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Multicore Disease in Sibs With Severe Mental Retardation, Short Stature, Facial Anomalies, Hypoplasia of the Pituitary Fossa, and Hypogonadotrophic Hypogonadism

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We describe a family in which two adult sibs presented with a history of congenital nonprogressive myopathy, severe mental retardation and evidence of mild generalized weakness, short stature, musculoskeletal deformities, facial anomalies, sexual infantilism, and radiologic evidence of pituitary hypoplasia. The parents were first cousins. An excess of other, apparently unrelated, genetic conditions were present in other family members. Results of histochemical and electron microscopy studies of muscle biopsies from both affected individuals were compatible with multicore disease. This newly described syndrome likely is an autosomal recessive trait and appears to be the first reported association of multicore disease with mental retardation.

Key words: mental retardation, short stature, congenital myopathy, multicore disease, sexual infantilism, pituitary hypoplasia, frontal sinus enlargement, autosomal recessive inheritance

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INTRODUCTION

Multicore disease is a rare form of a heterogeneous, usually nonprogressive congenital myopathy [Engel et al, 1971]. Although the basic pathogenesis of the lesion in this muscle disease is unknown, several reports suggest that this is an inherited disorder(s) [Engel et al, 1971; Heffner et al, 1976; Lake et al, 1977; Van Wijngaarden et al, 1977; Bethlem et al, 1978]. Previous reports have commented on normal intellect in affected individuals. We report on a family in which a brother and sister presented with severe mental retardation, unusual facial appearance, short stature, sexual infantilism with associated hypoplasia of the pituitary fossa, and a nonprogressive congenital myopathy with histopathological findings consistent with multicore disease.

CLINICAL REPORTS

Family History (Fig. 1)

This family was first referred to our clinic after the birth of a stillborn infant (V-4) with multiple birth defects consisting of hemifacial microsomia, ipsilateral meatal atresia and microtia, congenital heart defect, esophageal atresia, and multiple rib and vertebral anomalies. The father of this child (IV-4) is the brother of the two sibs IV-2 and IV-6 of major interest in this report; IV-4 had no musculoskeletal complaints and had no evidence of muscle weakness. However, he was mildly mentally retarded. Cytogenetic studies uncovered the fra(X); this prompted further studies of other relatives. The parents (III-1 and III-2) were first cousins and of English ancestry. They were phenotypically and neurologically normal. No other relatives had muscle weakness or mental handicap, apart from IV-33, a first cousin of IV-2 and IV-6. IV-33 was examined at 18 years; her profound mental retardation was attributed to birth asphyxia. She had many anomalies quite different from those of her cousins; she had a large head and no evidence of a myopathy. A muscle biopsy was not obtained.

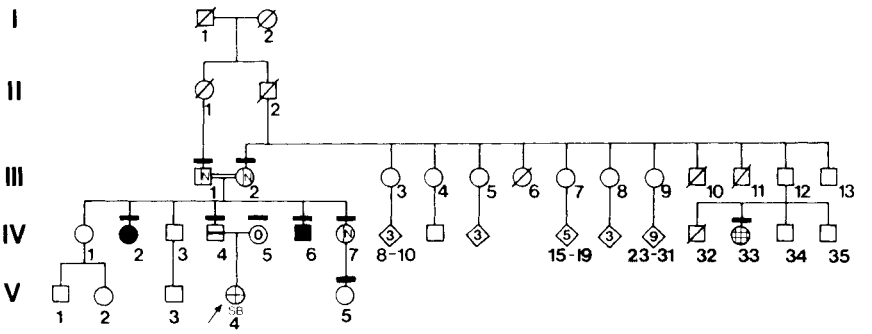

Fig. 1. The family pedigree. Affected persons are presented by solid black symbols (IV-2 and IV-6). Arrow points to stillborn (SB) proposita (V-4). ⊟ ⊖, normal chromosomes and phenotype; ⊟, mild MR, fra(X)(q27, or q28); ◎, 47,XXX; ⊕, severe MR, short stature, ? etiology. Bar over symbol, personally examined.

IV-2

This 38-year-old woman had a nonprogressive congenital myopathy and severe mental retardation. She was born at term weighing 2,100 gm. The pregnancy was uneventful with no history of exposure to teratogenic agents or of birth asphyxia. She was floppy from birth and had feeding difficulties. She sat unsupported at 9 mo and walked at 18 mo. All other motor and cognitive development was severely delayed. At 17 yr she was admitted to an institution for the mentally handicapped. She was on medication for "arthritis" over the past 10 yr but was otherwise in good health.

On examination, she was obviously retarded but cooperative. She walked with a shuffling, spastic, wide-based gait and had an exaggerated lumbar lordosis (Fig. 2a,b). She was short with a height of 141 cm (< 3rd centile) and a weight of 39.6 kg (< 3rd centile). Her arms appeared disproportionately long compared to her trunk (arm span, 148 cm; upper segment/lower segment ratio, 0.93). She had borderline microcephaly with a head circumference of 52 cm (5th centile). She had bilateral facial weakness and an unusual facial appearance with bilateral ptosis, apparent hypertelorism, antimongoloid slant of palpebral fissures, right exotropia, reduced upward gaze, a mild reduction in downward gaze, prominent bridge of nose, highly arched palate with reduced palatal mobility, structurally normal but carious dentition and normally placed, and anteverted ears (Fig. 2c,d). Fundi were normal. She wore glasses for myopia. There was moderate wasting of the sternocleidomastoid muscles. Heart, lungs, and abdomen were unremarkable. She was sexually immature with almost-absent breast tissue, no axillary hair, and fine silky pubic hair with infantile female external genitalia. She had a severe lumbar lordosis, mild limitation of extension at elbows, hips, knees and ankles, and bilateral pes planus. There was bilateral clinodactyly, but the palmar creases and dermatoglyphics were normal (Table I).

She had moderate bradykinesia and weakness of the trunk, and hip girdle and mild proximal muscle weakness of the upper limbs. The deep tendon reflexes were symmetrically mildly increased with bilateral upgoing toes on plantar stimulation. Sensation appeared intact. No myotonia was elicited.

IV-6

The severely retarded 25-year-old brother had a phenotype very similar to that of IV-2. He was the fifth-born in the family after an uneventful term pregnancy. He weighed 3,250 gm at birth and cried immediately. His gross motor and cognitive development also was severely delayed. He sat at 9 mo, walked at 20 mo, and began speaking single words at 36 mo. His mother noted "weak" muscles in him since infancy. He was admitted to an institution for the mentally handicapped at 10 yr. At 18 yr he underwent a laparotomy for a bowel obstruction due to ingested foreign bodies. Otherwise, he has been healthy. On examination, he was short with a height of 147 cm (< 3rd centile), weighed 41.5 kg (< 3rd centile), and had a small head (OFC 53 cm, 5th centile). He had a mild lumbar lordosis and his arms looked disproportionately long compared to his trunk (arm span was 152 cm with an upper segment/lower segment ratio of 1.0) (Fig. 3a,b). He had bilateral ptosis, apparent hypertelorism, bilateral facial weakness, antimongoloid slant of the palpebral fissures, left exotropia, a marked reduction of upward gaze with moderate limitation in downward gaze, moderate myopia, and normal fundi (Fig. 3c,d). He had a highly

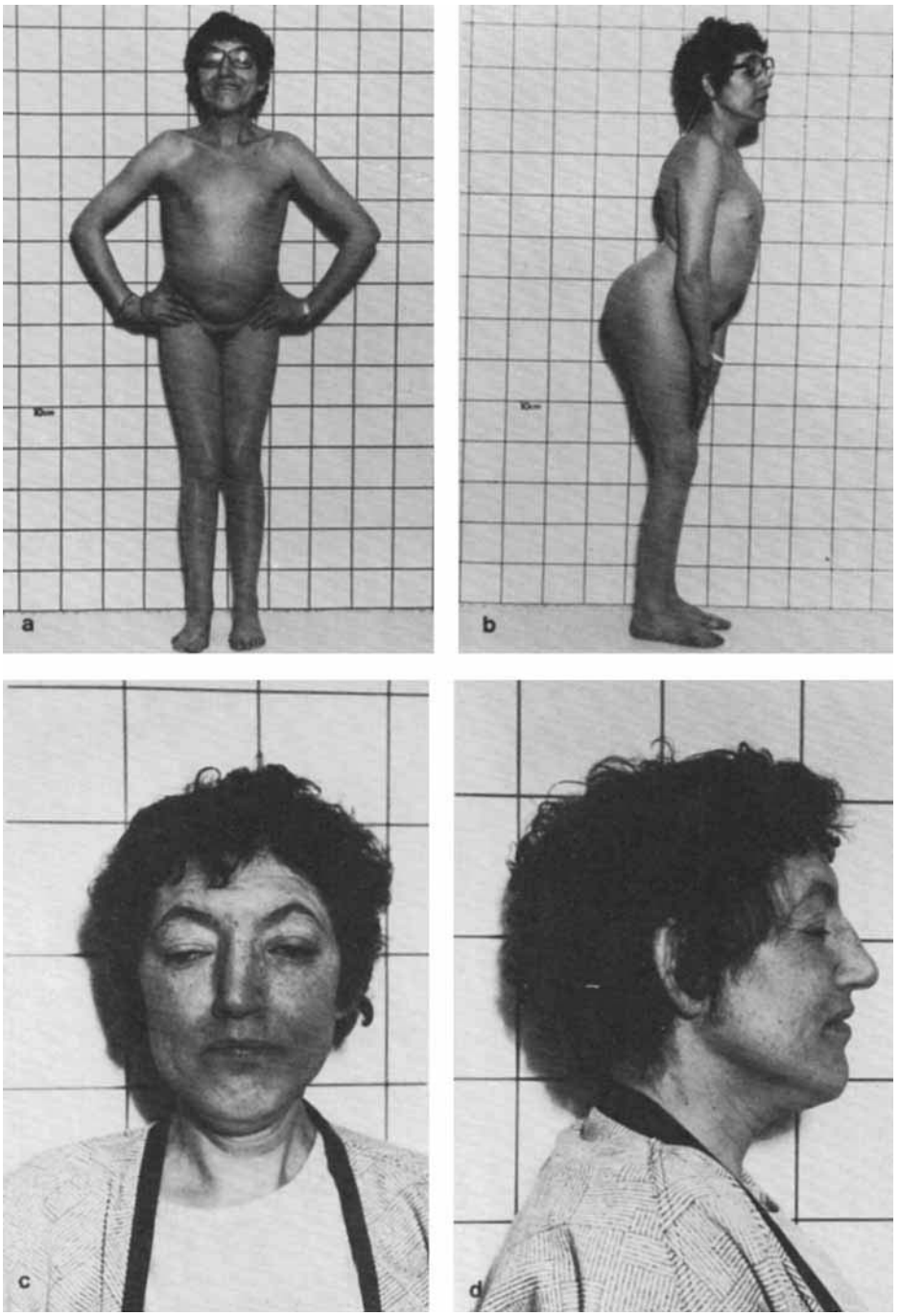

Fig. 2. IV-2, age 38 yr, (a) and (b) full body AP and lateral views: note short stature, sexual infantilism, and marked lumbar lordosis. (c) and (d) close up face, AP and lateral: unusual facial appearance with facial paresis, apparent hypertelorism, exotropia, ptosis and wasting of sternocleidomastoid muscles.

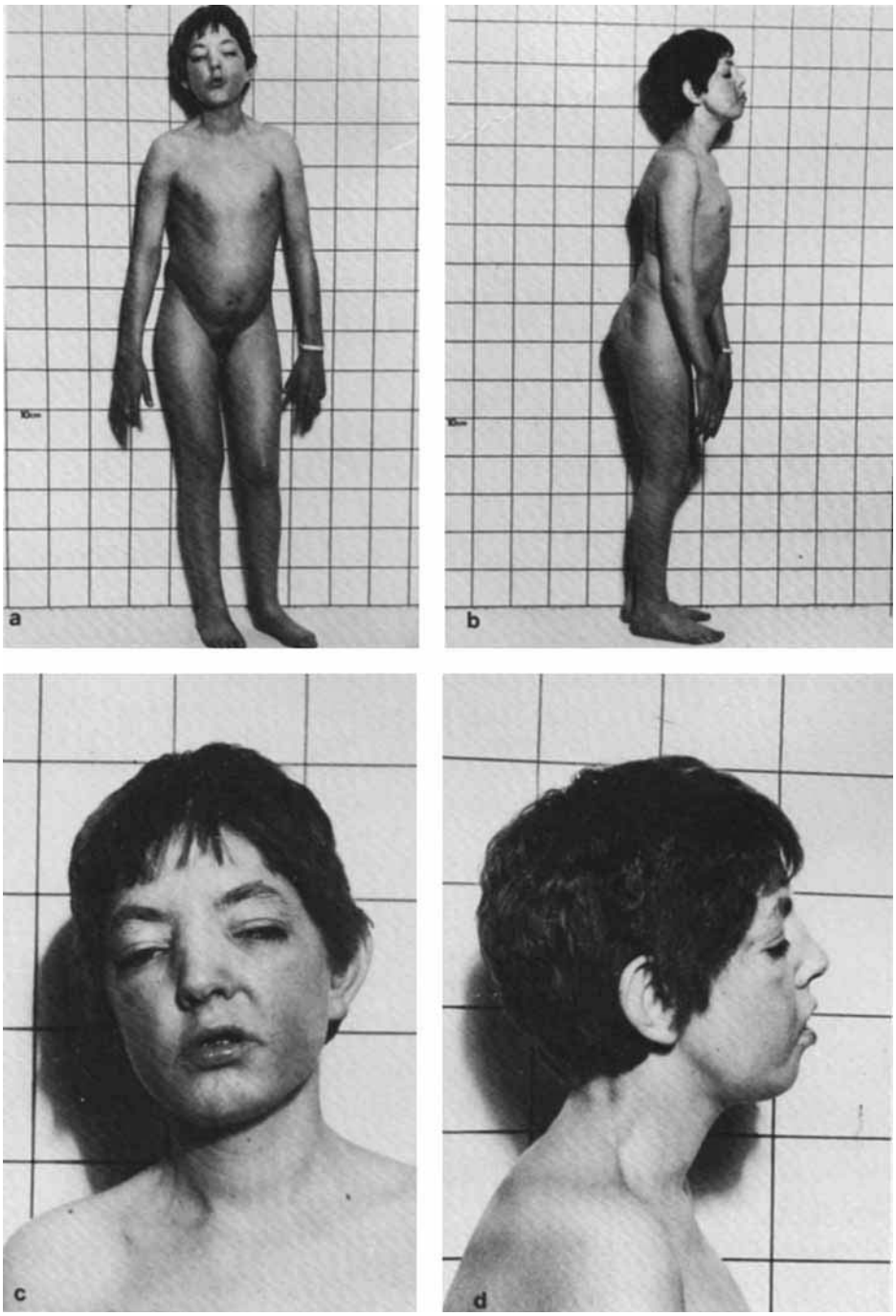

Fig. 3. IV-6, age 25 yr, (a) and (b) full body AP and lateral views: note short stature, mild lumbar lordosis and sexual infantilism. (c) and (d) close up face, AP and lateral: Note similar facial changes as in IV-2.

Table I. Dermatoglyphic Analysis

		Digits[a]										Total ridge count	*atd* angle (degrees)		Palm
		Left					Right								
		5	4	3	2	1	1	2	3	4	5		Left	Right	
IV-2	Patterns	L^u	L^u	L^u	L^r	W^s	W^s	A	L^u	W^s	L^u	100	39	40	Unremarkable
	Ridge count	13	13	4	5	20	16	—	5	14	10				
IV-6	Patterns	L^u	L^u	L^u	L^r	L^u	L^u	L^r	L^u	L^u	L^u				Normal creases
	Ridge count	13	16	10	3	9	19	4	11	15	14	114	55	58	Bilateral *t″* Ulnar loop in both hypothenar regions

[a]L^u, ulnar loop; L^r, radial loop; W^s, spiral whorl; A, simple arch.

arched palate with reduced palate movement and frequent drooling of saliva. Several teeth had been extracted because of gum abscesses and trauma. There was mild wasting of the sternocleidomastoid muscles. He also had evidence of a mild pectus carinatum. Heart, pulses, lungs, and abdomen were normal. The genitalia were infantile, the penis was small (2.4 cm long), and the testes were undescended. Pubic hair was scant with a female escutcheon. Facial and axillary hair was absent. Bilateral clinodactyly was present; palmar creases were normal and dermatoglyphics showed *t″* axial triradii (Table I). He had mild limitation of extension at the elbows, hips, and knees, and bilateral pes planus. Muscle strength in the limbs was mildly diminished (proximally more than distally) and there was mild truncal weakness. He demonstrated a partial Gowers manoeuver on arising from a sitting position on the floor. Deep tendon reflexes were symmetrical and brisk. Babinski sign was present bilaterally. Position and vibratory senses were intact. There was no evidence of pseudohypertrophy or myotonia.

METHODS

Standard histochemical methods were used in preparing and staining the muscle biopsies [Dubowitz and Brooks, 1973]. Cytogenetic studies followed the routine methods utilized in our laboratory [Chudley et al, 1983]. Growth hormone assays were performed using a radio immunoassay (courtesy of Dr. H. Friesen, University of Manitoba, Winnipeg, Manitoba). All of the laboratory testing was performed using standard methods in University Hospital, Saskatoon, Saskatchewan. The revised Stanford-Binet test was used for psychometric studies of the patients.

RESULTS

Laboratory Investigations

ECG and EMG studies were normal in both individuals. Nerve conduction studies were not carried out. The following studies were performed with normal results in both IV-2 and IV-6; complete blood count, electronmicroscopy studies of the white cells, urinalysis, blood gases, serum glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, urea nitrogen, total proteins, SGOT, SGPT, LDH,

CPK, alkaline phosphatase, cortisol, T3, T4, TSH, urine screen for amino acids, mucopolysaccharides, and reducing sugars. Arginine, L-Dopa, and propranolol stimulation resulted in normal growth hormone responses. Serum gonadotropin levels were low in both individuals. In IV-2, serum FSH was 4 IU/L (nonovulating normal 5.9–17 IU, postmenopausal normal 37–200 IU/L), serum LH was 5 IU/L (premenopausal normal 6–30 IU/L, postmenopausal > 30 IU/L). In IV-6, serum FSH was 3 IU/L (normal 4–25 IU/L), serum LH was < 5 IU/L (normal 7–24 IU/L), and serum testosterone was low, 3.9 nl/L (normal 10–42 nl/L).

Radiological Investigations

IV-2. A skeletal survey documented mild generalized osteopenia, with markedly delayed maturation and lack of union of growth plates of the medial aspects of the clavicles, manubriosternal joints, along the superior iliac crest and at the ischiopubic junction. There was mild bilateral coxa valga. Anterior inferior notches of the bodies of the cervical vertebrae reflected incomplete development of the normal ring apophyses. The overall bone age was 17 yr (chronological age 38 yr). The cranial vault was small with a thickened calvaria, hypoplastic pituitary fossa, incompletely fused lambdoid sutures, and large frontal sinuses. On CT scan, the brain was normal.

IV-6. Similar and more severe retardation in skeletal maturity was seen and all major growth lines were still open with a bone age of 15.5 (chronologic age 25.5 yr). The cranial vault was small with a moderately thick-walled calvaria and massive overdevelopment of the frontal sinuses. The pituitary fossa was shallow and hypoplastic (Fig. 4a,b). There was mild bilateral coxa valga. A CT scan of the brain showed mild dilatation of the lateral ventricles suggesting mild cerebral atrophy.

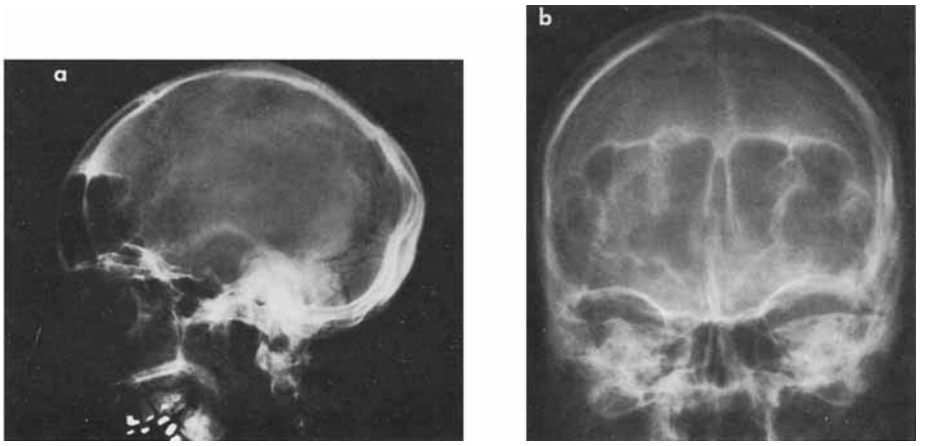

Fig. 4. (a) lateral view of skull: note the prominence of all sinuses, small brain, thick calvaria, and hypoplastic sella turcica. (b) AP view of skull: note large frontal sinuses.

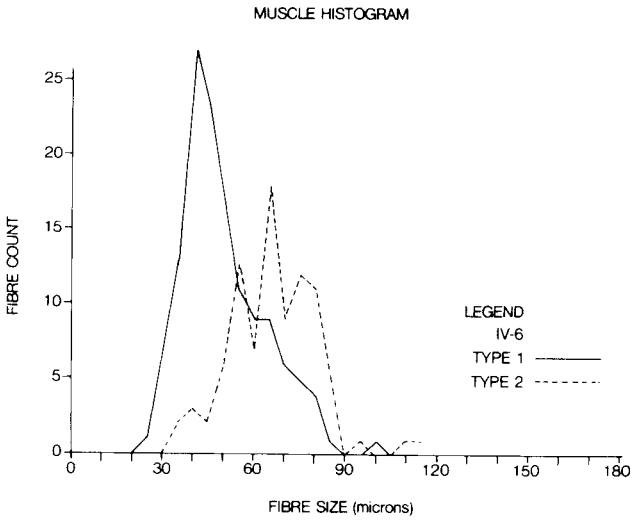

Fig. 5. Muscle histogram of IV-6. Note predominance of type I fibre atrophy.

Cytogenetic Studies

Chromosome studies were done on a number of relatives. Extended chromosome preparations on IV-2, IV-6, and IV-33 showed no evidence of aneuploidy, deletions, duplications, or fragile sites. IV-4, showed the fra(X) in 3% of his cells examined [46,XY,fra(X)(q28)]. His wife, IV-5, had an extra X chromosome present in all her cells examined (47,XXX). The findings in IV-4 and IV-5 and birth defects in their stillborn offspring, the proposita (V-4), were considered coincidential findings. Results of the chromosome studies in this family are described in detail (Family "E") in another report [Chudley et al, 1983].

Psychometric Studies

IV-2 was cheerful and talkative throughout the assessment, although her speech was dysarthric and hypernasal in quality. She scored an IQ of 21, which places her in the severe retardation range of mental ability.

IV-6 appeared quite distractible but was friendly and cooperative. His speech was unclear, highly dysarthric and for the most part unintelligible. He scored an IQ of 19, which is at the top end of the profound retardation range of mental ability.

Histopathology

Muscle biopsies were taken from the right quadriceps from both individuals. Histopathological changes were essentially identical in both sibs. There was moderate variation in fiber diameter and approximately one half of the fibers contained internal nuclei. There was no evidence of muscle necrosis, inflammation, regeneration or replacement fibrosis. Enzyme histochemical stains (ATPase, STH, LDH, PAS) were done. There was type I predominance in most small fibers (Fig. 5). There were numerous cores of myofibrillar disruption and focal absence of cross striations. The small focal "multicore" lesions, usually multiple in each involved muscle fiber, were frequently located in a somewhat eccentric position and oriented perpendicular to the long axis of the fiber (Figs. 6 and 7). Although easily discernible in the routine

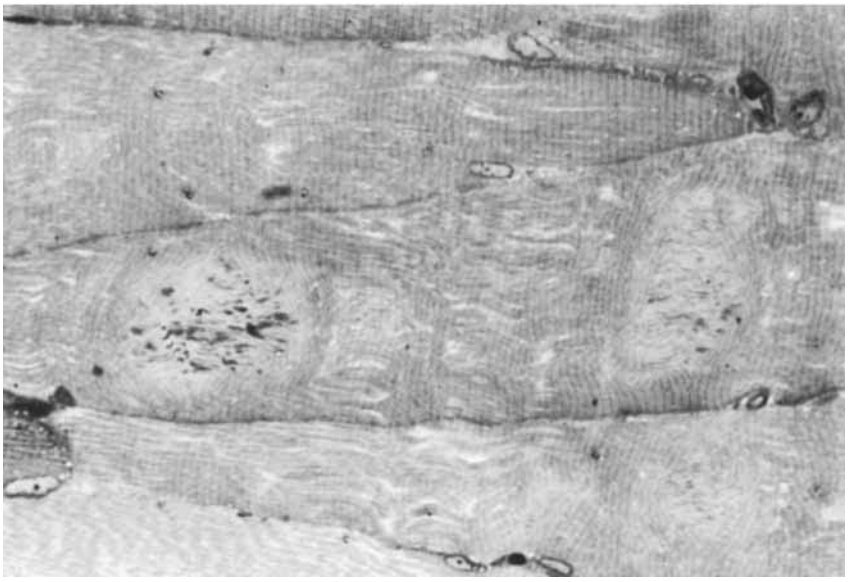

Fig. 6. IV-2. Facal loss of striated pattern in longitudinal section of muscle. Centrally located fiber shows two cores with numerous rod-like structures. 1 μ section of epoxy-embedded tissue, Toluidine blue stain, × 250.

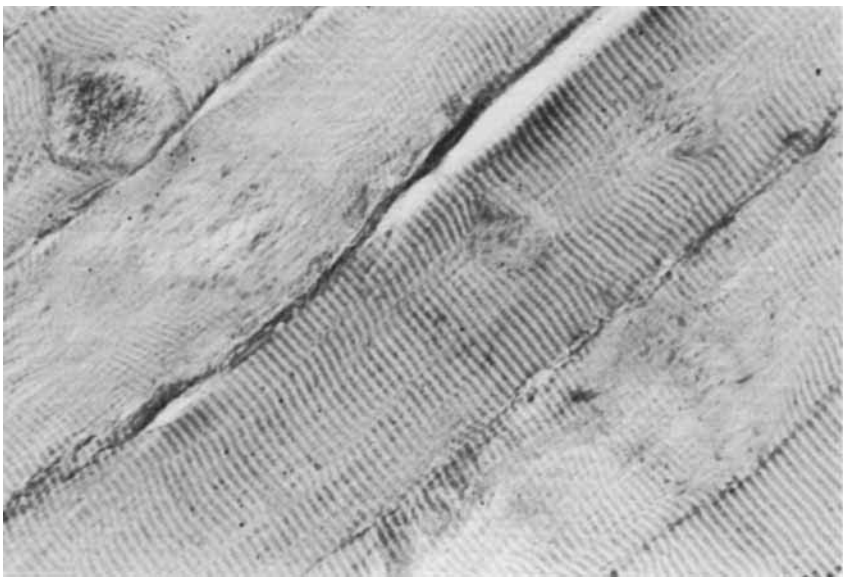

Fig. 7. IV-6. Several adjoining muscle fibers with several multicore lesions. Phosphotungstic acid hematoxylin, × 250.

chromatic stains, the multicore lesions were better seen in PTAH (phosphotungstic acid hematoxylin) stains. In the one micron epoxy-embedded section, many of the multicore lesions contained collections of minute, elongated, dark-stained, rod-like structures. There was evidence of disturbance of the longitudinally arranged myofibrils within those lesions in which the main characteristic was focal loss of cross-striations. A few vesicular nuclei with prominent nucleoli were found within or around the multicore lesions. Electron microscopy studies showed myofilament disruption and/or total disorganization of the filaments, associated with derangement and fragmentation or streaming of the Z-bands (Figs. 8 and 9). There was a notable absence of mitochondria within the lesions (Fig. 10). In surrounding normal tissue, no definite abnormality in mitochondrial structure was present. The transition between the normal and abnormal portion of the fiber was usually abrupt.

In summary, the biopsies from both sibs showed variation in fiber diameter, internal nuclei, type I atrophy, focal loss of cross striations, and cores of myofibrillar disruption with associated absence of mitochondria.

DISCUSSION

The association of multicore disease with severe mental retardation, secondary facial anomalies, short stature, pituitary fossa hypoplasia, and selective hypogonada-

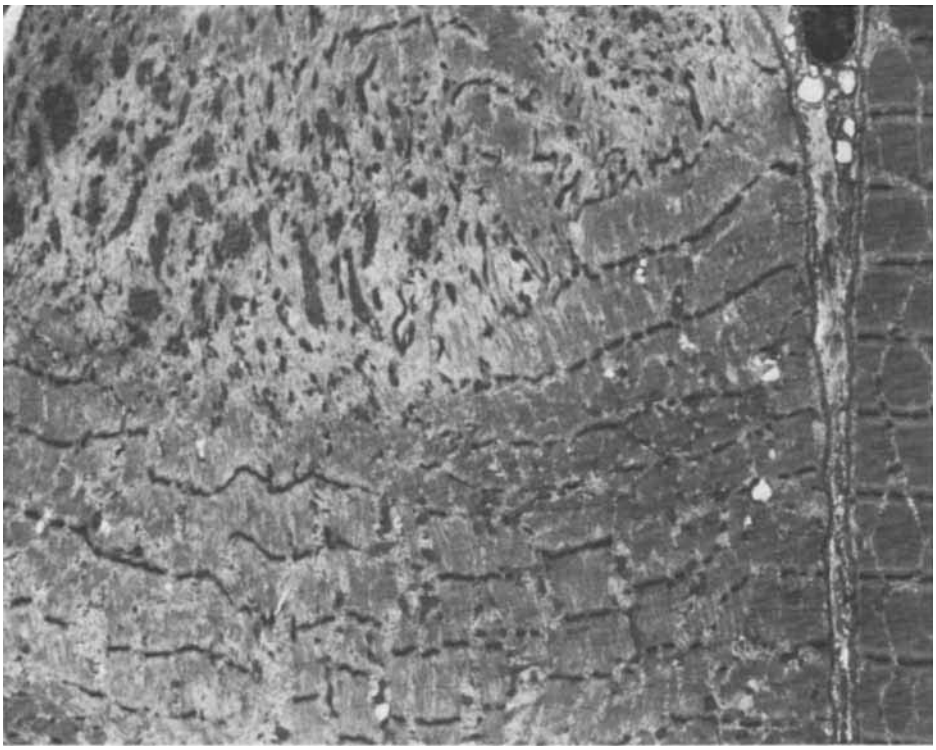

Fig. 8. IV-2. Ultrastructure of multicore lesion with disruption of myofilaments and numerous streaming segments of Z bands and rod-like fragments of electron dense material, × 18,000.

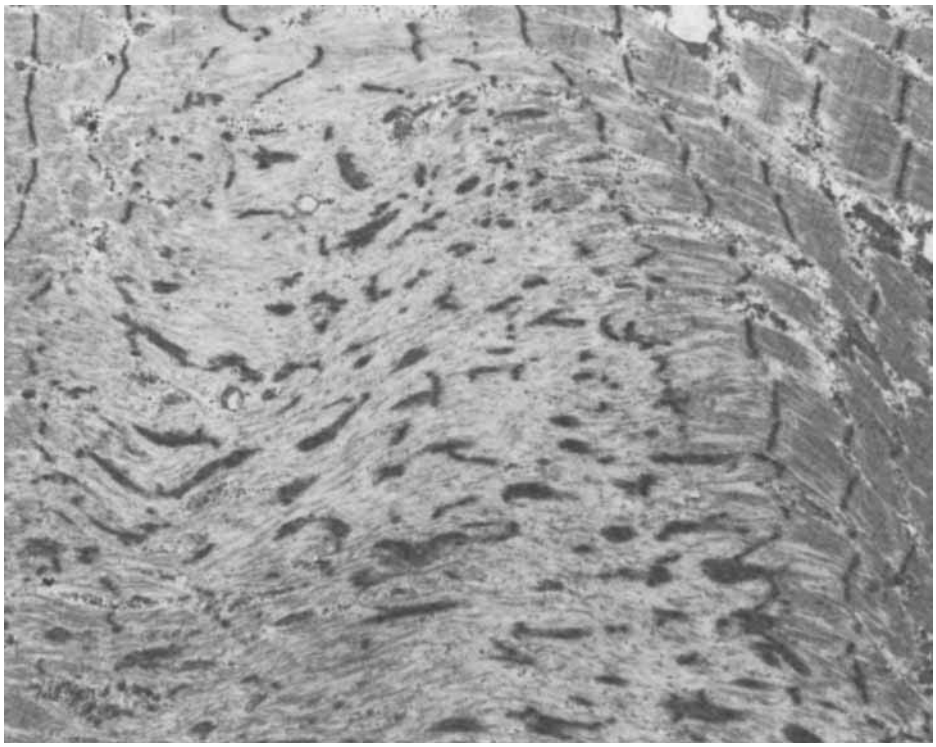

Fig. 9. IV-6. One of multicores showing widespread streaming of Z disc material and complete disorganization of sarcomeres, × 18,000.

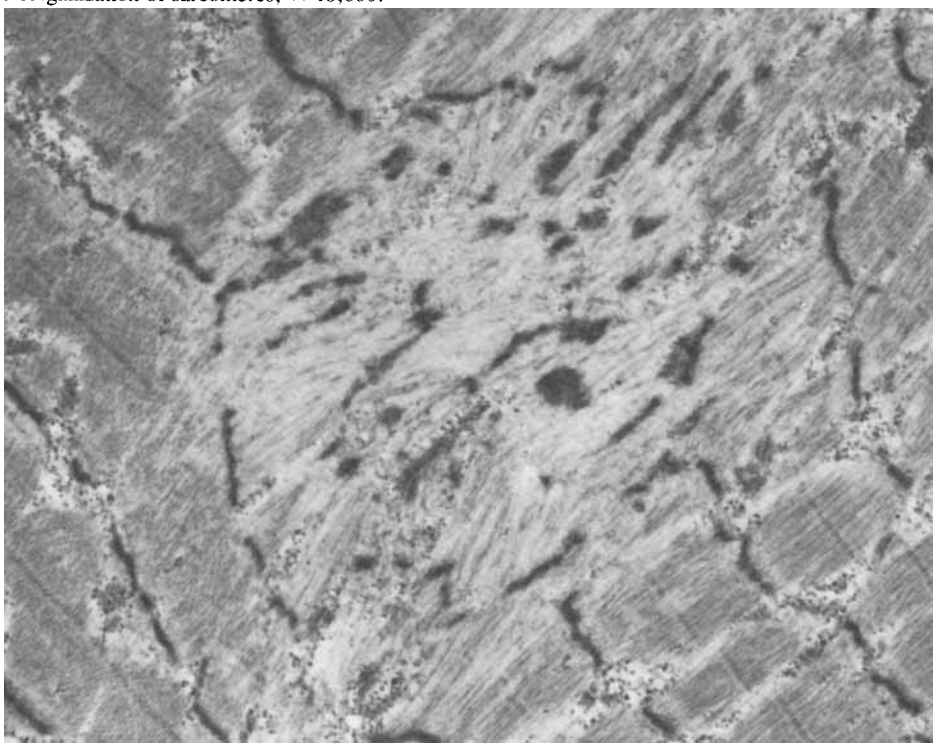

Fig. 10. IV-6. Loss of mitochondria with partial preservation of glycogen granules within multicore, × 48,000.

trophic hypogonadism in the two sibs of this report appears unique. Although muscle biopsies were not obtained from unaffected relatives, all were phenotypically normal, and all had normal sexual development. Based on the presence of consanguinity in the parents of these similarly affected sibs of different sex, the condition is likely inherited in an autosomal recessive manner. The excess number of individuals with different genetic abnormalities in the pedigree is noteworthy but probably unrelated to the disease in the sibs of this report. It is unlikely that the association of this congenital nonprogressive myopathy with multicore lesions and the other abnormalities in these individuals is coincidental. The odds are in favour of this disorder being the result of the homozygous state of a single autosomal recessive gene rather than the homozygous state of autosomal recessive genes at two different loci (0.264 vs 0.007, based on expansion of the binomial equation and where there are two affected of five in the sibship). Extended chromosomes did not show evidence of any cytogenetic abnormality.

Since the first description of multicore disease [Engel et al, 1971], a few reports identified similar findings in individuals with a congenital myopathy [Engel et al, 1967; Schotland, 1967; Heffner et al, 1976; Lake et al, 1977; Van Wijngaarden, 1977; Bethlem et al, 1978; Godath et al, 1978; Taratuto et al, 1978]. The myopathy is characterized clinically by a benign, congenital, nonprogressive muscle weakness, although onset of disease in a middle-aged man [Bonnette et al, 1974] is described in one report. Lee and Yip [1981] reported on a fatal case of congenital myopathy with histopathological findings consistent with multicore disease. To date, individuals affected with multicore disease have been intellectually normal. Reported associated anomalies include congenital heart disease and dolichocephaly [Engel et al, 1971; Heffner et al, 1976]. Although the disease has been seen in sibs, the mode of inheritance is not known [Heffner et al, 1976; Lake et al, 1977; Van Wijngaarden et al, 1977].

The diagnosis of multicore disease is confirmed in muscle biopsies demonstrating the presence of numerous lesions similar to, but smaller than, those found in central core disease. The lesions are generalized and are usually multiple within each involved fibre. They can best be seen in fresh frozen specimens stained with oxidative enzyme methods. Ultrastructural characteristics of the lesions include myofilament disruption and Z-band streaming with absence of mitochondria. Although the multicores affect both fiber types, type I fiber predominance with atrophy is usually present [Bethlem et al, 1978]. All of the above characteristics of multicore disease were present in the affected sibs of this report.

Several congenital myopathic syndromes are noted for structural changes in muscle including central core disease [Shy and Magee, 1956], nemaline myopathy [Shy et al, 1963] and focal loss of cross striations [Van Wijngaarden et al, 1977]. Historically, these diseases were considered separate entities, but Bethlem et al [1978], in their 12 cases of congenital myopathy, found an overlap in the same biopsies of at least two such morphological lesions (rods, cores, minicores, and focal loss of cross striations) and they suggested that an unknown common pathogenetic mechanism may be producing a variety of lesions. This hypothesis was supported by the findings of cores, minicores, and rods in a muscle biopsy from a woman with a nonprogressive myopathy [Vallat et al, 1982]. Our two patients showed the association of multicore lesions with focal loss of cross striations. No true rods (as identified in nemaline or "rod" myopathy) were seen, but small rod-like structures were present within each of the multicore lesions. Engel et al [1971] thought these lesions were nonspecific and secondary to a variety of pathogenic stimuli. They suggested that similar lesions can be observed in some selected fibers of progressive types of muscular dystrophy,

inflammatory myopathies, experimental denervation atrophy, in red muscles of emetine or glucocorticoid-treated rats, and occasionally in human endocrine myopathies. Z-band streaming and myofibrillar disruptions have also been seen in normal healthy individuals [Meltzer et al, 1976]. However, multicore disease affects a high proportion of the muscle fibers and in contradistinction to the above, usually is nonprogressive. The basic pathogenesis of the muscle lesions remains unknown, although theories include a neurogenic origin or a developmental abnormality in the life cycle of muscle mitochondria [Engel et al, 1971].

In general, association of mental retardation and congenital myopathy is rare. Duchenne muscular dystrophy [Kozicka et al, 1971], myotonic dystrophy (especially the neonatal form) [Harper, 1979], and Fukuyama disease [McMenamin et al, 1982] may be associated with mental retardation. It is not clear what pathogenetic relationship exists between the myopathy and mental retardation in the condition of this report. In addition to the myopathy both patients had a pyramidal tract abnormality and one had mild cerebral atrophy.

Differential diagnosis of this syndrome is limited in light of the specific myopathic, endocrine, and radiological characteristics. The Börjeson-Forssman-Lehmann Syndrome, an X-linked recessive disorder associated with short stature, hypotonia, obesity, mental deficiency, large ears, coarse facial features, variable skeletal anomalies and hypogonadism can be differentiated from our cases by the pattern of inheritance, radiologic and muscle histology findings, and differences in the facial dysmorphic features (Robinson et al, 1983). Because of the sexual immaturity, retardation, short stature, limitation of joint movement, and mental retardation, we also considered the diagnosis of Noonan syndrome [Smith, 1982]. However, this diagnosis was dismissed because of the lack of many important clinical characteristics, and the presence in our patients of multicore disease, selective gonadotrophin deficiency, and the hypoplastic sella turcica. Other mental retardation syndromes with associated hypotonia and short stature that should be included in the differential diagnosis are the Cohen syndrome [Cohen et al, 1973] and the Prader-Willi syndrome [Smith, 1982]. Clinical phenotypic differences will help separate these conditions from the syndrome in this report.

Radiological evidence of hypoplasia of the pituitary fossa with selective gonadotrophin deficiency is rare. Abnormal flatness of the sella turcica and hypophyseal hypoplasia or aplasia resulting in panhypopituitarism has been reported [Ferrier and Stone, 1969; Sipponen et al, 1978]. Most occurrences of familial hypopituitarism or isolated growth hormone deficiency are thought to be inherited in an autosomal recessive manner [Rimoin et al, 1966; Ferrier and Stone, 1969; Sipponen et al, 1978]. There was no resemblance of the patients in the previously described reports with pituitary involvement and hypoplasia of the sella turcica to the patients in this report supporting the apparent uniqueness and/or rarity of this newly described syndrome.

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