Autosomal dominant multicore disease

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SUMMARY Two girls and their mother with multicore myopathy are described. The cores consisted of Z band disorganisation and decreased or absent enzyme activity. Only one case has clinical signs of myopathy. Muscle enzyme activity was elevated in the two children. The mode of inheritance was autosomal dominant.

The first case of benign congenital nonprogressive myopathy with multiple cores was reported in 1966 by AG Engel.¹ Histochemical and electron microscopic studies in this and subsequent case reports²⁻⁷ revealed strikingly similar patterns. Three additional cases—two girls and their mother—are now described. They present some particular features: creatinekinase activity was elevated in the two children, the severity of clinical signs and histological changes varies in the three cases and the mode of inheritance seems to be autosomal dominant, in contrast with previous case reports.

Case reports

Case 1 A five-year-old girl presented in 1977 with complaints of excessive muscular fatiguability of the lower legs and cramps in the calves, the latter disappearing when standing on tiptoe. Pregnancy and birth (in June 1972) were uneventful. Birth weight was 3200 g. Motor development was normal; she sat at 6 months and walked at the age of 1 year. When she was 4 years old she became unable to walk long distances because of muscular fatiguability. At school, gym lessons had to be missed for the same reason. During the last year (1980-1981) improvement of the walking difficulties occurred. Examination in 1977 showed a 5-year-old leptosomatic girl with decreased muscle bulk of the trunk and the extremities and winged scapulae. Although the shoulder and pelvic girdle musculature was hypotrophic, only slight weakness of the proximal muscles was present. The patellar reflexes could not be elicited and all other myotatic reflexes were hypoactive. Plantar responses were flexor. Sensory examination was normal. Abnormal laboratory findings consisted of increased muscle enzyme activity with a creatine kinase of 206 U/l (normal

less than 40 U/l) in 1977 and 150 U/l in 1978. Lactic dehydrogenase activity was slightly elevated at 220 U/l (normal to 170 U/l) with increased LDH₂ isoenzyme fraction (46.2%). The ECG was normal. Neurophysiological investigations showed normal conduction velocities, on electromyogram a normal interference pattern was seen and there was a slight increase of polyphasic motor-unit potentials. Amplitudes were within normal ranges. Muscle biopsy was performed when she was 5 years old. The patient was followed for 5 years and during this period improvement of muscular complaints was noted (fig 1).

Case 2 The older sister of patient 1 was born in August 1968 after a pregnancy of 7½ months. The labour was without complications and she remained in an incubator for three weeks. There was no history of floppiness and the developmental milestones were normal. Speech developed rather late—possibly due to social neglect—but reached a normal level during her stay at the kindergarten. At the age of six she noticed some excessive muscular fatigue on running which slowly improved during the following 6 years. Examinations in 1978 showed a healthy 10-year-old girl with livedo reticularis on both legs. The muscles seemed well developed and only slight winging of the scapulae was present. There was no muscular hypotonia or weakness. Tests for abnormal muscle fatiguability were unremarkable. Sensory examination was normal. Neurophysiological investigations showed neither neurogenic nor myopathic changes. Abnormal laboratory findings were confined to increased creatine kinase activity (106 U/l, normal to 40 U/l) and increased LDH activity (206 U/l, normal to 170 U/l) with a raised LDH₂ fraction. A slight rise of both creatine kinase and aldolase was again present at the age of 13 (1980). The ECG showed multiple extra systoles, but was otherwise normal. A muscle biopsy was performed when she was 13 years old in March 1981 (fig 2).

Case 3 The mother of the two girls was examined in 1978, at the age of 37 yrs. During her childhood she experienced the same muscular fatiguability as her

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Fig 1 Case 1, at the age of 9 yr (1981).

daughters, with a predominance in the lower legs. In the same period she possibly suffered from spontaneous patellar luxation on both sides. No more details concerning this episode could be obtained. Muscular complaints progressively disappeared during her adolescence. Reexamination in 1981 showed a 40-year-old woman with leptosomatic habitus. Muscular strength was normal and no excessive fatigability was found. Myotatic reflexes were brisk and symmetric. Muscle enzyme activities and electrophysiological investigations were normal. A needle muscular biopsy was performed in May 1981.

Methods

Biopsies from the left quadriceps muscle in the two girls were obtained at the age of 5 yr (1977) in case 1 and the

age of 12 yr (1981) in case 2, under local anaesthesia. In case 3 a percutaneous needle biopsy of the right quadriceps muscle was performed at the age of 40 yr (1981), under local anaesthesia. Specimens for paraffin sections were fixed in neutral formalin. Specimens for electron microscopy were fixed with a 2% glutaldehyde solution, post-fixed in 2% osmium tetroxide and embedded in Epon 812. Sections of one μm were stained with toluidine blue. Ultra-thin sections were cut on a LKB-3 ultramicrotome and examined with a Zeiss EM-9 electron microscope. Paraffin sections were stained with haematoxylin and eosin (H and E), modified Gomori trichrome and phosphotungstic acid haematoxylin (PTAH). Specimens for histochemistry were cut at 6 μm in a cryostat at -18°C and serial sections were stained with H and E, modified Gomori trichrome, myofibrillar adenosine triphosphatase (ATPase) at pH 9.4 and (after preincubation) at pH 4.3

Fig 2 Case 2, at the age of 13 yrs (1981).

and with nicotinamide-adenine dinucleotide-tetrazolium reductase (NADH-TR). Longitudinally and cross-sectional oriented sections were processed to localise NADH-TR and ATPase activity.

Results

Case 1 On light microscopy a marked variability of muscle fibre diameter was observed reaching from 10 μm to 100 μm . There were some internal nuclei. Some fibres showed splitting, resulting in small clumps of fibres of the same type. In addition some small angular fibres were found. In some places slight endomysial fibrosis was observed. There was no cellular infiltration. The ATPase at pH 9.4 stained

sections revealed a fibre I predominance of 90%. Focal decrease of myofibrillar ATPase activity appeared in many fibres. On cross sections, these cores of decreased enzyme activity had variable sizes, ranging from 5 μm to 45 μm . In sections with NADH-TR reaction many fibres of both type I and type II disclosed areas with loss of intermyofibrillary oxidative activity. These cores were localised either in the centre of the fibres or eccentrically near the sarcolemma (fig 3). In the Epon-embedded sections multiple randomly distributed foci showing loss of cross striations and Z band disintegration were observed. Electron microscopic examination revealed circumscribed areas of Z band material disintegration surrounded by normally structured muscle

Fig 3 Case 1, transverse section of the left quadriceps muscle. The cores are located both centrally and eccentrically. NADH-TR. $\times 78$.

Fig 4 Case 1, partial lysis of Z banding, focal disintegration and streaming of Z band material 1500.

fibres whereas other fibres showed focally-containing spotted Z band material (fig 4). There were no mitochondria in the abnormal areas. In longitudinal sections decrease or even absence of mitochondrial population was seen, both in normally structured fibres and in areas with disorganised Z band material.

Case 2 On light microscopic examination a moderate variability of the muscle fibre diameter was found. Cellular infiltrations were not present. On the basis of the myofibrillar ATPase reaction at pH 9.4 a slight fibre I predominance of 60% was observed. Stains with ATPase and with NADH-TR reaction demonstrated multiple irregularly distributed areas of decreased or absent enzyme activity. These cores were randomly distributed either near the sarcolemma or in the centre of the fibres. Their

diameter varied from 3 to 30 μm . The number of affected fibres varied in the different fascicles ranging from 4 to 17%. In the Epon-embedded sections some fibres showed areas with loss of cross-striations with whirling or even complete disintegration of Z band material. Electron microscopic examination of longitudinal sections revealed a marked decrease of the mitochondria population in regions with intact myofibrillar structures and absence of mitochondria in the areas with irregularly shaped spots and streaming of Z band material (fig 5). In cross sections multiple cores were seen, consisting of disorganised Z band material and absent mitochondria.

Case 3 Paraffin sections disclosed a normal variability of the muscle fibre diameter. In the ATPase preparations about 50% of the fibres were of type I. In sections stained with NADH-TR some fibres showed small cores with loss of cross-striations. The length of these cores was 7 to 10 μm and the diameter was between 10 and 12 μm . Electron microscopic examination revealed the same disintegration or even complete disappearance of Z band structure in some fibres, as seen in the two other cases. In transverse sections, foci of spotted Z band material were present, wherein no mitochondria were detected (fig 6). In contrast with the two previous cases, a normal mitochondrial population was found in the areas with structurally normal myofibrils.

Discussion

Since the first report of a young boy with multicore myopathy, several patients with very similar multi-

Fig 5 Case 2, detail of unstructured core with distortion and measuring of Z band material. $\times 6000$

Fig 6 Case 3, transverse section of right quadriceps femoris muscle. One of the fascicles displays an eccentrically located core with electron-dense Z band material. $\times 415$

core disease have been described, both in children and in adults.¹⁻⁹ The latter however showed a slowly progressive course in contrast with the children, in whom non-progression² or improvement³ has been observed.

The similarities of histochemical and ultrastructural changes consist of multiple haphazardly distributed cores with loss of cross striations, Z band streaming or disruption, severely diminished or absent oxidation enzyme activity and—if present, to a variable extent—myofilament disorganisation. The diameter of the cores usually vary between 5 μm and 50 μm . One family in which muscles contained very small cores with thinning of Z band material and loss of myofibrillar structure was described as having minicore disease.⁷ However, being very similar to multicore disease it has already previously been considered as identical to it.⁴ The same considerations can be made about cases with focal loss of cross striations,^{8,9} whose unique difference consisted of a better preservation of myofibrillar structure⁸ and the presence of vesicular nuclei with prominent nucleoli in the abnormal areas.⁹

Additional common features in myopathies with multicores are a marked fibre I predominance^{5,7,9} and a greater decrease of mitochondrial oxidative enzyme activity compared with reduction of ATPase activity.² Less frequent abnormal findings are an increase of internal nuclei^{3,4,9} and abundance of sarcotubular profiles or ribosomes in normal muscle areas.^{2,3}

In late-onset forms, fibre II hypertrophy and arrays of transverse tubules were noted in Bonnette's case,³

whereas Aström⁶ noted spiral annulets, numerous autophagic vacuoles and occasional fibre disfiguration. The mode of inheritance in previously reported multicore disease families was thought to be an autosomal recessive one.^{4,9}

The present family with three cases of multicore disease show some interesting features: only one member (case 1) displays clinical signs and symptoms of myopathy; the severity and extent of histopathological changes are variable in the three members, muscle enzyme activity was elevated in both children and finally the mode of inheritance seems to be an autosomal dominant one. The youngest girl (case 1) appears to be a "classical" multicore disease, very similar to Engel's patients,² both in clinical presentation and in its morphological and cytochemical aspects. In case 2, there are no apparent signs or symptoms suggesting a myopathy but an elevated CPK activity raised the possibility of myopathy and muscle biopsy was performed, revealing milder multicore disease than in her younger sister: fibre I predominance was limited to 60%, the cores were smaller and less numerous but decreased mitochondrial population occurred also in normally structured fibres without cores, as in case 1. The mother of the two girls (case 3) presented morphologically as a slim, mannequin-looking woman, without complaints of muscular fatigability and without clinical or biochemical signs of myopathy. The biopsy however revealed small areas of Z band disintegration and loss of mitochondria. When Meltzer's and coworkers report¹⁰ concerning Z band abnormalities in healthy young people is considered, these scanty ultrastructural changes in muscle biopsy could be construed as normal. However, on inquiry into her history it was found that she noticed excessive muscular fatigue during her childhood and that her physical performance had been poor. Progressive improvement occurred in adolescence. The hypothesis that the muscular lesions may have been more pronounced during infancy and that they progressively regressed in the second decade cannot be excluded.

The genetic aspects in this family are unique in the way that the two afflicted girls have undoubtedly different fathers—indicating an autosomal dominant mode of transmission; the presence of multicores in the quadriceps muscle of their mother confirmed this assumption. A variable penetrance in the mode of transmission seems to be the most plausible explanation.

The search for myopathic changes—even in non-symptomatic family members—is not only of academic interest, since cases of life-threatening malignant hyperthermia and myoglobinuria induced by general anaesthesia have been described

in patients with different myopathies including multicore disease.^{11 12} It seems wise to avoid drugs which have been implicated in the production of malignant hyperthermia, such as succinylcholine and halothane.^{11 12} When this mode of anaesthesia cannot be avoided or has been given inadvertently and malignant hyperthermia has developed, immediate intravenous administration of dantrolene sodium at the dose of 4 mg/kg may prove beneficial.^{13 14}

In conclusion, it can be stated that the present three additional cases of multicore disease with their particular features supports the hypothesis of other authors¹⁵⁻¹⁷ that the presence of multiple cores within one muscle fibre represents probably a non-specific finding, only presenting a similar ultrastructural expression of different neuromuscular diseases. The diminished mitochondrial population and oxidative enzyme activity in normally structured muscle areas in both our young patients provide arguments to Engel's hypothesis² that the basic process possibly begins in the mitochondria. In contrast with previous suggestions of an autosomal recessive inheritance in multicore disease, the present cases indicated an autosomal dominant mode of transmission. Finally, care and adequate measures must be taken with general anaesthesia in both multicore disease patients and apparently healthy siblings.

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