Rare disease

Ovarioleukodystrophy: report of a case with the c.338G>A (p.Arg113His) mutation on exon 3 and the c.896G>A (p.Arg299His) mutation on exon 7 of the EIF2B5 gene

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Summary

The authors present a 28-year-old lady with progressive neurological deterioration beginning in childhood. She had clinical, radiological and genetic features of ovarioleukodystrophy. This is part of the spectrum of vanishing white matter disease and the first such case reported in the UK. The authors also discuss the literature on the disease.

BACKGROUND

This is the first reported case of this condition in the UK.

CASE PRESENTATION

This 28-year-old left-handed lady was first seen at the age of six-and-a-half years, with a 6-month history of abnormal gait. Symptoms started shortly after a fall following which she developed a tendency to trip and stumble. Over the following 9 months she developed rapidly progressive incoordination and stiffness, and eventual difficulty with feeding, writing, fine motor tasks and mobility.

She was born of unrelated Caucasian parents who, along with her two younger male siblings, were completely asymptomatic. Her developmental history was normal. She had no cognitive symptoms apart from some difficulty in getting her words out. She had no convulsions.

On first examination, she had no dysmorphic features or neurocutaneous stigmata. Her eye movements were abnormal with jerky pursuits and saccadic intrusions. Limb tone was normal but coordination was impaired with an extremely ataxic gait. Romberg's test was negative and she

had no sensory deficits. Her full-scale IQ was 95; verbal IQ was 94 while performance IQ was 98; this remained stable during the course of her illness.

While there were no convulsions at presentation, she subsequently developed generalised seizures. Later in the course of her illness she developed vitiligo, hypothyroidism and Crohn's disease. She eventually developed contractures and was wheel-chair dependent for most activities by the age of 10 years.

Examination on follow-up revealed that her gait had worsened and she had developed spasticity manifested by hyperreflexia and extensor plantar responses. By the age of 21 years she had not experienced any menstrual periods; examination at that time showed minimal secondary sexual characteristics in terms of breast development and pubic hair.

INVESTIGATIONS

MRI of the brain showed frontal periventricular white matter hypointensities that progressively became more extensive with T2 signal similar to cerebrospinal fluid

Figure 1 MRI images of the patient – sagittal T1 (A), axial T2 (B) and coronal T1 (C) images.

(CSF) (figure 1). Initial visual evoked potentials (VEPs) and electroretinogram were normal but became abnormal on follow-up – VEPs became poorly formed with the pattern reversal electroretinogram showing low amplitudes suggesting retinal ganglion cell defects. Lumbar puncture showed normal CSF constituents including amino acids, lactate and folate with negative oligoclonal bands. By the time she developed seizures her electroencephalogram showed abundant slow wave activity, frequent runs of rhythmic slow waves especially anteriorly with occasional spikes and sharp waves fronto-centrally. She also demonstrated photosensitivity. Magnetic resonance spectroscopy showed altered ratio of n-acetyl aspartate to creatine of doubtful significance. Nerve conduction tests and electromyography were normal.

Her follicular phase hormone profile showed a high follicular stimulating hormone level of 128.6 U/l (normal 4–5) and low oestrogen level of 62.3 U/l (normal 3–22); this was consistent with primary ovarian failure. Pelvic ultrasound scan did not detect any ovaries and showed a small uterus with a prepubertal appearance.

She had DNA molecular analysis for eukaryotic inhibitory factor 2B5 and 2B2 (EIF2B5 and EIF2B2) genes in November 2006 to test for ovarioleukodystrophy. This confirmed that she had the c.338G>A (p.Arg113His) mutation located in exon 3 as well as the c.896G>A (p.Arg299His) mutation located in exon 7.

DIFFERENTIAL DIAGNOSIS

The clinical features in our patient were of a leukodystrophy with primary ovarian failure. Our patient had no clinical features of Turner's syndrome, fragile X syndrome or infections like herpes zoster or cytomegalovirus, which could all present with primary ovarian failure.¹ She had also not had surgery, chemotherapy or radiotherapy which all have primary ovarian failure as a side effect. Apart from ovarioleukodystrophy, the only other leukodystrophy that may present with ovarian failure is pigmentary type of orthochromatic leukodystrophy. This is adult-onset leukodystrophy typified by pigment inclusions in glial and microglial cytoplasm and associated with dementia, spasticity and seizures.²

TREATMENT

She is currently on levetiracetam for seizures, gabapentin for spasticity, mesalazine and azathioprine for Crohn's disease and thyroxine.

OUTCOME AND FOLLOW-UP

Her condition has steadily progressed.

DISCUSSION

Our patient's progressive neurological syndrome was consistent with ovarioleukodystrophy which is the association of vanishing white matter (VWM) disease with primary ovarian failure. The onset of illness following a fall is typical of patients with VWM disease which is triggered by physical trauma, illness or infection.^{3–5} Her MRI scans showed clear features of progressive loss of white matter which was replaced by CSF consistent with VWM disease.^{3–5} Genetic analysis showed her to be compound

heterozygote for ovarioleukodystrophy with two mutations that are both pathogenic for ovarioleukodystrophy.⁷

VWM disease is typically but not exclusively inherited as autosomal recessive with linkage to chromosome 3q27 and 14q24.^{6–8} The genes code for the five subunits of the eukaryotic inhibitory factor 2B (EIF2B 1–5) which functions to initiate and regulate protein synthesis.

Ovarioleukodystrophy is a rare disease with the ninth genetically confirmed case just recently reported.¹ Ovarioleukodystrophy describes cases of VWM occurring in association with primary ovarian failure. Neurological symptoms are the initial features as expected, but in some cases ovarian dysfunction precedes the onset of neurological deficits.⁹ The age of onset of neurological impairment seems to correlate with the severity of ovarian dysfunction and this might indicate a common pathogenetic mechanism underlying the dysfunction in both the nervous system and ovaries.⁹ As is typical of VWM, initial neurological development is normal but borderline cognitive impairment with frontal features are commoner than in typical VWM.^{9–10} Ovarian failure presents as pubertal arrest or failure of pubertal development.^{10–11} In keeping with a primary ovarian failure, hypothalamic-pituitary function is normal.¹⁰ Other findings reported in ovarioleukodystrophy are dysmorphic features and contractures.¹¹ Progressive urinary, speech and gait problems are also seen.⁹

The association of ovarioleukodystrophy with other autoimmune features in our patient (Crohn's disease, hypothyroidism and vitiligo) has not previously been reported. While this may be related to the disease, it is also possible that this is a coincidental finding in our patient.

A recent study has shown that patients with VWM disease who are homozygous for the pArg113His mutation have a milder disease phenotype and present late in life in adolescence or adulthood; the heterozygote states predispose to more severe phenotypes with disease manifestation in the antenatal or early infant ages.¹² Our patient is a compound heterozygote who however presented in early childhood. This intermediate severity phenotype may be a result of her female sex as females have milder phenotypes.¹²

Learning points

- ▶ Ovarioleukodystrophy is a rare disease.
- ▶ The radiological features of VWM disease are characteristic and should point to the diagnosis.
- ▶ The disease is confirmed by genetic testing.

Competing interests None.

Patient consent Obtained.

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