100-fold excess incidence of Creutzfeldt-Jakob disease among Libyan Jews was previously attributed to their eating lightly cooked sheep's brain and eyeballs.[6] Both this cluster of disease[7] and another cluster in Slovakia[8] are now known to be genetic in origin and associated with a missense mutation at codon 200 of the prion protein gene causing substitution of lysine in place of glutamate at residue 200 of the prion protein (inherited prion disease (PrP lysine 200)). In contrast to the other inherited prion diseases, this variant presents clinically like classic sporadic Creutzfeldt-Jakob disease, with a rapidly progressive dementia and myoclonus; pyramidal, cerebellar, or extrapyramidal signs; periodic complexes of 1-2 cycles/second in an electroencephalogram; and a short duration of disease (less than 12 months). Histological examination uniformly shows the classic features of spongiform encephalopathies: spongiform change, astrocytic proliferation, and neuronal loss.[7] The relative phenotypic homogeneity of this disease may, however, be the result of selection bias, and now that a DNA marker is available more variability may become apparent, as is seen in the other inherited prion diseases. Homozygotes for the mutation at codon 200 do not seem to differ clinically from heterozygotes, which indicates that inherited prion disease (PrP lysine 200) is a fully dominant disorder.[7]

While screening patients suspected of having Creutzfeldt-Jakob disease and other presenile dementias for mutations in the prion protein gene we identified a British patient with inherited prion disease (PrP lysine 200), which suggests a further focus of this disorder.

Methods

DNA was extracted from peripheral blood with standard techniques. The coding sequence of the prion protein gene was amplified by the polymerase chain reaction with synthetic oligonucleotide primers flanking the open reading frame. Products of the chain reaction were fractionated by size in agarose gels to detect the presence of insertions or deletions. The products were also immobilised on nylon membranes, and the presence of known point mutations or polymorphisms was assessed by sequential hybridisation with allele specific oligonucleotides labelled with phosphorus-32 as described previously.[4]

Case reports

A 58 year old man was well until May 1989, when he noticed pain in the front of both shins radiating into the feet. He became lethargic with poor concentration and intermittent unsteadiness. He then developed a right homonymous inferior quadrantanopia. Results of computed tomography and magnetic resonance imaging were normal. He deteriorated and became agitated, intermittently confused, and unsteady with jerky movements. On examination in August he was demented and ataxic with generalised myoclonus. Routine blood investigations gave normal results; computed tomography showed mild generalised atrophy; electroencephalography showed irregular slow activity and occasional triphasic sharp transients; and cerebrospinal fluid was normal. His dementia advanced rapidly, with further impairment of vision, and the myoclonus became more prominent. He died in September 1989.

Histological examination of the brain (Professor L W Duchen) showed the characteristic changes of Creutzfeldt-Jakob disease: patchy spongiform changes in the cerebral hemispheres, particularly the occipital cortex, where there was considerable loss of nerve cells and astrocytosis; spongiform change in the basal ganglia and brain stem; and widespread fine vacuolations in the molecular layer of the cerebellar cortex with loss of Purkinje cells.

The patient's father had presented in 1976 at the age of 69 with rapidly progressive dementia associated with ataxia, myoclonus, and pseudoperiodic complexes on electrocencephalography. He died three months after the onset of symptoms. This man and his parents originated from the south of England. His father died aged 72 from malignancy, and his mother died aged 99. There was no history of neurological disease in preceding generations, nor any known Libyan Jewish or central European ancestry.

Prion Disease Group, Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, London W2 1PG
John Collinge, *Wellcome senior research fellow in clinical sciences*
Mark S Palmer, *Wellcome research fellow*
Tracy Campbell, *research assistant*
Katie C L Sidle, *research assistant*

Royal Surrey County Hospital, Guildford GU2 5XX
Desmond Carroll, *consultant neurologist*

Institute of Neurology, London WC1N 3BG
Anita Harding, *professor of clinical neurology*

Correspondence to:
Dr Collinge.

BMJ 1993;306:301-2

We also investigated a British patient of Libyan Jewish ancestry who presented with symptoms characteristic of Creutzfeldt-Jakob disease. Results of histological examination of the brain were diagnostic of the disease.

Both patients described were heterozygous for the missense mutation at codon 200 of the prion protein gene. No other pathogenic mutation (insertions or missense mutations at codons 102, 117, 178, 198, and 217) was present. Both patients were homozygous for methionine at codon 129.

Discussion

We have identified a British family and a further patient of Libyan Jewish ancestry with inherited prion disease (PrP lysine 200). The clinical presentation of those affected and the course of the disease were characteristic of sporadic Creutzfeldt-Jakob disease; the other inherited prion diseases so far described generally present as an illness similar to Gerstmann-Sträussler syndrome with a much longer duration or as atypical dementia.[4 9]

The patient reported on in detail was of British origin with no evidence of either Libyan Jewish or central European ancestry, suggesting a separate, British focus of this disease. Whether these three foci have a common origin or arise from different mutational events is unknown. Interestingly, both patients reported on were homozygous for methionine at codon 129. Homozygosity for either allele of this common polymorphism is associated with earlier onset of inherited disease and predisposes the person to sporadic Creutzfeldt-Jakob disease.[10-12] Some people from both the Libyan Jewish and Slovakian foci of inherited prion disease have been found to carry the mutation at codon 200 and yet remain unaffected at ages similar to or greater than the upper age at onset in most affected relatives.[7 8] Such incomplete penetrance has not been reported in other types of inherited prion disease. These carriers of non-penetrant or late onset genes may be heterozygous at codon 129 since heterozygosity at codon 129 might be expected to delay or protect against the onset of clinical disease. Whether heterozygosity is protective could have an important bearing on genetic counselling in this disease now that presymptomatic detection of this and other mutations in the prion protein gene is possible.[13]

We thank Dr G Stern for referring patients and the Wellcome Trust, Agricultural and Food Research Council, and Brain Research Trust for financial support.

1 Masters CL, Harris JO, Gajdusek DC, Gibbs CJ, Bernoulli C, Asher DM. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol* 1979;5:177-88.
2 Hsiao K, Baker HF, Crow TJ, Poulter M, Owen F, Terwilliger JD, *et al.* Linkage of a prion protein missense variant to Gerstmann-Sträussler syndrome. *Nature* 1989;**338**:342-5.
3 Collinge J, Palmer MS. Prion diseases. *Current Opinion in Genetics and Development* 1992;**2**:448-54.
4 Collinge J, Owen F, Poulter M, Leach M, Crow TJ, Rossor MN, *et al.* Prion dementia without characteristic pathology. *Lancet* 1990;**336**:7-9.
5 Collinge J, Prusiner SB. Terminology of prion disease. In: Prusiner SB, Collinge J, Powell J, Anderton B, eds. *Prion diseases of humans and animals.* London: Ellis Horwood, 1992:5-12.
6 Herzberg L, Herzberg BN, Gibbs CJ, Sullivan W, Amyx H, Gajdusek DC. Creutzfeldt-Jakob disease: hypothesis for high incidence in Libyan Jews in Israel. *Science* 1974;**186**:848.
7 Hsiao K, Meiner Z, Kahana E, Cass C, Kahana I, Avrahami D, *et al.* Mutation of the prion protein in Libyan Jews with Creutzfeldt-Jakob disease. *N Engl J Med* 1991;**324**:1091-7.
8 Goldfarb LG, Mitrova E, Brown P, Toh BK, Gajdusek DC. Mutation in codon 200 of scrapie amyloid protein gene in two clusters of Creutzfeldt-Jakob disease in Slovakia. *Lancet* 1990;**336**:514-5.
9 Collinge J, Palmer MS. CJD discrepancy. *Nature* 1991;**353**:802.
10 Baker HF, Poulter M, Crow TJ, Frith CD, Lofthouse R, Ridley RM, *et al.* Amino acid polymorphism in human prion protein and age at death in inherited prion disease. *Lancet* 1991;**337**:1286.
11 Palmer MS, Dryden AJ, Hughes JT, Collinge J. Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease. *Nature* 1991; **352**:340-2.
12 Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991;**337**:1441-2.
13 Collinge J, Poulter M, Davis MB, Baraitser M, Owen F, Crow TJ, *et al.* Presymptomatic detection or exclusion of prion protein gene defects in families with inherited prion diseases. *Am J Hum Genet* 1991;**49**:1351-4.

(Accepted 10 November 1992)

Association of low birth weight with β cell function in the adult first degree relatives of non-insulin dependent diabetic subjects

Joanne T E Cook, Jonathan C Levy, Renee C L Page, J Andrew G Shaw, Andrew T Hattersley, Robert C Turner

Abstract

***Objective*—To examine the relation between birth weight and β cell function in the first degree relatives of non-insulin dependent diabetic subjects.**

***Design*—Cross sectional study of 101 adults of known birth weight from 47 families which had at least one member with non-insulin dependent diabetes.**

***Subjects*—101 white adults aged mean 43 (SD 7) years.**

***Setting*—Oxfordshire, England.**

***Main outcome measures*—Glucose tolerance was measured by continuous infusion glucose tolerance test. β cell function and insulin sensitivity were calculated from the fasting plasma glucose and insulin concentrations with homeostasis model assessment. β cell function was standardised to allow for the confounding effects of age and obesity.**

***Results*—Twenty seven subjects had non-insulin dependent diabetes, 32 had impaired glucose tolerance, and 42 were normoglycaemic. Birth weight correlated with the β cell function of the complete cohort (r_s=0·29, p=0·005), the non-insulin dependent diabetic subjects (r_s=0·50, p=0·023), and the non-diabetic subjects (r_s=0·29, p=0·013). The non-insulin dependent diabetic (n=27) and the non-diabetic (n=74) subjects had similar mean (interquartile range) centile birth weight 50% (19%-91%), and 53% (30%-75%) respectively. Non-insulin dependent diabetic subjects had significantly lower β function than the non-diabetic subjects: 69% (48%-83%) *v* 97% (86%-120%), p < 0·001.**

***Conclusions*—The cause of the association between low birth weight and reduced β cell function in adult life is uncertain. Impaired β cell function in non-insulin dependent diabetic subjects was not accounted for by low birth weight, and genetic or environmental factors are likely to be necessary for development of diabetes.**

Diabetes Research Laboratories, Radcliffe Infirmary, Oxford OX2 6HE
Joanne T E Cook, *research fellow*
Jonathan C Levy, *senior registrar*
Renee C L Page, *research fellow*
J Andrew G Shaw, *research fellow*
Andrew T Hattersley, *research fellow*
Robert C Turner, *clinical reader*

BMJ 1993;**306**:302-6

Introduction

Reduced growth in fetal life and infancy has been linked with an increased risk of developing impaired glucose tolerance in adult life.[1] Increased prevalence of hypertension[2] and death rates from cardiovascular disease[3] have also been reported in subjects with low birth weights. The mechanisms which link low fetal