Multicore disease in twins

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SYNOPSIS   Multicore disease in identical twin boys presented in infancy as generalized weakness and torticollis. Motor milestones such as sitting, standing, and running were delayed, although by the age of 6 years marked improvement in muscle strength had occurred. Serum enzymes were normal. Muscle biopsy revealed multifocal areas of decreased oxidative enzyme activity. Ultrastructurally, these areas were characterized by myofilament disruption and Z-band streaming.

The concept of congenital myopathy became established with the report of central core disease by Shy and Magee in 1956. In the subsequent 20 years, a large number of such myopathies have been described. Most cases begin in childhood and are slowly progressive or non-progressive. Each disorder is characterized by a typical, often specific pathological feature. We wish to report two cases of multicore disease, a rare and usually non-progressive congenital childhood myopathy with pathological lesions reminiscent of central core disease.

CASE REPORTS

The two patients are a pair of identical male twins, born on 22 September 1969. The birth weight in case 1 was 2.2 kg. The birth weight in case 2 was 2.4 kg. Pregnancy, labour, and delivery were uneventful. At birth the mother noted that in case 1 the child's head was turned to the left and in case 2 the head was turned to the right. The boys were seen by an orthopaedic surgeon at 8 months of age, and the family was informed that the children had wryneck.

As the boys grew older, they had persistently poor head control and generalized floppiness.

Case 1 sat at 8½ months of age while case 2 sat at 6 months of age. Both children walked at 13 months. They were unable to raise their heads voluntarily when in a supine position. When they started to walk they had to be lifted into an erect posture. To compensate for this deficit, the children began turning from a supine to a prone position and then climbing up their legs to an erect position. Neither child ran until 4½ years of age.

A sister also suffers from a neuromuscular disorder. The girl, who was born in 1968, weighed 2.4 kg at birth. She sat at 6 months and walked at 13 months. When she began to walk, she had to be pulled to a standing position before she was able to ambulate. Her muscle strength has gradually improved and currently her motor examination is unremarkable. No biopsy has been permitted. The mother, age 28 years, and the father, age 29 years, are in good health. No other members of the family have known neuromuscular disease.

On physical examination the twins at age 5 years were mirror images of each other. In case 1, the right hemiface was larger than the left and the patient tended to tilt his head with the occiput to the left. In case 2, the left hemiface was larger than the right, and the patient tended to tilt his head with the occiput to the right. Both children's heights were in the third percentile, their weights were in the tenth percentile, and the head circumferences were in the 97th percentile. The heads were dolichocephalic. In case 2 there was congenital cupping of the right ear. Both twins had marked head lag. Weakness was greater in

the deltoids and strap muscles of the neck. Both children had diffuse muscular weakness which appeared worse in the proximal musculature. The entire muscle mass appeared somewhat under-developed. Both children used the Gowers' man-oeuvre on rising from a prone position. Deep tendon reflexes were hypoactive throughout. Plantar responses were flexor. Sensory examina-tion was unremarkable.

Laboratory studies included normal chest radio-graphs. Electromyography in case 1 was normal. In case 2 bursts of single low voltage 100 to 200 μv polyphasic motor unit potentials were seen in the left sternocleidomastoid muscle. This phenomenon was interpreted as 'myopathic' in nature. Serum creatine phosphokinase (CPK) and aldolase in both patients were normal.

Since muscle biopsy 18 months ago, both twins have shown improvement in muscle strength. Head control in both boys is considerably im-proved and their gaits are essentially normal.

METHODS

Biopsy specimens from the left deltoid muscles in both cases were obtained at 5 years of age under local anaesthesia. Specimens for paraffin sections and electron microscopy were clamped in a Price isometric device and fixed in Zamboni's solution (Stefanini *et al.*, 1967). Paraffin sections were stained with haematoxylin and eosin (H&E), periodic acid-Schiff (PAS), phosphotungstic acid haematoxylin (PTAH), and Masson's trichrome. Tissue for electron microscopy was post-fixed in 2% osmium tetroxide and embedded in Epon 812. One μm 'thick' sections were stained with tolui-dine blue. Ultra-thin sections were cut on a Reichert OMU-3 ultramicrotome and examined with a Zeiss EM-10 electron microscope.

Fresh frozen specimens for histochemistry were frozen in isopentane cooled by liquid nitrogen. Serial sections were cut in an IEC cryostat and stained with H and E, modified Gomori tri-chrome, myofibrillar adenosine triphosphatase (ATPase), reduced nicotinamide adenine dinu-cleotide dehydrogenase (NADHD), succinic dehydrogenase (SDH), and phosphorylase. Speci-mens of fresh frozen tissue in longitudinal and cross-sectional orientation were prepared in both biopsy samples. Cross-sectional fibre diameters in ATPase-stained sections were determined ac-cording to standard methods (Brooke and Engel, 1969a).

RESULTS

In both cases, there was a marked variation in fibre size which was more striking than in the patients originally reported by Engel *et al.* (1971). The range of fibre diameters was 3–25 μm with a mean of 14 μm in case 1. The range in case 2 was 7–26 μm with a mean of 12 μm. The mean cross-sectional diameter of type 1 fibres was below the normal in both biopsies, while type 2 fibres were within normal range (Brooke and Engel, 1969b; Aherne *et al.*, 1971). Both patients had increased numbers of type 1 fibres as demonstrated on ATPase-stained tissue. In case 1 80% of fibres were classified as type 1; in case 2 72% were classi-fied as type 1.

Slightly increased numbers of internal nuclei (5–10%) were encountered. Fibre necrosis, regenerative activity, and endomysial fibrosis were absent. Numerous foci of decreased oxidative enzyme activity were seen in NADHD and SDH preparations (Fig. 1). These foci were usually small (2–8 μm), disc-
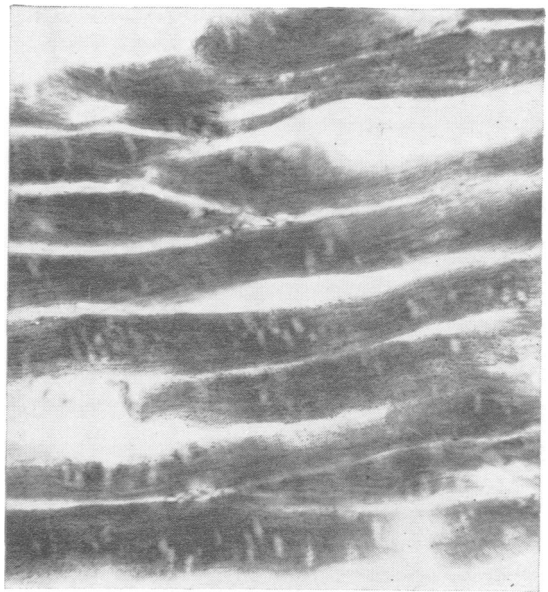

FIG. 1 *Case 1. Longitudinal cryostat section of deltoid muscle showing numerous foci of de-creased oxidative enzyme activity (multicores). NADH, × 265.*

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shaped, randomly distributed, and multiple within a fibre. In longitudinal sections, they were often oriented with their long axes perpendicular to the fibre axis. They were equally prevalent in type 1 and type 2 fibres. Approximately 90% of fibres were affected. Multicores were also seen with ATPase, trichrome, phosphorylase, and PTAH stains, but were less prominent and fewer in number.

Longitudinal Epon-embedded sections stained with toluidine blue revealed numerous areas of myofibrillar disorganization and Z-band streaming. These areas were better viewed with the electron microscope where the typical lesion involved five to 10 contiguous myofibrils and extended over four to eight adjacent sarcomeres. Myofibrillar disorganization could be detected in presumably early lesions as a loss of myofilament alignment causing the sarcomeres to appear out of register. Concurrent Z-band streaming and zig-zagging were invariably present. At a more advanced stage, the sarcomere pattern was obliterated by striking myofilament disruption accompanied by Z-band streaming (Fig. 2). Within areas of myofibrillar disorganization, mitochrondria were absent and glycogen stores

appeared reduced or absent. Occasionally abnormal collections of tubular profiles of apparent sarcotubular origin were demonstrated within the lesions.

DISCUSSION

Multicore disease was first recognized by Engel and Gomez in 1966 as a non-progressive congenital myopathy of childhood. Including the present report, a total of five patients have thus far been described (see Table). The disease usually begins in infancy, although Bonnette *et al.* (1975) have recently noted a case with onset at the age of 33 years. Four of five patients were male. A family history of neuromuscular disease was elicited in three cases. In this report the two patients were identical twins. A sister also had a similar neuromuscular disorder which improved clinically, but no muscle biopsy was performed. In case 2 reported by Engel *et al.* (1971), a maternal grandmother and a maternal uncle apparently suffered from neuromuscular diseases which were not described in detail. Associated somatic abnormalities were present in both cases reported by Engel *et al.* (1971). The boy

FIG. 2 *Typical multicore composed of myofilament disruption and Z-band streaming.* × 40080.

TABLE

SUMMARY OF REPORTED CASES OF MULTICORE DISEASE

	Heffner (1975)		*Engel et al. (1971)*		*Bonnette et al. (1974)*
	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Age of onset	Infancy	Infancy	Infancy	Infancy	33 yr
Sex	Male	Male	Male	Female	Male
Family history of neuromuscular disease	Yes	Yes	No	Yes	No
Associated somatic abnormalities	Dolichocephaly	Dolichocephaly	Dolichomorphism	Atrial and ventricular septal defects	None
Distribution of muscular involvement	Generalized; proximal > distal, esp. sternocleidomastoids	Generalized; proximal > distal, esp. sternocleidomastoids	Generalized; proximal > distal	Generalized; proximal > distal, esp. extraocular and neck muscles	Proximal
Serum enzymes	Normal	Normal	Normal	Normal	Slightly increased CPK
Course	Steady improvement	Steady improvement	Non-progressive	Non-progressive	Progressive

in their case 1 was noted to have a dolichomorphic habitus. The girl in case 2 had an atrial septal and ventricular septal cardiac defect which were repaired surgically. Dolichocephaly was apparent in both of our cases. Muscular weakness was generalized in all reported patients except the adult in whom striking proximal involvement was present. However, even when weakness was generalized, proximal exceeded distal weakness. In case 2 of Engel *et al.* (1971) ptosis and weakness of the neck muscles were observed. Neck involvement (sternocleidomastoid muscles) in our case was striking, leading to torticollis. Serum enzymology including CPK tended to be normal. In the case reported by Bonnette *et al.* (1975) mildly elevated serum CPK was seen. Multicore disease usually does not show progression of clinical symptoms, as originally stated by Engel *et al.* (1971). In fact, our two patients have shown encouraging improvement. The adult patient of Bonnette *et al.* (1975) seems the exception, since he has become progressively weaker during the 12 year period since onset.

Pathologically, the disease is characterized by the presence of numerous lesions similar to those found in central core disease. These lesions, which involve most muscle fibres and are multiple within each involved fibre, are best seen with the light microscope after fresh frozen tissue sections are stained with oxidative enzyme methods. They appear as areas of decreased or absent oxidative enzyme activity.

Ultrastructurally, the lesions are marked by myofilament disruption and disorganization accompanied by Z-band streaming. Mitochondria are absent in the lesions.

Multicores differ from central cores (Engel *et al.*, 1971; Heffner, 1975) in that they are frequently eccentric rather than central. They are smaller than central cores, which typically extend the length of the muscle fibre, and are much more numerous. Unlike central cores, multicores are not uncommonly oriented with their long axes perpendicular to the long axis of the muscle fibre. Whereas multicores affect both fibre types, central cores, like target changes, tend to occur primarily in type 1 fibres. Other pathological features of multicore disease include type 1 fibre predominance which was most noteworthy in the case reported by Bonnette *et al.* (1975). In three cases (Bonnette *et al.*, 1975 and our cases) type 1 fibre atrophy was present.

The pathogenesis of the muscle lesions in multicore disease is unknown. Similar lesions (target fibres) have repeatedly been observed in denervating diseases from many causes (Engel, 1961; Schotland, 1969) and in central core disease, a probable myopathy. Engel *et al.* (1971) have suggested that the basic process begins in the mitochondria. This idea is based partly on the fact that in all reported cases mitochondrial lesions seen on oxidative enzyme stains are more numerous than myofibrillar lesions seen on ATPase stains. Ultrastructurally, Engel *et al.* (1971) saw numerous

foci of mitochondrial loss which were far more numerous than areas of myofibrillar and Z-band changes. These authors postulated that the mitochondrial alterations therefore preceded the abnormalities in the contractile elements. We and Bonnette *et al.* (1975) were unable to substantiate these ultrastructural findings.

REFERENCES

Aherne, W., Ayyar, D. R., Clarke, P. A., and Walton, J. N. (1971). Muscle fibre size in normal infants, children, and adolescents. An autopsy study. *Journal of the Neurological Sciences*, **14**, 171–182.

Bonnette, H., Roelofs, R., and Olson, W. H. (1975). Multicore disease: Report of a case with onset in middle age. *Neurology (Minneap.)*, **24**, 1039–1044.

Brooke, M. H., and Engel, W. K. (1969a). The histographic analysis of human muscle biopsies with regard to fiber types. 1. Adult male and female. *Neurology (Minneap.)*, **19**, 221–233.

Brooke, M. H., and Engel, W. K. (1969b). The histographic analysis of human muscle biopsies with regard to fiber types. 4. Children's biopsies. *Neurology (Minneap.)*, **19**, 591–605.

Engel, W. K. (1961). Muscle target fibers, a newly recognized sign of denervation. *Nature*, **191**, 389–390.

Engel, A. G., and Gomez, M. R. (1966). Congenital myopathy associated with multifocal degeneration of muscle fibers. *Transactions of the American Neurological Association*, **91**, 222–223.

Engel, A. G., Gomez, M. R., and Groover, R. V. (1971). Multicore disease. A recently recognized congenital myopathy associated with multifocal degeneration of muscle fibers. *Mayo Clinic Proceedings*, **46**, 666–681.

Heffner, R. R. (1975). Electron microscopy of disorders of skeletal muscle. *Annals of Clinical and Laboratory Science*, **5**, 338–347.

Schotland, D. L. (1969). An electron microscopic study of target fibers, target-like fibers and related abnormalities in human muscle. *Journal of Neuropathology and Experimental Neurology*, **28**, 214–228.

Shy, G. M., and Magee, K. R. (1956). A new congenital non-progressive myopathy. *Brain*, **79**, 610–621.

Stefanini, M., DeMartino, C., and Zamboni, L. (1967). Fixation ejaculated spermatozoa for electron microscopy. *Nature*, **216**, 173–174.