CASE REPORT

Progressive external ophthalmoplegia (PEO) due to a mutation in the *C10orf2* (PEO1) gene mimicking a myasthenic crisis

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SUMMARY

We described a case of a patient with autosomal dominant progressive external ophthalmoplegia (PEO) who presented with the acute onset dysphagia, quadriparesis, ptosis and respiratory insufficiency following a cardiac procedure and mimicking a myasthenic crisis. A pathogenic mutation in the *C10orf2* (PEO1) gene was confirmed. The unusual presentation of our patient contributes to expand the clinical phenotype of PEO1 mutations and reinforces the need to consider mitochondrial myopathy as differential diagnosis of myasthenia gravis even in the case of acute onset symptoms.

BACKGROUND

Chronic progressive external ophthalmoplegia (PEO) is a mitochondrial disorder characterised by ptosis, ophthalmoparesis and proximal limb weakness. The most frequent molecular defect is a single large-scale mitochondrial DNA (mtDNA) deletion,[1] which is associated with a benign course and without significant risk of inheritance for other family members. On the contrary, autosomal-dominant progressive external ophthalmoplegia (adPEO) is due to mutations in the nuclear DNA genome and it usually manifests as more heterogeneous phenotypes that range from isolated PEO to multisystem disorders.[2–4] *C10orf2* (PEO1) gene mutations are the more frequent cause of adPEO.[2 5]

We presented the clinical and molecular features of an individual with adPEO, carrier of a mutation in the *PEO1* gene who presented with acute generalised weakness, swallowing difficulties and respiratory failure mimicking a myasthenic crisis. The peculiar clinical presentation expands the phenotype observed in PEO1 gene mutations.

CASE PRESENTATION

A 64-year-old man was referred to our institution because of acute onset quadriparesis and respiratory insufficiency following a cardiac pacemaker implantation. His personal history was irrelevant until age 40 when he had developed progressive bilateral ptosis and ophthalmoparesis without diplopia. He had remained without any additional symptoms until he was 64-year-old when he was admitted to a local hospital because of atrioventricular block<two words>. Cardiac pacemaker implantation was performed according to a standard procedure and during the first hours of post-operation he developed generalised weakness, inability to swallow, respiratory difficulties requiring referral to our tertiary institution.

At admission he presented with complete bilateral ptosis, complete bilateral ophthalmoplegia, neck weakness and severe quadriparesis. His respiratory function worsened over the following days requiring mechanical ventilation.

Because a diagnosis of myasthenic crisis was suspected, treatment with plasmapheresis, intravenous neostigmine and oral prednisone was started resulting in mild improvement of limb strength.

A subsequent review of his familial history revealed the presence of ptosis, limb weakness and sudden death in the patient's mother, sister and nephew (figure 1). Considering this data, the diagnosis of autoimmune myasthenia was discarded and a muscle biopsy was recommended.

INVESTIGATIONS

Serum lactic acid concentration was mildly increased and antibodies to acetylcholine receptors were absent.

Videofluoroscopic examination of swallowing function showed laryngeal penetration of barium. A muscle biopsy showed ragged red, cytochrome *c* oxidase-deficient fibres which were increased in number, size and accumulated in subsarcolemmal localisation.

Electromyography with repetitive nerve stimulation studies were not performed due to the risk of interference with the pacemaker.

We obtained the complete genomic sequence of mitochondrial DNA applying parallel massive pyrosequencing, as described elsewhere.[6] No mitochondrial DNA variation of pathogenic significance was identified. *C10orf2* sequencing revealed the heterozygous point mutation c.1433 G>T which results in F478C change at the protein level. p.F478C has previously been reported as causing adPEO[7] and bioinformatic analysis suggests it is likely to be deleterious.

DIFFERENTIAL DIAGNOSIS

PEO must be differentiated from other disorders associated with ophthalmoplegia, specially myasthenia gravis, oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy and myotonic dystrophy type 1.[8]

In this case, the acute and generalised compromise of muscle function and a partial response to neostigmine led to consider the diagnosis of myasthenic crisis. Consequently, treatment with plasmapheresis

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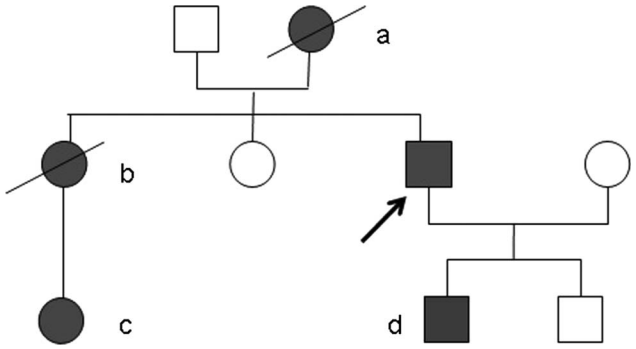

Figure 1 Family pedigree showing affected family members: (A) eyelid ptosis, external ophthalmoparesis and sudden death (B) eyelid ptosis, external ophthalmoparesis, limb weakness and sudden death (C and D) eyelid ptosis, external ophthalmoparesis.

was performed. However, the occurrence of atrioventricular conduction block and the existence of other affected members in the family were the key to revaluate the diagnosis and consider the PEO spectrum.[5]

TREATMENT

In patients with mitochondrial PEO complete neurological, cardiological, ophthalmological and endocrinological evaluation are needed to establish the extent of the disease, search for diabetes, conduction block, sensorineural hearing loss and pigmentary retinopathy.[9] Treatment of manifestations is appropriate with cochlear implants and hearing aids for neurosensory hearing loss and placement of cardiac pacemaker in individuals with a cardiac conduction block to reduce the risk of sudden death.[10 11]

OUTCOME AND FOLLOW-UP

During follow-up the patient persisted with severe quadriparesis, ophthalmoplegia and ptosis. He was confined to bed and unable to communicate or swallow effectively requiring a gastrostomy feeding tube.

After the diagnosis, his son developed ptosis and ophthalmoplegia. Father to son transmission may be observed in Autosomal Dominant traits. Furthermore, considering that: (A) this disorder has been expressed in all generations; (B) it has been transmitted to the next generation through either parent (see figure 1) and (C) sons and daughters have an equal chance of being affected, an autosomal dominant mode of inheritance can be confidently supported.

DISCUSSION

We identified a *C10orf2* heterozygous mutation causing adPEO in a patient presenting a very unusual manifestation. Pathogenic mutations in this gene are responsible for multiple deletions in mitochondrial DNA and have been associated with different clinical presentations.[5] The majority of adult-onset cases present with autosomal-dominant PEO characterised by ptosis and ophthalmoparesis with frequent involvement of other organs (CPEO plus). Another patient with adPEO was reported by Berardo *et al*[7] carrying the same (p.F478C) mutation supporting its pathogenic role.

Recently, Fratter *et al* contributed to a better characterisation of the *C10orf2*-linked adPEO spectrum describing the clinical and molecular features of 33 patients with this condition. Only 11 patients in Fratter's cohort had proximal muscle weakness and, as opposed to our patient, in all cases it was mild and minimally disabling. Moreover, although myopathy of respiratory muscles leading to respiratory insufficiency has occasionally been reported in *C10orf2* mutations,[12] our case is unique for an acute presentation that mimicked a myasthenic crisis.

Noteworthy, our patient showed an acute deterioration after a cardiac procedure. We believe that this could be explained by drug interference, for example, propofol, in mitochondrial function. It has been previously reported that certain drugs may lead to adverse reactions and side effects in patients with mitochondrial diseases.[13] So far, it cannot be predicted if such type of drugs may lead to an adverse reaction in a single patient. The fact that other patients[7] with the same mutation manifested a significantly milder phenotype may suggest that environment agents may contribute to a more severe phenotype. More evidence is needed to discriminate if patients with PEO due to defects leading to multiple mtDNA deletions are more susceptible to toxic agents than patients with a single PEO deletion.

In conclusion, this case provides important information about the clinical phenotype, prognosis and molecular background in adPEO due to the *C10orf2* mutation. We propose that a mutation in this gene should be considered in individuals with acute generalised weakness and respiratory failure, particularly if there is a family history of extraocular muscle weakness.

Learning points

- Progressive external ophthalmoplegia (PEO), and particularly autosomal-dominant progressive external ophthalmoplegia (adPEO), should be considered as a differential diagnosis of myasthenic crisis.
- A more severe phenotype in a patient with PEO may suggest a mutation in nuclear DNA genome instead of a mitochondrial DNA deletion.
- Mitochondrial-toxic agents may lead to acute exacerbations in adPEO and should be avoided in the management of these patients.
- Molecular diagnosis in case of adPEO is required for genetic counselling.
- Classic PEO due to mitochondrial DNA deletion has very low risk of recurrence in offspring of affected women and no risk of recurrence in offspring of affected men. By contrast, adPEO has a 50% risk of recurrence in offspring of affected women and men.

Contributors All authors were involved in the patient's diagnostic approach and manuscript preparation.

Competing interests None.

Patient consent Obtained.

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