Tubular aggregate myopathy with abnormal pupils and skeletal deformities

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A patient is described with a novel syndrome characterised by progressive muscular weakness, contractures, pupillary muscle dysfunction, and skeletal deformity. The main myopathological feature was an abundance of tubular aggregates in both type I and type II muscle fibres. Myopathies in which tubular aggregates are the defining feature are rare and either present with progressive muscle weakness or exercise induced myalgia. Tubular aggregate myopathy with symptomatic smooth muscle dysfunction and skeletal deformities has not been described before.

Examination
General physical examination revealed a tall man (1.96 m) with a mild saddle nose deformity and pectus excavatum (fig 1). There were no clinical features of a connective tissue disease. He could tandem walk with difficulty but was unable to walk on tiptoes or on his heels. He was unable to stand from sitting without using his arms.

His uncorrected visual acuity was 6/6 in both eyes. Both pupils were circular, regular in outline, equal in size, but markedly constricted (1.5 mm) in the dark. On slit lamp examination, there were small but brisk responses to light and near. There was no pupillotonia, no segmental palsy, and no light-near dissociation. Instillation of tropicamide 1% plus phenylephrine 10% dilated the pupils to only 2.5 mm. The fundi and external ocular movements were normal.

There was a minor degree of wasting of the temporalis and masseter muscles on both sides. There was symmetrical wasting and weakness of the sternomastoid and trapezius muscles, with grade 4/5 weakness on the MRC scale. Examination of the cranial nerves, including the muscles of facial expression and the tongue, was otherwise unremarkable. Contractures affecting the neck extensors limited neck flexion.

There was symmetrical wasting of both proximal and distal muscles in the upper and lower limbs, particularly involving the periscapular muscles, the flexor compartment of the forearms, and the quadriceps femori. There were contractures that limited finger and wrist extension. There was symmetrical proximal and distal weakness throughout the upper and lower limbs of grade 4/5 and 4+/5 on the MRC scale. The biceps, triceps, supinator, and ankle reflexes were absent on both sides. The knee jerks were absent on the right and present with reinforcement on the left. Planter reflexes were flexor. Sensory examination was normal.
Tubular aggregate myopathy

Investigations

Routine biochemistry was normal, including tests of renal, liver, and thyroid function, and plasma calcium and phosphate. The erythrocyte sedimentation rate was 7 mm/hour (normal range 1–20) and C reactive protein was 15.3 mg/l (normal range < 10). Serum creatine kinase ranged between 376 and 3854 IU/l (normal range < 150). A random venous lactate concentration was normal. Screening for autoantibodies indicated neither succinic dehydrogenase (SDH) nor cytochrome oxidase (COX) activity (fig 2). There was a considerable increase in interstitial connective tissue. Split fibres were present, internal nuclei were frequent, and there were small numbers of actively regenerating fibres. No inflammation or fibre necrosis was seen. Electron microscopy confirmed the presence of tubular aggregates (fig 2).

DISCUSSION

We describe a patient who had a novel myopathic syndrome with tubular aggregates. The distinctive features in our case are prominent contractures, skeletal deformity, and abnormal pupils.

While there are many causes of tubular aggregates (for example, periodic paralysis, paramyotonia congenita, familial myasthenia, gyrate atrophy of the retina and choroid, and metabolic insults14–16), we can exclude all these in our patient on the basis of the clinical history and routine investigations. In addition, there is a group of patients with prominent symptoms of exercise induced myalgia and fatigue in whom the principal pathological finding is numerous intramuscular tubular aggregates.3–5 Our patient gave a history of reduced exercise tolerance from childhood, but the prominent and progressive weakness, contractures, ocular involvement, and skeletal abnormalities distinguished him from that group of patients.

Tubular aggregates have also been described in mouse models of autoimmune connective tissue diseases7 and have been described rarely in polymyositis in humans.20 Although our patient had a family history of arthritis, he had no clinical, biochemical, or serological evidence of a connective tissue disorder. Furthermore, there was no histological evidence of inflammatory muscle disease.

There have been reports of several patients with idiopathic tubular aggregate myopathies, without the other features of the syndromes mentioned above. These can occur as sporadic cases2–3 or as part of familial syndromes.19 In some of the familial cases, tubular aggregates occur in both type I and type II muscle fibres. In contrast, most other patients with tubular aggregate myopathies—including those with prominent exercise induced myalgia—have tubular aggregates restricted to type II fibres only.22 In this respect, our patient resembles the rarer familial cases. While these cases have a variable range of clinical features we are unaware of a description of a case with the same combination of musculoskeletal and pupillary features found in ours.

An interesting feature of our patient was the marked bilateral pupil abnormality. The extreme degree of meiosis suggested that these pupils may be either Argyll-Robertson or old Holmes-Adie pupils, but such descriptions are inappropriate because of the regularity of the pupillary outline, the presence of brisk, though inevitably small, light reflexes, and the lack of light-near dissociation. Could the meiosis be the result of a sympathetic deficit such as occurs in Horner's syndrome? Two observations make this unlikely: the pupils were too small for this condition, and they did not dilate with phenylephrine. Taken together, the presence of reflex activity and the failure of phenylephrine mydriasis indicate that the abnormality is unlikely to be neuropathic in origin. In the circumstances, we are inclined to believe that it arises from a myopathy of the iris musculature, particularly the pupil dilator.

Abnormalities of pupillary smooth muscle have been described in association with a tubular aggregate myopathy in a small number of patients with gyrate atrophy of the choroid and retina. These patients have a deficiency of ornithine transaminase and present with progressive blindness caused by photoreceptor and choroid degeneration.15 Symptoms of skeletal muscle disease are uncommon in such patients, but many have tubular aggregates in their skeletal muscle. Although these patients have normal pupillary function, samples of the pupil dilator muscle contain structures resembling tubular aggregates.24 This is surprising as tubular aggregates are thought to arise from the sarcoplasmic reticulum, a structure which is not present in smooth muscle. Either the tubular aggregate-like structures seen in the iridectomy samples are completely different entities from those seen in skeletal muscle, or tubular aggregates can represent a more generalised pathological feature of intracellular calcium stores.

In contrast, our patient presented with widespread skeletal muscle disease and symptoms and signs suggestive of pupillary muscle dysfunction but with normal visual acuity and fundi. We hypothesise that he has a tubular aggregate myopathy affecting his pupillary smooth muscle in addition to his skeletal muscle.
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