## TITLE OF CASE

Gerstmann-Sträussler-Scheinker disease with atypical presentation.

## SUMMARY

**We describe a 37 year old woman who presented with progressive deafness, visual loss and ataxia. She latterly developed neuropsychiatric problems, including cognitive impairment, paranoid delusions and episodes of altered consciousness. She was found to be heterozygous for the Q212P mutation in the prion protein gene. She died over a decade after initial presentation and a diagnosis of prion disease was confirmed at post-mortem.**

## BACKGROUND

Prion diseases are a group of rare, invariably fatal, neurodegenerative conditions which can be acquired, inherited or arise sporadically. They are thought to occur due to misfolded forms of the prion protein which accumulate in the nervous system. Genetic prion disease accounts for about 10-15% of cases.[1] It results from mutations in the prion protein gene (*PRNP*) and has an autosomal dominant pattern of inheritance. Genetic prion diseases have historically been classified into three main subtypes based on clinicopathological features, namely genetic Creutzfeldt Jakob disease (CJD), fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker disease (GSS).[2] We describe an unusual presentation of genetic prion disease with clinical and neuropathological features most in keeping with GSS.

## CASE PRESENTATION

A 37 year old, previously well, woman developed progressive deafness. This was followed, 2 years later, by painless, gradual, binocular visual loss. Clinical examination revealed bilateral optic atrophy, saccadic intrusion on pursuit eye movements and bilateral sensorineural hearing loss. Her reflexes were globally brisk and she had an ataxic gait. She had a history of polydactyly. Both of her parents were alive and in good health, as was her sister. Her elder sister died previously from a glioblastoma. Her grandmother died at 92 with vascular dementia.

## INVESTIGATIONS

Initial blood tests were unremarkable, except for mildly positive anti-neutrophil cytoplasmic antibody against myeloperoxidase at 7 U/mL (normal 0-5 U/mL) and an elevated anti-cardiolipin antibody at 23 U/mL (normal 1-10 U/mL). Serum angiotensin converting enzyme (ACE), syphilis serology and paraneoplastic antibody testing were either negative or normal. Visual evoked responses were delayed. Electroretinography and fluorescein angiography were normal. MRI brain with contrast was unremarkable with no white matter or inflammatory changes. CSF analysis was normal in cell count, protein, glucose and lactate levels. There were no oligoclonal bands detected. Initial genetic tests for ataxic and mitochondrial disorders were negative, as were tests for mutations commonly associated with hearing and vision loss (Table 1). A muscle biopsy showed no evidence of mitochondrial disease. While being investigated for breathlessness, she was found to

have abnormal pulmonary function tests and a subsequent CT chest scan revealed bronchiectasis.

Table 1.

| Genetic tests |
| --- |
| Spinocerebellar Ataxia (1, 2, 3, 6, 7 & 8) |
| Friedreich's ataxia |
| MELAS |
| MERRF |
| NARP syndrome |
| Leber's hereditary optic neuropathy |
| m.1555 A>G & m.7445 A>G mutations (associated with deafness) |

## TREATMENT

In view of her positive immunology and despite the lack of inflammatory change on brain imaging and spinal fluid analysis, an immune mediated process was initially considered. Accordingly, steroids and other immunosuppressive agents were administered, but without meaningful response. She was also prescribed warfarin for a short time, which unfortunately resulted in a subdural haematoma requiring neurosurgical intervention.

## OUTCOME AND FOLLOW-UP

Her condition continued to deteriorate and it became clear that she was suffering from a neurodegenerative process. At almost ten years since the onset of her symptoms, she now had severe ataxia, increased tone in all four limbs and very brisk reflexes. Her visual acuities were nil perception of light and she had bilateral cochlear implants. She also developed neuropsychiatric problems, including cognitive impairment, paranoid delusions and episodes of altered consciousness.

Further genetic testing revealed that she was heterozygous for the Q212P mutation in the *PRNP* gene, raising the possibility of a genetic prion disease. Serial brain imaging showed mild cerebellar atrophy (Figure 1). EEG revealed non-specific features only. CSF analysis for protein 14-3-3 was not performed. Her condition rapidly worsened over the following two years. She became severely disabled, requiring care in a nursing home, where she died aged 49 from aspiration pneumonia.

Neuropathological examination demonstrated abnormal prion protein deposits confined to the cerebellar cortex and vermis (Figure 2), confirming the diagnosis of prion disease. The cerebellar cortex and dentate nucleus showed mild to moderate neuronal loss, astrocytic gliosis and microglial proliferation. No spongiform change was identified in any brain region.

## DISCUSSION

GSS was first described by three neuroscientists from a case they mutually treated in 1936.[3] The original description was of a slowly progressive cerebellar ataxia, with later onset of cognitive decline. Since then, it has been associated with a range of different

clinical features including parkinsonism, seizures, spastic paraparesis, amyotrophy, myoclonus, and dysarthria.[2] It has also been linked to numerous different mutations in the *PRNP* gene.[2]

The case we describe was heterozygous for the Q212P mutation in the *PRNP* gene. This particular gene mutation has been described in two cases previously.[4,5] Young et al (1998) describe a 60 year old male who developed progressive incoordination, dysphagia and slurred speech.[4] He died 8 years after disease onset and was cognitively intact at the time of his death. He was heterozygous for the Q212P mutation. Beck et al (2010) describe a 36 year old female who presented with unsteadiness, worsening of handwriting, and slurred speech.[5] She had global ataxia, hypertonia and hyperreflexia. She latterly developed severe cognitive impairment. Somewhat unusually she was homozygous for the Q212P mutation, which is attributed to consanguinity within the family.

Our case's initial presentation with hearing and visual impairment is somewhat unusual. These features have been reported in GSS previously,[6,7,8,9] but they are not common and, to the best of our knowledge, they have not been observed in patients with the Q212P mutation. This might suggest that the occurrence of these symptoms in association with this mutation is merely coincidental in our case. Alternatively, it may just reflect the considerable phenotypic variability that exists within genetic prion diseases, even in families with the same *PRNP* gene mutation.[10,11] The reason for this clinical heterogeneity is not well understood. Its existence makes diagnosis of GSS difficult and can lead to patients being misdiagnosed with other conditions.[2]

Diagnosis is also made more challenging by the fact that routine neurological investigations, including MRI, EEG and CSF analysis, tend to show non-specific features only and can be normal, even in advanced disease.[12] The possibility of a genetic prion disease is often only considered after identification of other family members with a similar disorder. However, as in our case, a positive family history is absent in a significant proportion of patients with genetic prion disease (12-88%, depending on the mutation).[2] Possible explanations for this include inaccurate family history data, death of family members prior to the development of disease, the occurrence of de novo mutations, or mutations with incomplete penetrance. Interestingly, Young et al (1998) mention an asymptomatic octogenarian sibling who is heterozygous for the Q212P mutation.[4] This would suggest that Q212P in its heterozygous state may have incomplete penetrance. The living family members of our case did not wish to undergo genetic testing.

Early diagnosis of prion disease is important, not only because it allows patients and their families to access much needed counselling and support, but also because of the significant public health implications. This was particularly pertinent in our case because of the history of previous neurosurgery. Once diagnosed, our case was referred to the local infection control team so that contacts could be traced and measures put in place to minimise transmission risk in accordance with guidance from the Transmissible Spongiform Encephalopathy Subgroup of the Advisory Committee on Dangerous Pathogens.[13] It is important that family members are also informed of the potential to transmit disease via dental or surgical procedures.[14]

The unusual presentation of a very rare condition, together with the absence of a positive family history, made diagnosis particularly challenging in this case. We hope that by highlighting these difficulties, others might learn from them.

**LEARNING POINTS/TAKE HOME MESSAGES**

- Genetic prion disease can be difficult to diagnose because of its clinical heterogeneity, rarity in everyday clinical practice, and lack of characteristic findings on routine neurological investigations.
- The absence of a family history of neurodegenerative disease should not dissuade clinicians from considering the possibility of a genetic prion disease.
- PRNP (prion protein gene) analysis should be considered routinely in all patients with unexplained ataxia or dementia.
- Early diagnosis of prion disease is important because of its public health implications and also because it enables patients and their families to access support services.

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**FIGURE/VIDEO CAPTIONS** ***figures should NOT be embedded in this document***

**Figure 1. MRI brain scan showing mild cerebellar atrophy.**

**Figure 2. (A) Abnormal prion protein deposits in the cerebellar cortex (12F10 antibody 20x) with multicentric plaques, typical of GSS. (B) Abnormal prion protein deposits in the cerebellar vermis (12F10 antibody 10x).**

**PATIENT'S PERSPECTIVE** ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

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