Case report of homozygous E200D mutation of PRNP in apparently sporadic Creutzfeldt-Jakob disease

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patient with CJD and a homozygous E200D mutation, not previously described.

**Case presentation**

A 61 year old man of Chinese ethnicity with no significant past medical history presented with a 6 week history of behavioural change including aggression, poor memory, praxis problems, slurred speech and loss of balance. There was a recent history of weight loss and vomiting. On examination he appeared to understand and speak English but the content of his speech was disorganised and he appeared confused. Examination revealed normal eye movements. He was dysarthric and demonstrated ataxia in all four limbs with truncal ataxia also. There was no myoclonus, or pyramidal or extrapyramidal signs at this stage.

The patient’s father died aged 61 of a non-neurological condition, the status of the patient’s mother is not known. There were no prior diagnoses of CJD or dementia in the wider family known to the patient’s children.

Initial work-up showed normal full blood count, standard biochemical profile, B12 and folate. Paraneoplastic, VGKC and anti-NMDA antibodies were negative as were HIV, syphilis and hepatitis serology. EEG was reported as mild slowing only, with no periodic sharp wave complexes. A brain MRI showed abnormal symmetric restricted diffusion in the corpus striatum bilaterally and cortical diffusion restriction in the frontal lobes and around the parieto-occipital fissure bilaterally (Fig. 1). CSF was acellular, with normal protein and glucose. CSF Viral PCR was negative but 14–3-3 and S-100b were abnormal. A diagnosis of CJD was confirmed by a positive reaction when CSF was analysed in quadruplicate by RT-QuIC (real-time quaking induced conversion, Fig. 2). The E200D mutation was detected by bidirectional sequencing and was linked to a methionine homozygous genotype at polymorphic codon 129.

Over the course of his admission his neurological state rapidly worsened. He began to exhibit startle responses

![Fig. 1 Axial diffusion weighted image showing bilateral high signal in the striatum and cortex](image1)

![Fig. 2 CSF RT-QuIC trace of reaction seeded with 30 μl of CSF (blue) and 15 μl (orange). Results expressed as the mean of the two highest of four replicates](image2)
and multifocal myoclonus. Later he became increasingly agitated with distressing visual hallucinations which were managed with lorazepam. In the final days of his illness he became mute and bed bound with generalised spasticity. Following discussion with his family palliative care was commenced. Death was certified within 4 weeks of admission (total duration 10 weeks).

**Discussion and conclusions**

Although no post-mortem examination was done the diagnosis of this patient is almost certain. The MRI findings and RT-QuIC test are both highly specific in isolation. We are not aware of a single report in the literature of a false positive diagnosis when both of these tests are abnormal. The E200D variant has been found in the East Asian population with an allele frequency of approximately 1 in 10,000 (based on 2 occurrences in 18,394 East Asian exomes reported on gnomAD) [3]. As the variant has not been reported in the heterozygous state in any CJD patient, it is highly likely to be benign as this genotype.

The homozygous E200D genotype has never been observed in population databases. It should be extremely rare and found predominantly in families with some degree of consanguinity, which was possible but not certain in this case. Family history is a good guide to help decision making about the penetrance of novel PRNP variants, however in this case we would not expect a family history as the parents are expected to be heterozygous carriers of a benign variant. In our opinion, it seems likely that the homozygous E200D genotype was causal in this patient, the alternative possibility is of a coincidental occurrence of sCJD with a genotype of PRNP never before observed [4]. The situation seems similar to the Q212P variant of PRNP which appears to have low penetrance in the heterozygous state, but has caused an atypical early onset prion disease in the homozygous state [5].

**Abbreviations**

CJD: Creutzfeldt-Jakob disease; PRNP: Prion protein gene; VGKC: Voltage-gated potassium channel; NMDA: N-Methyl-D-aspartic acid; RT-QuIC: Real-time Quaking Induced Conversion Assay; PCR: Polymerase chain reaction

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**Authors’ contributions**

AH, HO, SM assessed the patient and/or family; TC and LD did genetic analysis; JC, SM provided supervision. AG did the RT-QuIC analysis. All authors were involved in drafting the case report. The author(s) read and approved the final manuscript.

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**Availability of data and materials**

All data is available on reasonable request to the corresponding author.

**Declarations**

**Ethics approval**

The patient was a participant in the National Prion Monitoring Cohort (UK) a prospective research study approved by NHS Research Ethics Committee.

**Consent for publication**

Written consent for the publication, including clinical details of the deceased and their family, was obtained from the next of kin.

**Competing interests**

None.

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