Adult-onset mitochondrial myopathy

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Summary: Mitochondrial diseases are polymorphic entities which may affect many organs and systems. Skeletal muscle involvement is frequent in the context of systemic mitochondrial disease, but adult-onset pure mitochondrial myopathy appears to be rare.

We report 3 patients with progressive skeletal mitochondrial myopathy starting in adult age. In all cases, the proximal myopathy was the only clinical feature. Mitochondrial pathology was confirmed by evidence of ragged-red fibres in muscle histochemistry, an abnormal mitochondrial morphology in electron microscopy and by exclusion of other underlying diseases. No deletions of mitochondrial DNA were found.

We emphasize the need to look for a mitochondrial disorder in some non-specific myopathies starting in adult life.

Introduction

Mitochondrial diseases consist of various polymorphic pathological entities which usually involve many organs and systems. They represent a wide clinical, pathological and biochemical spectrum.1 Involvement of skeletal and ocular muscles, central and peripheral nervous system, liver, heart, blood vessels, retina and endocrine system has been described.2-4 Although they are considered diseases of genetic origin,5 and maternal transmission has been suspected in some cases,6 no clear hereditary pattern has been established.7 Recently, mitochondrial DNA genomic deletions have been described and correlated with biochemical defects.8,9

Muscle involvement in mitochondrial diseases is frequent,2 usually affecting patients under 20 years of age and clinically progressive. These patients usually have life-threatening multisystemic involvement and a poor prognosis.10

A different pattern of muscle involvement in mitochondrial diseases has also been described, in adult patients over 40 years of age who present a chronic and slowly progressive myopathy as the only clinical feature of their mitochondrial disorder11 or an additional feature.12 This is an infrequent condition, clearly different from classical mitochondrial myopathy in young patients.

These patients usually have proximal muscle weakness and myalgia. Muscle atrophy of the affected areas is frequent. The whole clinical picture is not specific and there is a wide differential diagnosis including inflammatory, toxic, neoplastic, metabolic and endocrine myopathies. Skeletal muscle studies providing evidence of mitochondrial pathology give the diagnosis.13

We describe 3 patients finally diagnosed as having adult-onset mitochondrial myopathy by skeletal muscle biopsy in whom progressive proximal myopathy was the only clinical feature.

Case reports

Case 1

A 67 year old woman with a family history of long-standing bilateral ptosis in her mother and one brother had observed progressive ptosis for the past 10 years. Afterwards, she also noticed progressive limb weakness, dysphagia and occasional diplopia.

Physical examination revealed bilateral ptosis with vertical and horizontal restriction of ocular motility and proximal limb muscle atrophy. Muscle strength in the arms was IV/V proximal and V/V distal (according to the MRC scale). Deep tendon reflexes were diminished.

Biochemical blood studies including creatine kinase, aspartate aminotransferase, lactic dehydrogenase, and aldolase were normal. There was no
evidence of lactic acidosis. Electromyography revealed slight nerve motor conduction slowness and a clear myopathic pattern. The electromyographical studies for myasthenia were negative and acetylcholine receptor antibodies were not detected. Endocrine studies including thyroid hormones and cortisol were also normal.

Case 2

An 80 year old man without a remarkable family history developed myalgia and progressive weakness of his pelvic girdle muscles over 6 months. Physical examination and blood biochemical analysis were normal. He was clinically diagnosed as having polymyalgia rheumatica and put on 20 mg/day of prednisone. Six months later, the patient was no better and was referred to us. He showed clear proximal limb muscle atrophy. Muscle strength was IV-/V proximal and V/V distal. Usual biochemical blood analysis and muscle enzymes were normal as well as thyroid hormones and cortisol. No evidence of lactic acidosis was found. An electromyographic study showed a myopathic pattern.

Case 3

A 78 year old woman without a remarkable family history developed intermittent diffuse myalgia and moderate but slowly progressive proximal weakness, involving mainly the pelvic girdle. Muscle strength was IV/V proximal in pelvic muscle, but normal distally. Deep tendon reflexes were normal. Muscle enzymes as well as endocrine studies were within the normal range. An electromyographical study revealed a myopathic pattern in clinically affected muscles.

Muscle studies

Open left deltoid muscle biopsy was performed in all 3 cases. Processing included 8 µm cryostat sections and routine histochemical stainings. A piece of muscle was fixed in glutaraldehyde and included in durecopan resin for semi-thin and ultrathin electron microscopy studies.

Case 1: trichromic cryostat stains revealed a large quantity of ragged red fibres (5–6% in a 100 × magnification field) involving predominantly type I fibres, a clear variability of fibre size and type II selective atrophy (Figure 1). Electron microscopy confirmed the mitochondrial abnormal pattern with changes on size and morphology of mitochondria and cristae, and osmiophilic mitochondrial inclusions. No biochemical muscle studies were available in this case.

Figure 1 Muscle deltoid biopsy. Modified Gomory trichrome staining (original magnification × 400). Two ragged red fibres are clearly seen in this field.

Case 2: trichromic cryostat stains also revealed a large quantity of ragged red fibres (6% in a 100 × magnification field), random fibre atrophy, and some fibre type grouping. Electron microscopy revealed clear changes of size and morphology of mitochondrial cristae. No muscle biochemical studies were available in this case.

In case 3, 5% of ragged red fibres were found in trichromial stains in a 100 × power field. NADH reaction revealed an abnormal oxidative pattern. Electron microscopy also revealed subsarcolemmic mitochondrial clusters with abnormal and bizarre morphology (Figure 2). Some of these mitochondria were giant, with cristae loss and osmiophilic paracrystalline inclusions. State 3 respiratory activity, respiratory control ratio and ADP/O index of these muscle mitochondria were normal on polarographic studies with different substrates.

Figure 2 Muscle deltoid biopsy. Electron microscopy (original magnification × 15,000). We can observe subsarcolemmal deposition of abnormal mitochondria. The mitochondria appear rounded with loss of cristae and with occasional osmiophilic inclusions.
A mitochondrial DNA study was performed in all cases by established methods. No deletions of mitochondrial DNA were found.

Discussion

Munsat et al. first proposed in 1967 the term mitochondrial myopathy to describe many different clinical diseases presenting with abnormal pathological muscle mitochondria. Some years later, Shibasaki et al. described a 60 year old man with a progressive proximal myopathy as the first case of adult-onset pure mitochondrial myopathy. Since then, many different clinical patterns of mitochondrial disease have been reported, the muscle pathology being a frequent finding in the context of multisystem involvement, such as in Kearns–Sayre syndrome. However, other clinical reports referring to pure skeletal or ocular muscle disease starting in adults are rare. Our cases presented with a pure proximal myopathy, without clinical evidence of involvement of other organs. Case 1 also had ptosis and ophthalmoplegia as a further manifestation of skeletal muscle involvement. Criteria used for diagnosis of mitochondrial myopathy were evidence of almost 5% of ragged red fibres in a 100 × magnification field in the muscle biopsy, with an abnormal pattern or morphology of mitochondria in the electron microscopic studies in a patient with a clinical appropriate phenotype in whom other underlying muscle diseases were excluded. For the majority of authors, the pathological muscle findings described here are specific of mitochondrial disease. Lack of deletions of mitochondrial DNA in these patients is in concordance with previous clinical series. Only some patients with Kearns–Sayre syndrome and external ophthalmoplegia show these features. Ragged red muscle have been described in many circumstances or even in otherwise normal muscle biopsies. For that reason, a very careful clinical and biological work-up must be done in all patients with this finding to rule out inflammatory, autoimmune, toxic, metabolic, neoplastic and endocrine myopathies. Probably, in the near future, research in biochemical and neuromuscular fields will allow other criteria for the diagnosis of the mitochondrial diseases in both young and adult-onset types. These criteria will probably be based on biochemical muscle findings, although for the moment no clear pathological–biochemical relationship has been described.

Because of the different clinical patterns seen, we presume there are also different pathogenetic mechanisms. Some authors suppose a toxic or infectious origin. In one of our cases, a clear family history was obtained, suggesting a genetic origin. It could be a mutation of mitochondrial DNA or the lack of control of nuclear DNA on mitochondrial function due to ageing and decrease of protein synthesis regulation.

The interest in reporting these 3 cases is to emphasize the possibility of a muscle mitochondrial disorder as the cause of some adult-onset myopathies. The potential treatment and the reversibility of a few mitochondrial abnormalities is another reason to encourage clinicians and researchers in the identification and in the better characterization of such diseases.

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References

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