Internalised capillaries, neuromyopathy and myalgia

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Abstract

Internalised capillaries are described in the muscle fibres of two adult males who complained of exertional myalgia. In one patient, "bundles" of internalised capillaries were found in 2% of the Type 1 fibres and many of the Type 1 fibres exhibited non-specific cytoarchitectural changes. The other had hereditary motor and sensory neuropathy (HMSN) Type 2 and his muscle biopsy exhibited the more conventional single and double internalised capillaries in 3% of the muscle fibres in addition to the anticipated neuropathic changes. Electron microscopy revealed the presence of paracrystalline inclusions in the mitochondria of muscle of both patients. Dystrophin was normal on both immunogold/silver staining and immunoblotting. Sixty five of 77 recorded patients with evidence of internalisation of capillaries have been males and 10 are known to have complained of muscle cramps or severe myalgia. An ischaemic pathogenetic predisposition is proposed as a possible stimulus to the capillary internalisation, formation of paracrystalline mitochondrial inclusions and myalgia.

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Internalised capillaries are a rare and unexplained finding in muscle. This descriptive term was first used by Shafiq *et al* in 1972.¹ Internalised capillaries have been described in diverse disorders, the commonest of which is the Becker type of muscular dystrophy. Vascularisation was reported in a patient with the Prune Belly Syndrome by Afifi *et al*,² Huntington³ described internalised capillaries in a 54 year old man who complained of aching legs and was reported to have peripheral neuropathy; Sulaiman *et al*⁴ reported two cases with muscle fibres showing evidence of chronic destruction and capillary internalisation; Kuhn *et al*⁵ recorded myalgic cramps in a male patient with Becker dystrophy with centralised capillaries in the gastrocnemius muscle. This patient had two uncles with Becker dystrophy who suffered exercise-induced myalgia; Hastings *et al*⁶ described internalised capillaries in four patients from two families who presented the phenotypical appearance of Becker dystrophy, one of whom complained of myalgic pains; Pascuzzi *et al*⁷ described a patient and his son who exhibited the Schwartz-Jampel syndrome, both of them in addition, com-

plained of distal extremity weakness, stiffness, aching pains and slowly deteriorating ambulation. The muscle histology revealed mild to moderate "dystrophic changes" and internalisation of capillaries; Sulaiman and Kinder⁸ reviewed 1091 muscle biopsies and observed internalised capillaries in 54. However, the symptoms of the patients were not discussed and thus the presence or absence of myalgia is not known; Gutmann *et al*⁹ carried out a prospective study over three years, specifically examining muscle biopsies for internalised capillaries, they encountered seven examples in 1146 routine diagnostic biopsies, the gastrocnemius muscle was most frequently involved and four of the seven complained of exercise-induced myalgia.

Biopsies were carried out on the patients presented to help clarify their complaint of severe exertional myalgia.

Case reports

Patient 1

A 45 year old male complained of muscle and joint pain during and after exercise. He described his problem as if he was continually "pulling tendons" of his various muscles. The complaint was mainly referable to the shoulder girdle and calf muscles. There was no history of neuromuscular disease in the family.

The physical examination was normal. The response to direct pressure to both muscles and tendons was normal. Strenuous muscle contraction particularly of the hamstrings, deltoids and calf muscles, evoked pain.

Routine blood, metabolic studies and lactic acid production on ischaemic exercise was normal. The creatinine kinase (CK) was 111 IU/l (normal 0-195 IU/l), aldolase 4.5 IU/l (normal 0.5-7.6 IU/l). Doppler study of peripheral blood flow was normal. Chromosomal studies with particular reference to the Xp21 region was normal. Dystrophin content as measured by immunoblotting was normal.

Electromyographic examination using concentric needle electrodes was normal. Motor and sensory nerve conduction velocities were normal in both upper and lower extremities. Muscle from the right gastrocnemius revealed an abnormal variation in fibre size, scattered degenerating fibres and fibres of hyaline appearance. Clusters of large muscle nuclei of degenerated fibres as well as occasional regenerating muscle fibres could be seen scattered throughout the sections. The striking abnormality affecting 2% of the fibres was the

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Figure 1 An H & E stain showing the presence of an internalised capillary bundle. Photographed at $400\times$ magnification.

Figure 2 An electron micrograph of an internal capillary bundle. Photographed at $1000\times$ magnification.

Figure 3 An electron micrograph demonstrating paracrystalline transformation in case 1. Photographed at $5000\times$ magnification.

presence of internally placed capillary "bundles" (fig 1). On histochemical study the capillary "bundles" were confined to the larger Type 1 fibres which constituted 43.5% of the fibres. Patchy disorganisation presenting a moth-eaten appearance affecting mainly the Type 1 fibres was best seen on the phosphor-ylase and oxidative preparations. The myoadenylate deaminase preparation was qualitatively normal. Immunogold/silver preparations demonstrated a normal dystrophin distribution. Electron microscopy clearly demonstrated the presence of centralised grouping of capillaries (fig 2). There was in addition evidence of Z-line streaming and disorganisation in which scattered T-tubules and mitochondria were noted. Other areas, particularly in the subsarcolemmal region contained large collections of mitochondria and many were distorted with paracrystalline inclusions (fig 3).

Patient 2

A 27 year old male complained of a progressive problem with walking due to deformity of his feet and ankles and of exertional myalgia in the muscles of his legs. There was family history of high-arched feet involving the father and members of the father's family.

On examination the patient exhibited advanced bilateral pes cavus with evidence of thinning of the muscles of the lower third of both legs. The ankle tendon jerks were only just obtainable as opposed to the tendon reflex responses in the upper extremities and knees which were normal. The intrinsic muscles of the hands were slightly weaker than normal and clawing of the little fingers was noted. There was slight weakness of the peroneal and extensor groups of muscles. The extensor brevis, the abductor and flexor hallucis brevis muscles of both feet were atrophic.

Routine blood and metabolic studies were normal. CK was 180 IU/l. Peripheral blood flow was normal.

On electromyography recruitment of motor unit activity in the distal musculature was inadequate, particularly observed in the anterior and lateral compartments of the legs where high-voltage polyphasic units were noted. The extensor brevis, flexor hallucis brevis and abductor hallucis muscles of both feet were atrophic, only single motor unit activity occurred on movement and fibrillation activity was recorded. The motor velocities for the right median and common peroneal nerves were 59.7 and 44.6 m/s respectively. Sensory nerve conduction studies achieved by stimulating the median plantar and anterior tibial nerves failed to induce a response at the recording site 14 cm proximally. The median and ulnar nerve stimulation via ring electrodes around the respective finger, produced abnormally flat peaks with a latency of 4.68 and 3.53 ms respectively, recorded over a distance of 14 cm.

Histology and histochemistry of the anterior tibial muscle revealed a marked variation in fibre size, fibrous and fatty tissue infiltration was excessive and occasional regenerating

Figure 4 An H & E preparation demonstrating internalised capillaries in a large muscle fibre associated with fibre splitting. Photographed at 100 $\times$ magnification.

Figure 5 An electron micrograph of an internalised capillary (case 2). Photographed at 2000 $\times$ magnification.

fibres were noted. Some fibres contained multiple nuclei which were frequently seen to occur in rows, and areas of grouped atrophy were visible. Internalised capillaries were noted in 3% of the fibres, occurring singly or doubly in the Type 1 fibres and fibre splitting was obvious (fig 4). There was evidence of fibre type grouping which involved both fibre types, and 87% of the fibres were of the Type 1 variety. In many of the fibres the cytoarchitecture was abnormal demonstrating a moth-eaten appearance and targetoid formation. The myoadenylate deaminase preparation was qualitatively normal. Immunogold/silver preparations revealed a normal distribution of dystrophin. Electron microscopic study confirmed the presence of centralised capillaries (fig 5) and revealed widespread breakdown of myofibrils with core formation, particularly in the subsarcolemmal region. There were occasional myelin bodies, streaming of Z-lines was obvious and phagocytes were noted within the sections. In areas, particularly in the subsarcolemmal regions, scattered distension and

breakdown of mitochondrial structure was present and paracrystalline inclusions were noted. Sural nerve electron microscopy revealed that many of the myelin sheaths were thin and the axonal tissue shrunken in keeping with HMSN Type 2.

Discussion

A notable observation in analysing the published cases is that the majority have occurred in men (65 of 77). The possibility of Xp21 linked dystrophies was considered and this prompted the dystrophin and chromosomal studies in our first patient which proved to be normal.

Guttman *et al*⁹ confirmed the findings of Hastings *et al*⁶ by noting that the centralised capillaries occurred in the Type 1 fibres and that the fibres were excessively split. They proposed that the occurrence of internalised capillaries in the Type 1 fibres relates to the increased capillary density of fibres with high oxidative activity as described by Carry *et al*.¹⁰ They suggested that the presence of two separate internalised capillaries was due to a single capillary making a hairpin bend and returning within the same fibre.

A great deal of speculation has surrounded the association of capillaries and fibre splitting suggesting that the presence of the capillaries mechanically predisposes to splitting in an already compromised fibre or that the capillaries were conversely opportunistic. However, Sulaiman and Kinder⁸ in their study failed to find an association between internal vascularisation and muscle fibre splitting, and this is contrary to general experience.

Sulaiman and Kinder⁸ found that the centralisation occurred mainly in neurogenic disorders of muscle and suggested that the vascularisation probably occurs as a "healing" or "reparative" process. The paracrystalline inclusions observed in the presented cases could be relevant in that this transformation, though non-specific, may provide a clue to a possible aetiology in that we have noted sequential morphological changes in the mitochondria of muscle at necropsy. When muscle is studied 48 hours after death, there is an invariable transformation within the mitochondria which resembles paracrystalline formation, a change that we attribute to the altered biochemical environment and anoxia. Anoxia may be pathogenically important in the evolution of paracrystalline formation in some cases, and this may explain the prevalence of centralised vascularisation in the more distal muscles as these are generally more prone to ischaemia. It is proposed that the pathogenesis of capillary centralisation, be it a compensatory "reparative" process, the myopathy, the fibre splitting, the paracrystalline change, as well as exertional myalgia, may share a common ischaemic aetiology. We believe myalgia is symptomatic of the primary neuromuscular pathology and not a consequence of internalisation of capillaries.

The presence of multiple centralised capillaries seen in case 1 is unusual and has not to

our knowledge been described before. We assume, however, that the aetiological basis proposed for single capillaries is applicable. The aetiology of the myopathic fibres found in case 1 is unknown as is the case in many of the previously described patients with centralised capillaries. Dystrophin and chromosomal studies should be undertaken in all cases with unexplained myopathic features in an attempt to explain the male preponderance.

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Silas Weir Mitchell (1829–1914)

Born in Philadelphia in 1829, this distinguished American was the seventh physician in three generations. Webb Haymaker recounts¹ his smuggling *Midshipman Easy* into a dark corner of a church pew to lessen the boredom of his rather puritanical upbringing. His early university career in Philadelphia was poor indeed. His preference for daydreaming, writing poetry and billiards prompted his father, Dr John Kearsley Mitchell to remark “You are wanting in nearly all the qualities that go to make a success in medicine.” Nonetheless, he enrolled at Jefferson Medical College in 1848, qualifying MD in 1851. He boarded a ship for Europe and in Paris fell under the spell of Claude Bernard who probably sowed the seeds of his lifelong sense of scientific enquiry. Returning to Philadelphia he investigated the effects of snake venom. Haymaker records how he nearly lost his life when a six foot rattler climbed on his chair, poised at his shoulder and was only distracted when inadvertently it touched the hot lamp and withdrew, allowing Mitchell to leap up and escape.

During the American civil war he was seconded with Dr G Morehouse to a purpose built 400 bed neurological hospital on Christian Street, Philadelphia. Dr WW Keen was an associate. Together they collected “cartloads of wounded soldiers” from Gettysburg, attended to their wounds and prepared “thousands of pages of notes” on their injuries, culminating in several classic books and papers.^{2,3} At the suggestion of

Professor Robley Dunglison he applied the term *causalgia* to the consequences of partial nerve injury.

In “Reflex Paralysis”⁴ he described the sudden weakness of the limbs on the side opposite to forebrain injury, thus anticipating the lateralisation of motor function by Fritsch and Hitzig by five years. He studied post-paralytic chorea, erythromelalgia (Weir Mitchell’s disease) and deduced that the cerebellum augments and reinforces movement. He advocated the rest cure for psychoneurosis, but at times was less than orthodox. Attending a lady, “sick unto death” he dismissed his assistants from the room and then soon left himself. Asked of her chances of survival he remarked “Yes she will run out of the door in two minutes; I set her sheets on fire. A case of hysteria”. His prediction proved correct.

In the 1880s he turned to literature and published several novels, drama and verse. He died of influenza in his 85th year. Harvey Cushing summed him up: “He was vain, but had much to be vain about”.

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