SHORT REPORT

Acute myopathy associated with large parenteral dose of corticosteroid in myasthenia gravis

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Abstract

A 13 year old Greek girl with myasthenia gravis developed widespread muscle paralysis and atrophy after large parenteral doses of corticosteroids (5·48 g methylprednisolone). An electromyogram showed myopathy, creatine kinase concentration below normal, and a muscle biopsy showed severe myopathy with selective loss of the thick filaments (myosin). Previous reports of myopathy associated with large steroid doses have mostly been in patients who were also receiving non-depolarising neuromuscular blocking drugs. This patient is unique in that severe myopathy was associated with neuromuscular blockade caused by antibodies to acetylcholine receptors. The findings in this case suggest that high doses of parenteral corticosteroids in patients with myasthenia gravis may be dangerous and that blocking the neuromuscular junction with drugs or antibodies predisposes skeletal muscles to the injurious effects of corticosteroids.

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Orally administered corticosteroids are among the commonest causes of drug induced myopathy.[1] This is usually characterised by an insidious onset, proximal muscle weakness and wasting, myopathic units detectable on electromyography (EMG), and type 2 fibre atrophy on muscle biopsy. Large parenteral doses of corticosteroids are also recognised as causing a severe acute myopathy, usually in patients who have also received neuromuscular blocking drugs.[2] We report severe muscle damage after large parenteral doses of steroids in a patient whose neuromuscular blockade was due to antibodies to the acetylcholine receptor.

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Case report

A 13 year old Greek girl had been fit and well until July 1991, when she developed limb weakness. After one week her face and neck muscles were affected, and she experienced increasing difficulty talking and swallowing. An edrophonium test gave positive results and antibodies to acetylcholine receptors were detected. She became much better after taking pyridostigmine. In mid September prednisolone 45 mg/day was started and after eight days she developed acute respiratory failure requiring intubation and ventilation. She developed subcutaneous emphysema and bilateral pneumothoraces on two occasions. Oral prednisolone was increased to 50 mg daily. This was supplemented by intravenous methylprednisolone (total 5·48 g) between 24 September and 25 October 1991, of which 4 g was given over a 24 hour period (16–17 October). Azathioprine 75 mg/day was given for four weeks. Intravenous immunoglobulin (23 g/day for three days) was administered and she received seven courses of plasma exchange (removing a total of 5 l of plasma), which did not improve her condition. She was also given ceftazidime, clindamycin, netilmicin, ceftriaxone, and vancomycin during her management in intensive care in Greece. Neuromuscular blocking drugs were not given. She was transferred to Oxford on 25 October.

On arrival she was receiving assisted ventilation. There was bilateral partial ptosis, but a full range of ocular movements, and only mild weakness of facial muscles. She had generalised limb muscle wasting, most severe in the quadriceps and tibialis anterior muscles. There were no fasciculations. She had severe weakness of her arms. She was unable to raise her legs off the bed, and there were no movements of the knees or ankles. All the deep tendon reflexes were absent, except for the triceps jerks, which were evokable with reinforcement. The plantar responses were flexor. There were no sensory abnormalities.

Creatine phosphokinase activity was 31 IU/l (normal 75–200). Electrophysiological studies showed normal sensory and motor conduction. The mean jitter of 10 single fibre pairs was 68·4 μs, half of them exceeding the normal value of 42 μs, thus confirming the defect in neuromuscular transmission. Concentric needle examination of the left biceps showed a crowded pattern of motor unit recruitment, with motor units up to 0·5 mV often with spiky and polyphasic waveforms suggestive of a primary muscle disease. The concentration of antibody to acetylcholine receptors was strongly positive at 18 900 pg/l (normal <200 pg/l).

The deltoid muscle was biopsied on 31 October. Frozen sections stained with haematoxylin and eosin showed two populations of fibres. Most fibres were small, angular, and basophilic. Many of these fibres had large central nuclei, some forming large, densely staining clumps (figure 1). With trichrome staining these small fibres stained a diffuse dark blue colour, and they showed little or no ATPase activity. NADH activity showed a totally disorganised myofibrillar pattern. The remaining fibres were normal in size and in their staining pattern with haematoxylin, eosin, and trichrome. ATPase activity was seen, but there was often a large central area of pallor. Fibre typing was not possible because of these gross abnormalities in ATPase activity. NADH activity in the large fibres was normal. Acid and alkaline phosphatase activities were normal in all fibres. Blood vessels and connective tissue appeared normal; occasional macrophages were identified in the endomysium, but there was no significant inflammatory infiltrate. Electron microscopy showed loss of thick filaments with preservation of thin filaments and Z bands in many of the small fibres (fig 2). Large fibres were well preserved.

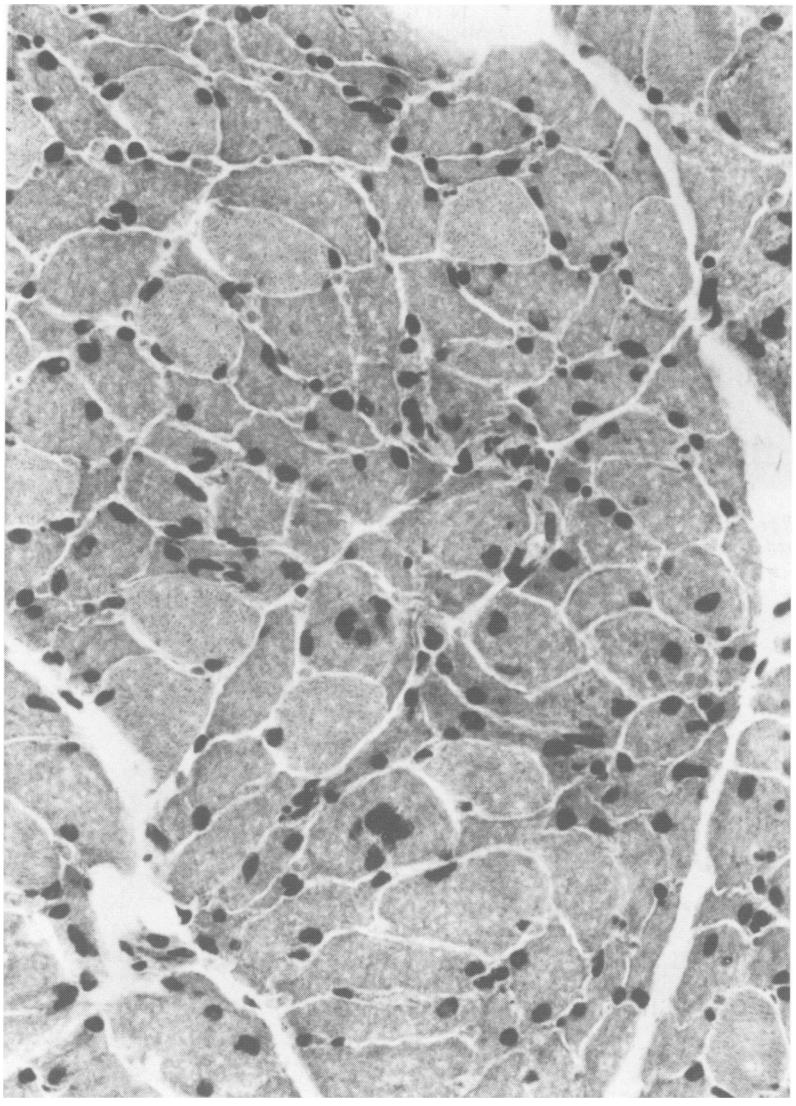

Figure 1 Frozen section of deltoid muscle showing many atrophic fibres with a disorganised myofibrillar pattern. Many have large, irregular, central nuclei (haematoxylin and eosin, magnification x 230).

Her corticosteroid treatment was steadily reduced. After five daily plasma exchanges she had a thymectomy. Histopathologically the thymus showed only involutional changes. Her muscle strength progressively improved after thymectomy, and she was eventually able to breathe spontaneously. The tracheostomy tube was removed, and her vital capacity rose to 1·5–2·1. Before her discharge she was able to take a few steps with the support of a frame. She did not require pyridostigmine and was transferred to Greece on the 13 December 1991 taking prednisolone 80 mg on alternate days. Two months later improvement was reported to be continuing, and she was able to ride her bicycle.

Discussion

The clinical features which pointed to an additional (non-myasthenic) cause of muscle weakness in this patient were the initial failure to respond to plasma exchange, the extreme and generalised paralysis with complete sparing of ocular movements, and the absence of deep tendon reflexes (which are typically brisk in myasthenia gravis even in weak muscles). In support of a non-myasthenic process, single fibre electromyography showed only a moderate increase in jitter, half of the pairs of unit studied being within the normal range. The diagnosis of associated acute myopathy was established by electromyographic muscle sampling, and the unequivocal histological findings. The low serum creatine kinase value probably reflects the reduced muscle bulk caused by the myopathy.

Previous reports of steroid induced acute myopathy have concerned patients with status asthmaticus given non-depolarising neuromuscular blocking drugs such as pancuronium[3] and vecuronium.[2] In other cases of status asthmaticus associated with steroid myopathy the use of neuromuscular blocking drugs was not stated.[4] Our patient is distinct from these other patients in that the severe myopathy was related not to neuromuscular blocking drugs but to the presence of autoantibodies to muscle acetylcholine receptors. This suggests that muscle inactivity induced by blockade of neuromuscular transmission either by pharmacological agents or by myasthenic antibodies renders skeletal muscle acutely vulnerable to the myopathic effects of corticosteroids.

The mechanisms by which corticosteroids might damage skeletal muscles are unknown. Experimental studies suggest a decrease in protein synthesis,[5] which is independent of fibre type.[6] A light and electron microscopic study of the progressive changes in rabbit skeletal muscle have shown a progressive loss of contractile elements, an accumulation of glycogen, and abnormalities in mitochondria.[7] Denervated muscles in animals

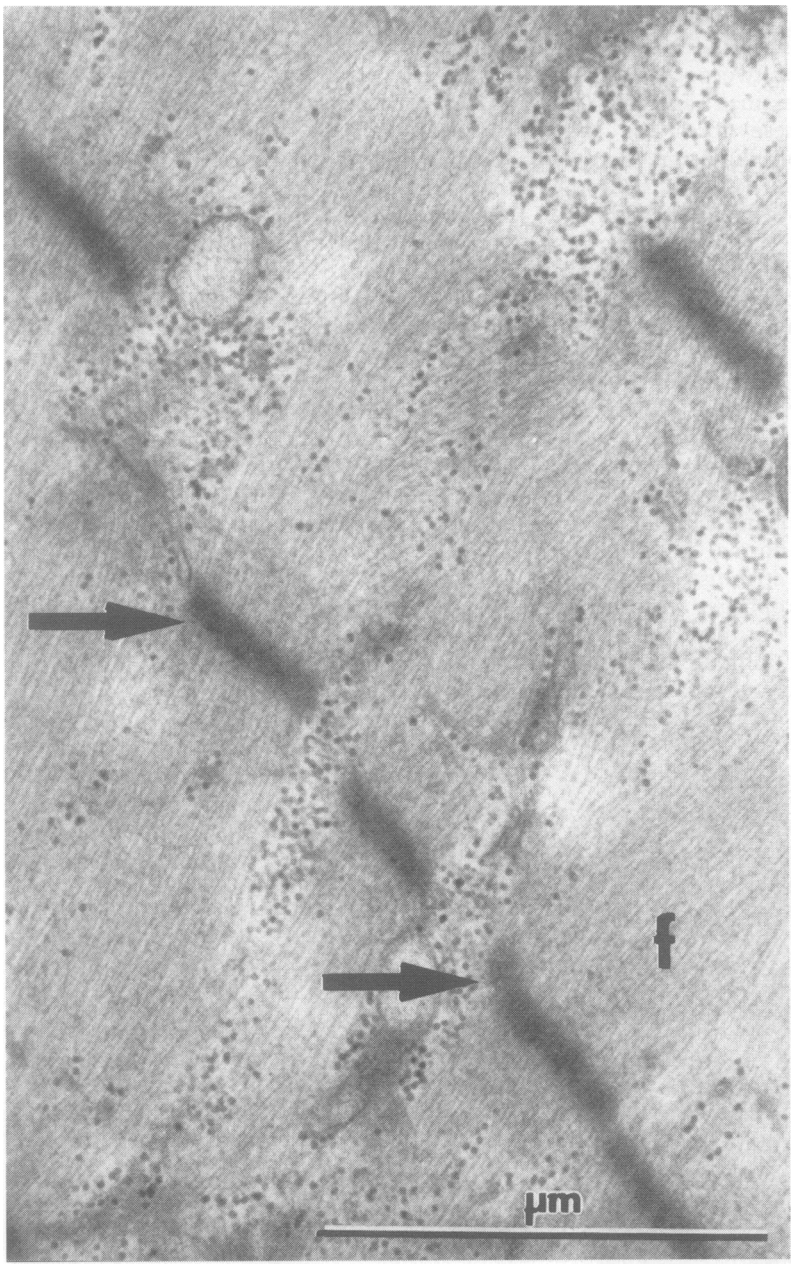

Figure 2 Electron micrograph of an atrophic fibre showing well preserved Z bands (arrows) and fine filaments (f). Thick filaments have disappeared. Bar shows 1 μm.

given corticosteroids show myosin loss.[8] This has been confirmed in two human cases.[2 9] The histological findings in our patient are similar to those previously reported in showing atrophic fibres, loss of myosin ATPase pattern without type 2 fibre atrophy or fibre type grouping, and electron microscopic evidence of selective thick filament loss. Vacuolation previously described in one patient was not identified.[4]

We conclude from our case that large doses of parenteral corticosteroids should be avoided in myasthenia gravis because of the risk of increasing muscle weakness by inducing an acute myopathy.

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