The dystrophy of Duchenne

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Case report
A 5-year-old boy was noted to have difficulties when walking and running from 3 years of age. He would tire easily, which had become more pronounced over the last year. He started to fall frequently, and when climbing stairs he had to hold onto the banister to pull himself up with his hands. To get up from a sitting position, he had to push himself up with his hands to stand. There was a family history of a similar condition in his maternal uncle, who died at the age of 24 years because of respiratory failure, who had had progressive and severe muscle weakness.

The boy’s muscle strength was moderately diminished, more so proximally and in the legs. His calf muscles were enlarged and firm on palpation, and there was a mild contracture in his heel cords. Deep tendon reflexes were diminished. He had a positive Gowers’ sign and waddled when walking or running. Creatine phosphokinase concentrations were high (7532 μL, normal <250). Electrocardiography and echocardiography indicated left-ventricular hypertrophy. DNA analysis with computer-assisted laser densitometry with two sets of primers (CALD M1 and M2) to detect common deletions in the 18 of the 79 dystrophin exons was negative.

The skeletal muscle biopsy sample (figure 1) showed a dystrophic process with myofibre atrophy, hypertrophy fibre splitting, myofibre necrosis and regeneration, and endomysial and perimysial fibrosis with fatty infiltration. Immunohistochemical analysis by immunoperoxidase staining showed absence of dystrophin (N, midrod domain, and C-terminal antibodies) in the muscle biopsy sample (figure 1).

The boy was referred to physiotherapy and his family underwent genetic counselling. In the following years, his muscle weakness progressed; at 11 he became wheelchair bound and by 14 years he developed scoliosis, for which he underwent rod replacement. For progressive weakness of the respiratory muscles, he was offered tracheostomy and ventilation which he refused. He died of pneumonia at the age of 22 years.

The history, and physical signs and symptoms, in conjunction with the laboratory findings in the above case, are diagnostic of Duchenne muscular dystrophy, the pertinent features of which are summarised in the panel. The features to emphasise are the relentless and progressive muscle weakness leading to respiratory failure or cardiac failure and early death by the mid-twenties as well as the hereditary nature of the disease with X-linked genetic transmission.

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Figure 1: Immunoperoxidase staining for dystrophin
A: in normal control muscle. B: muscle biopsy of patient. Note the normal size and shape of fibres and uninterrupted membrane staining for dystrophin in the control muscle, and the complete absence of dystrophin in the patient’s muscle. There is also evidence of marked variability in fibre size, atrophy, hypertrophy, fibre splitting, and increased endomysial collagen in the patient (>250).

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Today, immunohistochemistry has an important role in the diagnosis of muscle biopsy in patients suspected to have muscular dystrophy. Typically, in DMD there is a complete absence of dystrophin in the muscle. The clinical heterogeneity of BMD gives rise to problems in differential diagnosis, and in the absence of a previous family history or positive DNA analysis, it may be difficult to distinguish BMD from other disorders such as limb girdle dystrophy. In patients with BMD, dystrophin staining can range from complete absence of dystrophin to substantially abnormal (partial/faint staining) in addition to qualitative and quantitative differences on western blot analysis. Abnormalities of sarcoglycans might be shown in limb girdle muscular dystrophy. Merosin immunohistochemistry can be helpful in the diagnosis of merosin deficient congenital muscular dystrophy, especially in early stage biopsy samples which might show non-specific findings without the characteristic dystrophic pathology.

The legacy of Duchenne

Muscular dystrophy was no doubt an affliction going back to antiquity. But its initial clinical descriptions, at least in the English language, probably date back to the 19th century. Charles Bell, famous for his description of facial nerve paralysis (Bell’s palsy) may have described a case of muscular dystrophy in 1830. Coste and Gioja of Naples are credited with a report of progressive muscle weakness and muscle enlargement in two brothers in 1838. In 1847, Partridge presented a case of a young boy who suffered from progressive muscle disease; at necropsy, there was striking fatty degeneration of muscle. Similarly, the report of Little in the same year alluded to marked fatty replacement of muscle at necropsy in a boy with progressive muscle wasting and abnormal gait. His brother had a similar affliction. These initial reports are most consistent with a muscular dystrophy affecting boys and fatty replacement of muscle is not an unexpected finding in an advanced case of dystrophy.

It was Edward Meryon (1809–80) of St Thomas’s Hospital, London, who first gave a full and vivid description of DMD. Meryon studied medicine in Paris and London, and got his MD degree in 1844. In 1851, Meryon presented a communication to the Royal Medical and Chirurgical Society, which was published the next year. His patients included eight affected boys from three families; one patient had been previously reported by Partridge in 1847. Meryon was quick to recognise the familial nature and predilection for boys in this disease. In his 1864 book entitled, Practical and Pathological Researches on the various forms of paralysis, Meryon described a family with four affected cousins and transmission through three sisters. On examining the muscle at necropsy, he noted oil globules, granular degeneration, and destruction of striped elementary fibres, no doubt suggesting fatty replacement and advanced myofibre disease. Thus Meryon’s description of this dystrophy antedated that of Duchenne by 10 years.

Guillaume-Benjamin-Amand Duchenne (1806–75; figure 2) was born in Boulogne, France. His father was a sea captain who had hoped that his son would follow in his footsteps. But Duchenne chose to study medicine in Paris. His inaugural thesis was on burns. After graduation in 1831, Duchenne returned to Boulogne with the intent of pursuing a lifelong career in neuromuscular diseases. Duchenne had an unorthodox career in Paris, amassing a wealth of clinical material, but never holding an academic appointment. Not burdened with academic duties or restrained by academic commitments, he pursued his research in neuromuscular diseases, as well as a wide array of other neurological conditions. Every morning, he visited one or more hospitals, often wandering from one to the other tracking patients down to trace the natural course of a disease.

Duchenne was fascinated with electricity—both for diagnostic and therapeutic purposes. He built a machine for electrical stimulation of nerves and muscles. He taught himself microscopy and photography. His extraordinary clinical experience was summarised in L’Electrisation Localisée, the third and final edition of which was printed in 1872. His clinical descriptions included a wide range of topics such as progressive bulbar palsy, cold paralysis, nervous deafness, cerebellar disease, polio, mechanism of facial expression, hysterical paralyses, and muscle prosthesis. Duchenne also wrote Physiologie des Mouvements. In 1883, GV Poore condensed and translated the many works of Duchenne for the New Research in Neuromuscular Diseases.
In 1861, Duchenne described his first case of the dystrophy that now bears his name, under the title, *Paraplégie hypertrophique de l’enfance de cause cérébrale*. Because of the intellectual impairment in the affected boys, Duchenne initially thought the condition was cerebral in origin. In 1862, in his *Album de photographies pathologiques*, he published some remarkable clinical photographs of the condition.

The association of two contradictory observations—ie, paralysis and muscle hypertrophy, greatly perplexed Duchenne. In 1865, he developed his own tool for muscle biopsy: “I have devised a little instrument, which I have named the tissue punch, by means of which, with very little pain, I have removed minute portions from the deep parts of muscles”. With this tissue punch, he was able to study the muscle pathology in a child: “Hyperplasia of the interstitial connective tissue, with production of more or less fibrous tissue, is the fundamental anatomical lesion of the muscles in pseudo-hyertrophic paralysis . . .”.

In a report published in 1868, Duchenne gave a comprehensive account of the condition based on his study of 13 cases. He drew attention to the unusual muscle enlargement and extreme fibrosis (*paralysie myosclerosique*) and proposed the term, *paralysie musculaire pseudohypertrophique*, which was popularised by William Gowers. By 1870, Duchenne had seen about 40 cases. He described three stages—one of feeble movements, one of apparent hypertrophy, and finally, of paralysis. His muscle biopsy samples showed gradual accumulation of fibrous and in later stages, fatty replacement of the muscle. He noted the grave prognosis of the disease and that the condition was more prevalent in boys. In 1871, he had the opportunity to examine the cord in one case and noted that there was no neurogenic lesion.

Duchenne died of a cerebral haemorrhage on his 69th birthday. Duchenne’s career was indeed unique—he was the physician at large in Paris, not affiliated with any institution in particular, but welcome in all. He had little interest in receiving honours or medallions from learned societies or grand academic appointments. When he died, Duchenne was recognised as an original medical scientist.

**References**


**EPONYM**

**Duchenne muscular dystrophy**

- Progressive muscle weakness, more proximal
- Onset between 2–4 years of age
- >95% in wheelchair by 12 years of age
- Death between 15–25 years of age
- Variable mental retardation
- Frequent cardiac involvement
- Orthopaedic deformities
- Calf hypertrophy
- High creatine phosphokinase concentrations
- Dystrophin deficiency in muscle
- Hereditary, X-linked disease
- Gene Xp21 mutations

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