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Two Norwegian sisters with late onset Creutzfeldt-Jakob disease caused by the E200K mutation

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Sirs: Human prion diseases are rare, neurodegenerative disorders associated with spongiform degeneration of the central nervous system. While sporadic Creutzfeldt-Jakob disease (sCJD) is the most common form, 10–15% of cases are dominantly inherited (familial CJD, fCJD) and caused by a variety of different mutations in the human PrP gene, some of which appear to show geographical restriction. We describe clinical and pathological findings from two Norwegian sisters with late onset fCJD caused by the E200K PrP mutation, a mutation not previously reported in Scandinavia.

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Subjects

Two sisters aged (II-2) and (II-1) with a rapidly progressive dementia were admitted to our department within two days of each other (Figure 1).

II-2 had a previous diagnosis of a well treated bipolar mood disorder and was admitted aged 80 to a psychiatric hospital because of mental deterioration. Over the course of the following month she developed dysphagia, upper limb spasticity and increasing dementia and was transferred to our department for further investigation. On admission she made no verbal contact. Myoclonic jerks were visible in the right arm and painful stimuli provoked limb flexion. Spasticity was present in all four limbs and plantar reflexes were extensor.

The second sister (II-1) was 82 and had a history of uncomplicated hypertension. She was admitted to her local hospital because of a left forearm fracture. Three weeks before she had become increasingly disorientated and developed upper limb dressing apraxia and jerky upper limb movements. On admission to our department she was disoriented with myoclonic jerks seen in all extremities. There was no obvious weakness, but spasticity and hyperreflexia were found in all four extremities. Following investigation and diagnosis, she was discharged to a nursing home 8 days after admission and died 12 days later.

Family history showed that another sister died aged 66 years of a rapidly progressive disorder suspect to be CJD (II-3). She lived in another region of Norway and was not seen at our hospital, and post mortem examination was not performed. One maternal uncle and aunt died in psychiatric hospitals with a clinical picture similar to our patients, but neither was examined neurologically or post mortem (shown in hatched symbols). The eldest son of II-2 was informed of the diagnosis, but wished no further investigation.

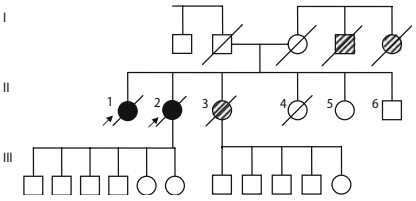

Fig. 1 Pedigree showing the two affected (II-1 and II-2) sisters with filled symbols

EEG in both showed low-voltage, 3–4 Hz activity with periodic sharp-slow wave complexes. MRI (diffusion weighted) showed symmetrically reduced diffusion in the basal ganglia. CSF examination showed normal protein and cell count, but both were positive for the 14–3–3 protein and had increased levels of S-100b. Genetic analysis showed codon 200 (G to A) mutation present on one allele (heterozygote) predicting a change in amino acid from glutamate to lysine (E200K). Both were M/M at codon 129.

Neuropathological examination performed in II-1 showed a macroscopically normal brain. Microscopically, there were moderate, focal spongiform changes in the cortex (Figure 2a), with prominent gliosis and nerve cell loss in the thalamus. Immunocytochemistry showed a strong, diffuse (synaptic) PrP staining (antibodies 3F4, KG9), especially affecting the medial part of the thalamus (Figure 2b). In other areas, the PrP staining was present, but inconsistent.

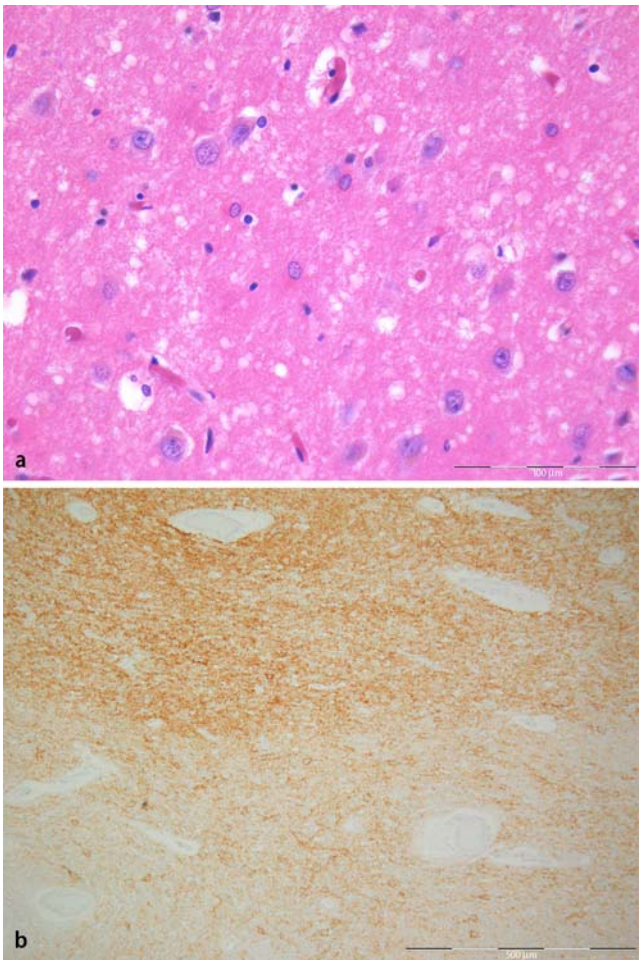

Fig. 2 **a**. Astrogliosis and moderate spongiform changes in the temporal cortex. H&E, ×40 (original magnification); the bar represents 100 μm. **b**. Accumulation of PrP in the thalamus. Anti-Prion protein (FKG), ×10 (original magnification); the bar represents 100 μm

There were moderate numbers of amyloid plaques (positive for betaA4) and scattered tau positive, neurofibrillary tangles within the cortex.

Discussion

The E200K is the commonest mutation causing fCJD [2] and was first described in a family from Poland [3, 4]. Jews of Libyan and Sephardic origin, and families from isolated communities in Slovakia and Chile show an increased prevalence of this mutation, but it has also been recorded in Germany, France, Austria, UK, Italy, Japan and USA. Microsatellite genotyping suggests that at least four independent mutational events have occurred, a factor that may explain the geographical distribution [4].

Mean age of onset in fCJD is lower than in sCJD, ranging from 39–59 years, although onset in the eighties is reported [2]. Our patients were 80 and 82 and both presented within days of each other. In addition, both were homozygous for methionine at codon 129, a factor associated with later onset of the disease [1]. Healthy codon 200 carriers have been found [1, 5], but penetrance increases with age and it is expected to be nearly complete at the age of 85 [5].

The pathological changes seen in our case are typical for CJD. The findings of amyloid plaque and neurofibrillary tangles expressing tau are consistent with the age of the patient and not necessarily indicative of an Alzheimer process. Moreover, both patients presented with a rapidly progressive dementia more consistent clinically with fCJD than Alzheimer disease.

Our cases are the first with the E200K mutation to be described in Scandinavia and show that this population is also at risk. The frequency of this mutation in our population is unknown, but the clinical and pathological similarity to sCJD particularly the late onset raises the possibility that fCJD is under reported.

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