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Distal myopathy with tubular aggregates: a new phenotype associated with multiple deletions in mitochondrial DNA?

Multiple deletions of mitochondrial DNA (mtDNA) are recognised in association with a number of clinical phenotypes, including chronic progressive external ophthalmoplegia (CPEO) and myoneurogastrointestinal encephalopathy (MNGIE). The abnormality may be sporadic or inherited in a recessive or autosomal dominant fashion and is generally considered to be secondary to an abnormality of nuclear DNA.[1]

Tubular aggregates (TA) are histological bodies consisting of densely packed, double walled tubules 50–70 nm in diameter, originating from the lateral sacs of the sarcoplasmic reticulum.[2] Their functional significance remains controversial: in a small group of progressive myopathies, TA form the dominant or even the sole structural abnormality, but more commonly they appear as an accessory histopathological feature in a wide variety of neuromuscular disorders, both inherited and acquired. The strongest association appears to be with periodic paralysis and myotonic disorders, but the finding is by no means consistent, and TA are never more than a minor element of the overall myopathology.[2]

To the best of our knowledge, an isolated late onset distal myopathy has never been described in association with multiple mtDNA deletions, and high densities of TA have not previously been described in association with mitochondrial myopathy. The present case therefore illustrates two original clinicopathological observations and may be a novel clinical phenotype.

A 73 year old man presented with a history of diffuse muscular pain and progressive gait disturbance over two years. The pain, which preceded the gait disturbance, affected his lower back, buttocks, and upper thighs, was maximal when he was supine, and was not exercise induced. He later noticed that his walking was becoming slower, and then he developed a tendency to drag his feet and trip over. Subsequently, arm elevation and fine finger movements became mildly affected. There were no symptoms of bulbar or sphincter dysfunction. Over the previous five years he had begun to suffer from mild angina and was treated successfully with metoprolol, but his medical history was otherwise unremarkable—specifically, there was no history of gastrointestinal problems. There was no family history of neurological illness.

On examination, cranial nerves were normal, with no ophthalmoplegia or facial weakness. There was symmetrical weakness of proximal and distal muscles in all four limbs, which was most pronounced distally, especially affecting ankle dorsiflexion (graded 3/5), giving rise to a pronounced foot-drop gait. The small hand muscles were wasted but no fasciculations were seen. All deep tendon reflexes were brisk but symmetrical and the toes downgoing.

Preliminary investigation found that the full blood count, erythrocyte sedimentation rate, renal, liver, and thyroid function, serum glucose and calcium, creatine kinase, vitamin

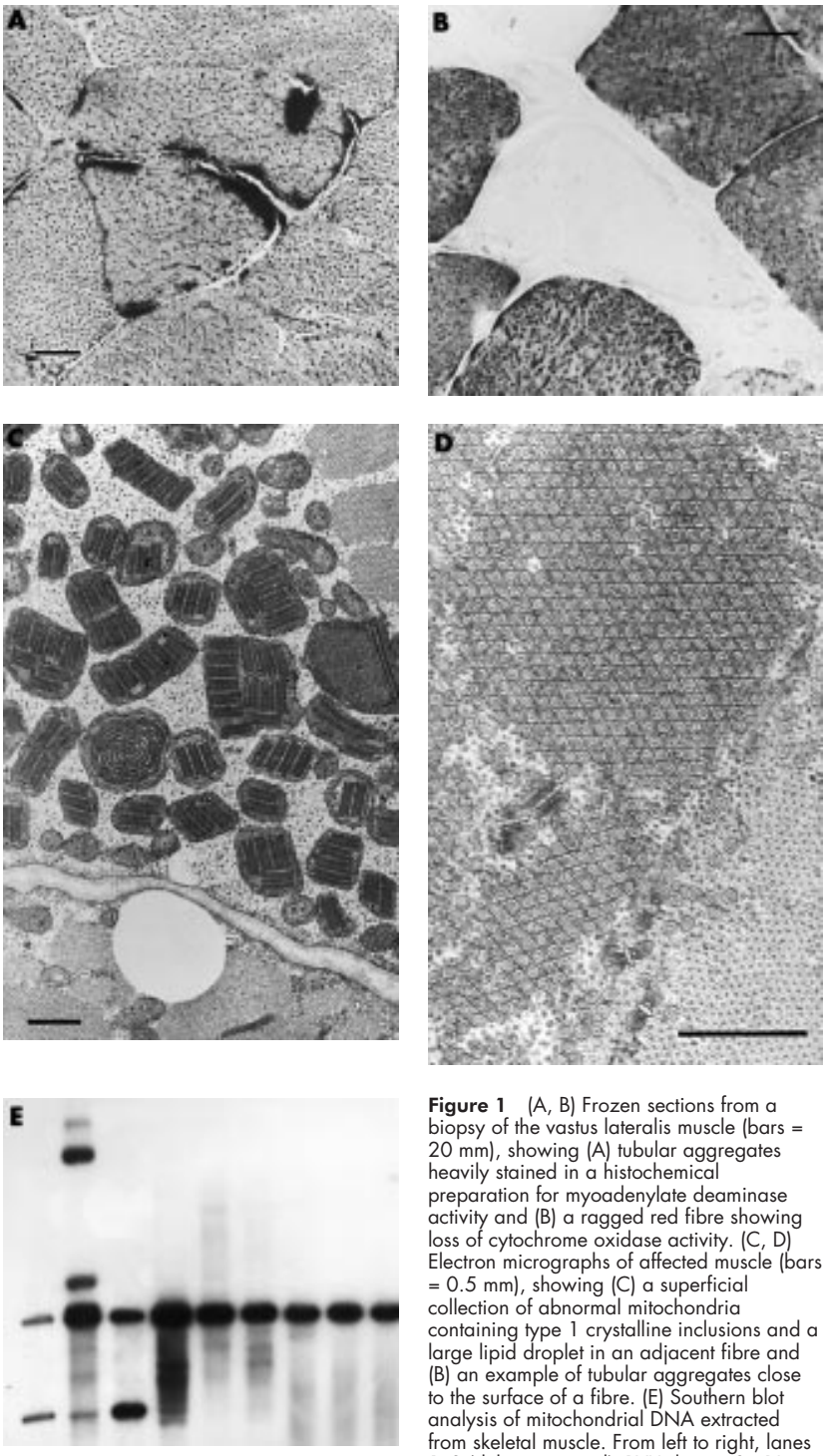

Figure 1 (A, B) Frozen sections from a biopsy of the vastus lateralis muscle (bars = 20 mm), showing (A) tubular aggregates heavily stained in a histochemical preparation for myoadenylate deaminase activity and (B) a ragged red fibre showing loss of cytochrome oxidase activity. (C, D) Electron micrographs of affected muscle (bars = 0.5 mm), showing (C) a superficial collection of abnormal mitochondria containing type 1 crystalline inclusions and a large lipid droplet in an adjacent fibre and (B) an example of tubular aggregates close to the surface of a fibre. (E) Southern blot analysis of mitochondrial DNA extracted from skeletal muscle. From left to right, lanes 1–3 (deletion control): PVU digest, *Sna*BI digest, *Bam*HI digest; lanes 4–6 (patient): PVU digest, *Sna*BI digest, *Bam*HI digest; lanes 7–9 (normal control): PVU digest, *Sna*BI digest, *Bam*HI digest.

B12 and red cell folate, immunoglobulins and electrophoresis, prostate specific antigen, an autoimmune screen, antineuronal antibodies, and antibodies against voltage gated calcium and potassium channels were all normal or negative. A chest radiograph and echocardiogram were both normal. Magnetic resonance imaging of the brain, spinal cord, lumbar roots, and plexus was normal. Cerebrospinal fluid examination showed an increased protein concentration (0.97 g/l, range 0.15–0.45), but other constituents were normal and oligoclonal bands absent.

Routine sensory and motor nerve conduction studies of the upper and lower limbs did not find any evidence for a peripheral neuropathy. All F latencies were within normal limits. Repetitive stimulation of the right median nerve showed no significant amplitude decrement. Electromyographic sampling of distal lower limb muscles showed an excess of low amplitude polyphasic units of brief duration and a full interference pattern (< 1 mV) during a weak contraction. The same features were noted in an upper limb forearm muscle. Other muscles sampled also showed similar though less pronounced changes suggesting a patchy but diffuse myopathic process.

A therapeutic trial of corticosteroids (prednisolone 60 mg/day) resulted in a significant reduction in pain but no change in the weakness and walking difficulties. Pain returned when the prednisolone was withdrawn after two months. Some months later a left vastus lateralis muscle biopsy was performed and showed changes of mitochondrial pathology (1% ragged red and 8% cytochrome oxidase negative fibres) together with accumulations of neutral lipid and TA in 12% of fibres (fig 1A–D). Muscle respiratory chain analysis was consistent with a reduction in complex IV activity. Serum lactate concentration was increased at 3.12 mmol/l (range 0.5–1.65), with a lactate to pyruvate ratio of 29 (range 10–20). mtDNA analysis by Southern blotting was positive for multiple deletions (fig 1E).

Mitochondrial myopathy is characterised by the presence on muscle biopsy of ragged red fibres and abnormal mitochondria with paracrystalline inclusions. The cardinal clinical features consist of proximal muscle weakness and exercise intolerance, which may be accompanied by a variable degree of resting or exercise induced lactic acidosis. Neither pain nor distal weakness is a typical feature.

From a genetic perspective, the disorder may be related to a single mtDNA deletion, a point mutation, or multiple mtDNA deletions probably secondary to defects in nuclear genes critical to intergenomic communication.[1] This last group has shown great clinical heterogeneity: to date, the phenotypes described are an autosomal dominant form of (CPEO),[3] disorders of neuromuscular function and intestinal motility (MNGIE) associated with mutations in the thymidine phosphorylase gene,[4] progressive encephalomyopathy,[5] skeletal and cardiac myopathy in a patient with consanguineous parents,[6] and a familial syndrome of myopathy and parkinsonism in Sephardic Jews.[7]

Our patient's clinical presentation was characterised by late onset, slowly progressive myalgia without exercise induced cramps and a predominantly distal pattern of muscle weakness in the absence of gastrointestinal disturbance, cardiomyopathy, or disturbances of eye movement. In the presence of multiple mtDNA deletions, such a combination of clinical findings constitutes a novel phenotype.

The pattern of abnormality on his muscle biopsy was also of interest: the density of TA seen was in keeping with a diagnosis of "myopathy with TA",[2] yet the finding was clearly accompanied by a second pathological process (mitochondrial myopathy). Although multiple mtDNA mutations are sometimes seen in inclusion body myositis (a condition that shares many of the clinical features of the present case and may be missed histologically), it is difficult to provide an independent explanation for TA (the known drug associations do not include prednisolone or metoprolol), suggesting that the two pathologies may be in some way linked. Animal models have suggested that structural changes in the sarcoplasmic reticulum in affected muscle may be the end product of a range of functional abnormalities, including genetic anomalies, hormonal influences, and intracellular calcium ion regulation.[8] The role of ATP in controlling the calcium release channel of sarcoplasmic reticulum and the importance of mitochondria to cellular calcium signalling may suggest a link between the two pathologies.

This case adds to the growing list of clinical phenotypes associated with multiple mtDNA deletions. Moreover, the clinical features cannot easily be accommodated into any of the recognised subtypes of either mitochondrial or TA myopathy, suggesting that the classification of these conditions is incomplete. Finally, although the co-occurrence of two extremely rare conditions may be random, it seems more likely that the coincidence of TA with mitochondrial dysfunction provides a clue to the functional significance of these poorly understood histological bodies.

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Topiramate induced manic episode

Topiramate is a novel antiepileptic drug (AED) that has been in use for several years, mainly as add on treatment for partial and secondarily generalising seizures that are otherwise refractory to treatment.[1] Despite the good efficacy of topiramate, dizziness, ataxia, double vision, and somnolence have been noted as the main side effects. While older AEDs such as carbamazepine and sodium valproate are now routinely used for the treatment of mood disorders, recent studies suggest that novel AEDs, such as lamotrigine, gabapentin, tiagabine, and topiramate, have mood stabilising efficacy as well.[2] Exacerbation of psychotic symptoms has been reported but mostly in patients with pre-existing psychiatric disorders.[3 4] However, more patients than previously assumed may be affected by a broader range of side effects. We present a case of a patient taking topiramate who presented with an acute manic episode, lacking any previous history of affective disorders or episodes.

A 57 year old woman with a history of temporal lobe epilepsy was referred to our hospital by her local general practitioner due to suicidal ideation and the intention of killing her husband. In the preceding weeks, her relatives had noted a progressive change of personality with verbal attacks, lack of sleep, expensive purchases, and the recurrent desire to give her house to a distant acquaintance. On admission, she was fully oriented, agitated, restless, suspicious, and laughing inappropriately. She refused any medical help and in turn was convinced that her spouse was mentally ill and needed urgent medical advice. Her speech was hasty, with pompous, overbearing, and self important utterances, obvious "flight of ideas", and high "pressure of thoughts". She boastfully admitted ideas about a relationship with a younger man and her own irresistible attractiveness, and threatened the psychiatrist verbally and physically during the initial interview. She had partially lost coherence of thought and she was "talking past the point". She denied hearing voices or other hallucinations; nevertheless, it was impossible to complete a full psychiatric interview. At this time, the patient scored 37 out of 44 points on the young mania rating scale (YMRS).

The patient had a well documented history of seizures (including video encephalographic monitoring), which had started 18 years previously with 7–10 attacks per month (on average) and were classified as single and complex partial seizures without secondary generalisation. Neuropsychological testing showed a pattern of medial temporal lobe dysfunction, and brain magnetic resonance imaging showed left hippocampal sclerosis. According to both the referring physician and her relatives, she had never experienced any psychiatric symptoms in her life. Apart from hypertension there was no relevant medical or neurological history. Reviewing her medication, we noted that 12 weeks before her admission topiramate had been added to her antiepileptic regimen of tiagabine (40 mg/day for more than one year), beginning with