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Genetic prion disease: D178N with 129MV disease modifying polymorphism—a clinical phenotype

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ABSTRACT

Background Human prion diseases are a group of rare neurological diseases with a minority due to genetic mutations in the prion protein (PRNP) gene. The D178N mutation is associated with both Creutzfeldt-Jakob disease and fatal familial insomnia with the phenotype modified by a polymorphism at codon 129 with the methionine/valine (MV) polymorphism associated with atypical presentations leading to diagnostic difficulty.

Case We present a case of fatal familial insomnia secondary to a PRNP D178N mutation with 129MV disease modifying polymorphism who had no family history, normal MRI, electroencephalography (EEG), cerebrospinal fluid (CSF) and positron emission tomography findings and a negative real-time quaking-induced conversion result.

Conclusion Patients with genetic prion disease may have no known family history and normal EEG, MRI brain and CSF findings. PRNP gene testing should be considered for patients with subacute progressive neurological and autonomic dysfunction.

CASE REPORT

A Caucasian, left-handed, office worker in her early 40s, presented with a 12-month history of progressive symptoms which began with intermittent diplopia and lightheadedness with an initially normal neurological examination. Over the following months, she developed cerebellar and brainstem dysfunction with macrosaccadic oscillations, saccadic smooth pursuit and bilaterally inaccurate saccades with significant leftwards hypermetric saccades (figure 1). Worsening dysarthria, limb and truncal ataxia resulted in numerous falls and communication issues forcing her to leave her job. Focal seizures began 4 months post disease onset with speech arrest preceded by an autoscopic phenomenon where she felt 'to the right' of herself. Focal to bilateral tonic–clonic seizures occurred 7 months post disease onset with post ictal left hemiparesis and expressive dysphasia.

She was admitted 8 months into the disease course at which point strength and sensory testing was unremarkable. However, there were upper motor neuron signs of upgoing plantar reflexes, generalised hyperreflexia and lower limb spasticity in addition to severe cerebellar findings resulting in an inability to mobilise independently. While she was alert and able to hold an appropriate conversation, an Addenbrooke's cognitive assessment revealed diffuse cortical dysfunction with a total score of 73/100 9 months post disease onset. In particular, there was executive dysfunction with deficits in letter more than category fluency and poor planning with visuospatial tasks. Memory was affected with impaired delayed recall, but there was relative sparing of language domains. Autonomic dysfunction with persistent borderline tachycardia of 90–100 bpm and a postural systolic blood pressure drop of 50–60 mm Hg was noted throughout her inpatient stay. Furthermore, she had a 6 kg loss of weight over 6 months despite a normal oral intake and no symptoms of malabsorption.

Her medical history was significant for long-standing mild insomnia, not worse in the recent months, with a normal sleep–wake cycle in hospital although formal sleep studies were not performed. She also had a history of depression and anxiety since her teenage years. Family history was incomplete as the patient's father was adopted and she had lost contact with her maternal extended family. However, her parents, and her two older brothers and one older maternal half-brother, along with her four nieces and nephews, had no neurological issues.

Given the presentation with subacute ataxia, dysautonomia, cognitive dysfunction and seizures, autoimmune, atypical infectious and rapidly progressive neurodegenerative conditions were considered. MRI brain, positron emission tomography (PET) brain and cerebrospinal fluid (CSF) studies, including 14-3-3 protein, tau and real-time

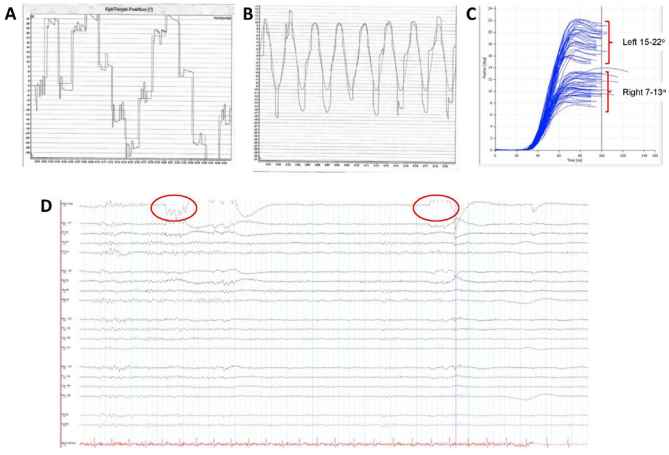

Figure 1 (A) Saccadic testing showing bilateral gaze evoked nystagmus. (B) Pursuit testing showing left sided ocular dysmetria. (C) Testing of saccadic accuracy (to 10° targets), right and left saccades overlayed showing normal rightward saccades. The leftward saccades are hypermetric, by comparison, consistent with the observed overshoot. (D) A routine interictal electroencephalography showing a normal background. The electro-oculography leads (top trace) shows direction changing nystagmus (circled).

quaking-induced conversion (RT-QuIC) were unremarkable as was testing for anti-neuronal, glutamate decarboxylase, tissue transglutaminase and antigliadin antibodies. Interictal electroencephalography (EEG) was normal and post ictal EEG showed non-specific frontal intermittent rhythmic delta activity. A small bowel biopsy did not have evidence of Whipple's disease and syphilis antibody testing was negative. Genetic testing for spinocerebellar ataxias 1, 2, 3, 6, 7 and 15, Friedreich's Ataxia and Huntington's disease was unremarkable. 24 hours urinary copper and organic and amino acid screens for inherited metabolic disorders was also negative.

Given the clinical features and rapidly progressive course, a prion protein (PRNP) genetic analysis was performed and revealed a heterogenic pathogenic variant, D178N (aspartic acid to asparagine substitution), in the PRNP gene combined with a heterozygous MV (methionine/valine) disease modifying polymorphism at codon 129 which is associated with Creutzfeldt-Jakob disease (CJD) and fatal familial insomnia (FFI).

DISCUSSION

Prions are pathogenic misfolded proteins which replicate by causing conformational change and misfolding in neighbouring proteins. This leads to an exponential increase in prion formation with consequent neuronal damage.[1] Since their discovery, several rapidly progressive human neurological diseases have been shown to be due to prions. These human prion diseases include CJD, Kuru and various genetic prion diseases.[1] In more recent times, the pathogenesis of other neurodegenerative diseases including the α-synucleinopathies and tauopathies, are also hypothesised to involve prion like spread.[2] In addition, multiple systems atrophy, which can present with rapidly progressive cerebellar and autonomic dysfunction akin to the classic human prion diseases, has been shown to be transmissible following animal inoculation with brain homogenate from deceased patients.[3] While the implications of prions in human disease is broad, this discussion will focus on the classic human prion diseases.

Human prion diseases are rare, with an annual incidence of around 1–1.5 per million people.[4 5] Genetic prion diseases account for around 8%–15% of human prion disease[1 4 5] and are classified into three clinicopathological subtypes: genetic CJD, FFI and Gerstmann-Straussler-Scheinker syndrome (GSS syndrome). There are over 30 PRNP gene mutations[1] that have been associated with human genetic prion diseases with significant genotype-phenotype variability and differing age dependent penetrance.

The D178N mutation on the PRNP gene is associated with the CJD or FFI phenotypes. The clinical presentation can be modified by a polymorphism in codon 129 of the PRNP gene—methionine homozygosity (129MM) at this position is associated with an FFI phenotype and valine homozygosity (129VV) is associated with a CJD phenotype, although significant clinical phenotypic overlap exists.[6 7]

CJD characteristically presents with a rapidly progressive cognitive impairment, cerebellar dysfunction, behavioural or psychiatric disturbance and visual changes with later development of extrapyramidal and pyramidal symptoms and myoclonus.[1] Compared with sporadic CJD, familial cases tend to present earlier with slower progression.[8] FFI typically presents with sleep disturbance, dysautonomia and visual deficits with subsequent development of extrapyramidal signs, hallucinations, disorientation and cerebellar signs and later myoclonus and pyramidal signs.[9]

Our patient presented with an atypical clinical syndrome with prominent early ataxia and less pronounced cognitive deficit and sleep disturbance in association with heterozygosity at codon 129. A D178N mutation with 129 heterozygosity (129MV) is less commonly reported but can also present clinically as CJD or FFI, typically with a longer duration of disease than the codon 129 homozygotes.[6 10 11] In terms of the clinical phenotype, a study by Krasnianski *et al* suggested that 129MV patients with FFI present with visual changes and ataxia earlier than their 129MM counterparts (6 vs 13 weeks and 9 vs 21 weeks, respectively) and tend to have a later onset of sleep disturbance (15 vs 3 weeks), hallucinations (57.5 vs 16 weeks), spatial disorientation (38.5 vs 20 weeks) and myoclonus (32 vs 16 weeks).[10] Montagna *et al* found similar phenotypic differences but also noted that the 129MV patients were more likely to suffer from tonic–clonic seizures.[11] This phenotype of FFI would align with our case's presentation with early ataxia and visual disturbance with relatively preserved cognition and sleep wake cycle.

Despite being an autosomal dominant condition, our case did not have a known family history. While a family

history may be identified in 76%–92% of patients with a D178N mutation,[7 12] not all patients will have a positive family history likely due to a combination of misdiagnosis of family members, variable age-dependent penetrance or a sporadic mutation in the index case.

While FFI patients with the D178N mutation frequently do not have a positive CSF 14-3-3 protein[7 9] and only have non-specific changes on EEG and MRI brain,[7 9] they often display thalamic and/or cortical hypometabolism, even pre-symptomatically, on [^{18}F] fluorodeoxyglucose PET scan[11 13] which our patient did not.

RT-QuIC is a relatively new technique that detects PrP^{Sc} (pathological scrapie isoform of the prion protein) in tissue and CSF[14] and has a reported specificity of 98% and a sensitivity that varies with genetic mutation.[15] In contrast, CSF 14-3-3 protein and tau have much lower specificities of 63% and 46%, respectively[15]. In FFI cases, only 7%–8.3% of patients demonstrate CSF 14-3-3 protein or tau positivity.[9 14] In comparison, RT-QuIC positivity is significantly higher but varies widely between studies from 17% in a Chinese study to 57% in a German study and 83% in a Japanese study.[14 16 17] The significant discrepancy in sensitivities between studies may reflect different populations studied with different disease modifiers or different testing protocols. While it is clear that the PRNP 129 codon affects the clinical expression of the D178N mutation, it is not certain whether it has an effect on the RT-QuIC positivity and most studies only contained 129MM homozygotes or very few 129MV heterozygotes.[14 16 17] While RT-QuIC is a promising new technique in the diagnosis of prion diseases, it may not be as useful in FFI cases with a PRNP D178N mutation and 129MV polymorphism as highlighted by our case.

This case is an uncommon presentation of a rare genetic prion disease. The patient presented without a known family history and with normal CSF, MRI and PET brain scans and interictal EEG. Promising new techniques such as RT-QuIC, which is highly sensitive in gCJD and GSS syndrome[14 16] may not be as reliable in the FFI cohort and perhaps especially so in patients with the less common codon 129MV disease modifier mutation, although further studies are required.

The variability in presentation and the insensitivity of investigations in detecting genetic prion diseases, as illustrated by this case, emphasises the importance of maintaining a high level of suspicion for these conditions. PRNP genetic testing is crucial to obtaining the correct diagnosis in this situation which, in turn, allows for the appropriate counselling and management of patients and their families.

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