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CASE REPORT

Fabry disease mimicking multiple sclerosis: Lessons from two case reports

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Abstract
Fabry disease is an X-linked lysosomal storage disorder that can mimic multiple sclerosis. We present two cases of heterozygous adult women where clinical and radiological features initially suggested a diagnosis of multiple sclerosis. This led us to review the early clinical course and neurological features of Fabry disease and highlight the importance of assessing non-neurologic (systemic) symptoms when considering a diagnosis of multiple sclerosis and the need for specialist interpretation of neuroradiological findings.

1. Introduction

Fabry disease (Anderson-Fabry disease) is an X-linked lysosomal storage disorder caused by deficiency of alpha-galactosidase A. Glycosphingolipids accumulate in a variety of tissues precipitating a diverse range of clinical phenotypes (Zarate and Hopkin, 2008). Neurologic, renal, dermatologic, cardiac, ophthalmologic and gastro-intestinal manifestations of the disease are recognized, but abnormalities in a single organ system can predominate. The disease can present initially with non-specific symptoms; it is estimated that the mean delay from symptom onset to diagnosis is more than a decade (Mehta et al., 2004).

Multiple sclerosis is an important differential diagnosis for the presentation of Fabry disease. Here we discuss two cases that illustrate how failure to consider all of the clinical features and misinterpretation of radiological investigations can lead to an incorrect initial diagnosis of multiple sclerosis in patients subsequently found to have Fabry disease.

2. Case 1

This 53-year-old right-handed lady, presented with a 2-year history of patchy sensory loss and paraesthesiae. It started with an episode of paraesthesiae in the right medial forearm

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before involving the left hand. Both feet were involved in a later episode but she also described an attack of sensory loss over her right thigh with unilateral paraesthesia of the scalp. These attacks were occasionally painful and would start suddenly or progress over several days. They typically lasted for several weeks but some symptoms became chronic. In the preceding decade she had also experienced recurrent episodes of severe fatigue lasting for weeks or months. In the last year she developed persistent vertigo with nausea that was worse in the morning. There was no prior visual disturbance, focal weakness, incoordination, dysarthria, urinary symptom or rash. Past medical history included hypertension, dyslipidaemia, depression, asthma and non-alcoholic steatohepatosis. Also reported was infrequent arthralgia and long-standing fluctuating bowel habit associated with abdominal discomfort. Her son suffered from Ehlers–Danlos syndrome. Medications included fenofibrate, beta-histine, lactulose and multivitamin supplementation. There was no significant family history and she did not drink alcohol or smoke.

On examination she had a normal gait with an unremarkable cranial nerve examination, including normal hearing. There was impaired pinprick sensation on the medial forearms bilaterally and the right anterior thigh. The tone, power and coordination in the limbs were normal and tendon reflexes were present and symmetrical with down-going plantar reflexes. Cardio-respiratory, abdominal and dermatological examinations were unremarkable. The blood pressure was 133/75 mmHg.

Urinalysis and a panel of blood tests including full blood count, renal profile, bone profile, liver profile, lipid profile, glucose, creatine kinase, c-reactive protein, erythrocyte sedimentation rate, protein electrophoresis, complement levels, iron studies, thyroid function tests, cortisol, prolactin, Hepatitis B, C, Lyme and HIV serology and homocysteine levels were normal. The anti-nuclear antigen was weakly positive (1:320) with normal extractable nuclear antigens, double-stranded DNA, rheumatoid factor, cardiolipin and lupus anticoagulant assays. The anti-nuclear antigen result was not considered relevant. A chest radiograph, echocardiogram, 24-h electrocardiogram monitoring and cardiac magnetic resonance imaging (MRI) were also subsequently negative and the patient refused to undergo lumbar puncture. Initial nerve conduction studies were normal but an MRI of the brain and spinal cord revealed scattered foci of T2 signal hyperintensity throughout the subcortical and periventricular white matter of both cerebral hemispheres (see Fig. 1a–e). No lesions were demonstrated in the corpus callosum, brainstem or spinal cord.

In the context of recurrent episodes of sensory dysfunction with intermittent severe fatigue in a young woman with periventricular white matter changes on MRI a diagnosis of relapsing–remitting multiple sclerosis was suggested by the general neurologist. No disease modifying agents were initiated.

Within the coming years the clinician retired and a second neurologist followed up the patient. Nerve conduction studies were repeated after a progression of the sensory symptoms and revealed mild axonal changes in the lower limb sensory and motor nerves with loss of amplitude. The large fibre function was relatively preserved and qualitative sensory testing showed abnormalities consistent with small fibre neuropathy. On review the neuro-radiologist reported that the multiple hyperintense T2 and FLAIR areas seen on MRI are non-specific but would be more consistent with small vessel disease on the basis of their distribution within the deep white matter. In light of this and in conjunction with the abnormal nerve conduction studies the neurologist tested for Fabry disease.

Alpha-GAL gene sequencing revealed a heterozygous mutation predicted to cause substitution of arginine with glutamine at nucleotide 356 within exon 7 of alpha-galactosidase A. This confirmed a diagnosis of Fabry disease and the patient was started on Replagel (enzyme replacement therapy). This made no difference to the symptoms but there was no further worsening of disease on subsequent MRI.

3. Case 2

This 47-year-old right-handed lady presented with a long-standing history of intermittent neurologic symptoms.

At the age of 26, she awoke with a horizontal diplopia present in all directions of gaze and worse on looking to the right. She underwent an MRI and lumbar puncture at this time and was told that the results were normal. Her symptoms improved over one week without treatment but similar episodes of diplopia recurred every few years over the following decade. At the age of 33 she also suddenly developed paraesthesia on the sole and the outer aspect of the right foot that was not painful. Similar symptoms in the left foot accompanied by tinnitus, in the absence of hearing loss, developed two weeks later. These symptoms persisted but did not progress.

Aged 42, there was an episode of left leg, arm and face weakness, with slurred speech. She had felt exhausted and left work early on the preceding day and awoke the following morning with the weakness that persisted for 5 weeks. Her marked fatigue did not improve and around 4 years later she awoke with sensory loss over the right side of the body that resolved over 2 months leaving a residual numbness in the right leg.

She was seen by a general neurologist who reported that serological tests for autoimmune and inflammatory processes were negative. Cerebrospinal fluid analysis, including cell count, protein and oligoclonal bands was again normal, as were visual evoked potentials and central motor conduction times. A further MRI scan was then reported by a radiologist to show several foci of high signal on the STIR and T2-weighted sequences within the brainstem, adjacent to the right lateral ventricle and within the left thalamus and internal capsule. Two lesions were new compared to previous images and were reported as ‘strongly suggestive of multiple sclerosis’. On this basis and with the history of recurrent episodes of central neurological dysfunction a diagnosis of multiple sclerosis was made. Disease-modifying treatments were discussed but not initiated and the patient was referred to the MS specialist nurse clinic for newly diagnosed patients.

After a further recurrence of diplopia lasting around 2 weeks and an unsuccessful course of oral steroids the general practitioner referred her for a second opinion. At the time of her review she was mostly troubled by fatigue and had no other systemic symptoms or rashes. The past medical history included depression and migraine and she was taking propranolol and sertraline. She was an ex-smoker with a 20-pack year history and had a brother with decreased sensation in his hands and cardiomegaly, the cause of which was unclear at the time. The remaining family history was non-contributory.