Congenital muscular dystrophy: light and electron microscopic observations¹

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Hypotonia beginning at birth or early in the neonatal period can be caused by one of the following: (1) infantile muscular atrophy; (2) benign congenital hypotonia; (3) symptomatic hypotonia (Walton, 1960).

Infantile muscular atrophy is an established clinicopathological disorder in which muscular atrophy is secondary to disease of the motor neurone. Benign congenital hypotonia is characterized by onset of hypotonia at birth or in the early neonatal period, improvement of hypotonia with age, and eventual complete recovery. No pathological alterations are noted in the muscles of these children. Symptomatic hypotonia refers to a variety of conditions characterized by hypotonia at birth and includes such varied diseases as myositis, myasthenia gravis, muscular glycogenosis, hypotonia of cretinism, and mental retardation. A much less frequent cause of symptomatic hypotonia is congenital muscular dystrophy. Greenfield, Cornman, and Shy (1958) considered congenital muscular dystrophy among disorders of muscle that can produce weakness and hypotonia at birth or in the early weeks of life. Banker, Victor, and Adams (1957) correlated clinicopathological findings in two male sibs suffering from congenital muscular dystrophy. One of their patients presented the clinical picture of arthrogryposis multiplex congenita, whereas the other had flaccid weakness without contractures at birth. Histological evidence of muscular dystrophy in children with congenital hypotonia has been recorded by various authors (Lereboullet and Baudouin, 1909; Councilman and Dunn, 1911; Haushalter, 1920; Turner and Lees, 1962; Lewis and Besant, 1962; O'Brien, 1962; Short, 1963). In contrast, reports of ultrastructure of muscle in congenital muscular dystrophy are few (Pearce, 1963, 1965; Gubbay, Walton, and Pearce, 1966).

The purpose of this report is to describe the pathology of muscle in six cases of congenital muscular dystrophy with particular emphasis on ultrastructure.

MATERIAL AND METHODS

All six patients presented with hypotonia at birth. Four of the patients were females and two were males. In three (cases 1, 2, 3) the hypotonia and weakness were severe and generalized. Neck muscles were most severely affected. Contractures developed in the post-natal period. Weakness either remained stationary, showed slight improvement, or slight and slow progression with age. In the other three cases (cases 4, 5, 6) hypotonia and weakness were of slight to moderate degrees of severity. The condition remained stationary or improved with age. Electromyography revealed a myopathic pattern in all six cases. Creatine phosphokinase values were normal or slightly elevated in the clinically severe cases and moderately elevated in the clinically milder cases. Details of clinical findings in each of the six cases are given in Table I. Criteria for clinical differentiation of congenital muscular dystrophy from other better known and more common types of dystrophy are presented elsewhere (Zellweger, Afifi, McCormick, and Mergner, 1967 a, b).

Muscle biopsies were obtained from the deltoid, quadriceps femoris, gastrocnemius, extensor digitorum longus, tibialis anterior, and vastus lateralis muscles. In all but one of the patients (case 5) two or more muscle biopsies were obtained at intervals varying between four months and two and a half years. Light microscopic studies were done on all biopsies, while material from only the second or third biopsy in each case was available for electron microscopy.

Muscles for light microscopy were fixed in Bouin or 10% formol-saline, dehydrated in alcohol, cleared in chloroform, and embedded in paraffin. Eight μ sections were stained with haematoxylin and eosin, trichrome, periodic acid Schiff, and phosphotungstic acid haematoxylin. Tissue for electron microscopy was fixed, stretched, in 3% glutaraldehyde and post-fixed in 1% phosphate buffered osmium tetroxide, dehydrated in acetone, and embedded in Araldite. Blocks were sectioned using a Porter-Blum ultramicrotome (Sorvall) and glass knives. Thin sections were stained with lead acetate or phosphotungstic acid and examined using an RCA EMU 3F electron microscope operated at 50 kv.

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FIG. 1. *Vastus lateralis* (case 2, at age 6 years). Skeletal muscle showing considerable proliferation of endomysial and perimysial connective tissue, variation in size of the muscle fibres and loss of muscle fibres. (a) Cross section, H. and E. $\times 125$. (b) Longitudinal section, H. and E. $\times 125$.

TABLE I
CONGENITAL MUSCULAR DYSTROPHY CLINICAL PICTURE

Clinical type	Case no.	Name	Sex	Age (yr) when last seen	Symptoms and signs											Creatine phosphokinase (normal range 1-5u)	Electromyography	
					Hypotonia at birth	Contractures	Muscular wasting	Pseudo-hypertrophy	Weakness				Clinical course					
									Extremity				Age (M) when walked	Improved	Stationary			Progressed
									Distal	Proximal	Neck	Face						
Severe	1	C.P.	F	3	+	+	+	-	+	+	+	+	0	+		1.6	Myo	
	2	K.D.	F	6	+	+	+	-	+	+	+	+	0		+	2.7	Myo	
	3	B.H.	F	6	+	+	+	-	+	+	+	+	0			9.0	Myo	
Mild	4	T.S.	M	15	+	-	-	-	-	+	±	±	14		+	39.0	Myo	
	5	G.C.	M	15	+	-	-	-	-	+	+	±	12		+	41.0	Myo	
	6	C.B.	F	14	+	±	-	-	-	+	+	+	16	+		22.0	Myo	

+ = present, - = absent, ± = questionably present, 0 = never, My = myopathic.

TABLE II
CONGENITAL MUSCULAR DYSTROPHY LIGHT MICROSCOPIC FINDINGS

Case no.	Degree of clinical severity	Patient	Age at biopsy	Muscle biopsied	Fibrosis	Variation in fibre size	Re-generative attempts	Central nuclei	Nuclei in rows	Phagocytosis	Hyaline and floccular changes in fibres	Adipose infiltration
1	Severe	C.P.	6 mth	Quad.	+++	++	-	Occ.	+	+	+	+
			10 mth	Deltoid	+++	++	-	Occ.	+	+	+	+
2	Severe	K.D.	15 mth	Gastroc.	+++	++	-	+	-	-	++	Occ.
			3½ yr	Quad.	+++	++	-	+	+	+	++	+
			6 yr	Vastus lat.	+++	++	-	+	+	+	++	+
3	Severe	B.H.	5 mth	Deltoid	++	+++	-	+	+	-	+	+
			1½ yr	Gastroc.	+++	+	-	+	-	-	+	++
			4 yr	Quad.	++	++	-	-	-	-	+	++
4	Mild	T.S.	14 yr	Tib. ant.	+	+	-	+	+	+	-	++
			15 yr	Vast. lat.	++	++	Occ.	+	++	+	Occ.	++
5	Mild	G.C.	13 yr	Ext. dig.	++	++	-	Occ.	++	+	++	+
6	Mild	C.B.	11 yr	Gastroc.	+	+	-	++	+	-	++	++
			13 yr	Quad.	++	++	-	++	+	++	+	+++

+ = minimal, ++ = moderate, +++ = marked, Occ. = occasional, - = absent.

RESULTS

LIGHT MICROSCOPIC OBSERVATIONS Marked to moderate endomysial, perimysial, and epimysial fibrosis were common and prominent features in most of the biopsies (Fig. 1). It was more marked in the clinically severe cases irrespective of age at biopsy or the muscle biopsied (Table II). Muscle fibres varied in size (Fig. 1) from the very small (6μ) to the very large (over 150μ). Fat infiltration was minimal in four of the patients and was more striking in amount in a second biopsy (at a later age) in two of the patients (cases 3 and 6). The degree of fat infiltration had no relation to the site of biopsy (Table II). Centrally placed sarcolemmal nuclei, sarcolemmal nuclei in a row, and vesicular nuclei were seen in some of the biopsies. Numerous clusters of sarcolemmal nuclei were buried in connective tissue while the respective myofibres had disappeared (Fig. 2). Muscle spindles seemed normal. Regenerative attempts were strikingly absent. There was no vasculitis, myositis, glycogen deposition, central cores, or nemaline changes. No histochemical studies were done. Details of the light microscopic findings in each patient are given in Table II.

FIG. 2. *Vastus lateralis* (case 2, at age 6 years). Muscle fibres are largely replaced by connective tissue. A few muscle fibres remain. Clusters of nuclei are seen in places where the respective myofibres have almost totally disappeared. H. and E. $\times 145$.

ELECTRON MICROSCOPIC OBSERVATIONS Morphological features considered to be abnormal were encountered in all six patients, and involved the following:

Myofilaments A great deal of variation was noted in the degree of involvement of myofilaments in the different biopsies. In some, myofilaments were

FIG. 3. *Quadriceps femoris* (case 1, at age 6 months). Severely affected fibre in which many myofibrils are lost and are replaced by mitochondria (M), dilated sarcoplasmic reticulum profiles (SR), and Z line remnants (Z). N: nucleus. $\times 1,850$.

intact and fibre structure was preserved. In others, there was a rather striking loss of myofilaments resulting in a decrease in size of the involved myofibrils and a corresponding increase in the intermyofibrillar space. The spaces left by the lost myofibrils were filled with remnants of Z line material, dense mitochondria, and dilated single

FIG. 4. *Quadriceps femoris* (case 3, at age 4 years). A ghost fibre is seen (arrow) between two intact fibres. The ghost fibre has lost its fibrillar organization and shows only a deeply indented nucleus (N) and a multitude of dense bodies (DB). $\times 1,250$.

FIG. 5. *Extensor digitorum longus* (case 5, at age 13 years). A massive aggregate of normal mitochondria (M) is seen in the subsarcolemmal area. SR: dilated sarcoplasmic reticulum sacs. $\times 1,800$.

membrane-bound sacs (Fig. 3). Myofilamentous changes were most marked in the biopsies from the clinically severe cases, and were always associated with mitochondrial and/or sarcotubular system alterations. An occasional ghost fibre was seen (Fig. 4) consisting of a sarcolemmal sheath surrounding an agglomeration of nuclei and osmiophilic dense bodies with no evidence of fibrillar organization.

Mitochondria Massive aggregates of mitochondria in subsarcolemmal (Fig. 5) or occasionally in perinuclear location were seen in otherwise intact fibres. Mitochondrial aggregates were not visible in the severely affected fibres. Instead scattered free mitochondria lay free amid fibrillar debris (Fig. 3).

Sarcoplasmic reticulum Sac-like dilatations of the sarcoplasmic reticulum (Figs. 3, 5) were more frequent in biopsies from the clinically mild cases, and, like mitochondrial alterations, were seen in relatively intact fibres and without associated myofibrillar change. Mitochondria often surrounded and distorted these sacs (Fig. 5).

Sarcolemma The relative intactness of the sarcolemma, even in the most severely affected fibres, was striking. In some fibres, the sarcolemma was irregular and tortuous. Fusion of sarcolemma with external masses of collagen was also observed (Fig. 6). Defects in the continuity of sarcolemmal membranes were not seen.

Nuclei Most nuclei of moderately or mildly affected fibres were similar to those seen in normal muscle. In severely affected fibres, rows or clumps of large vesicular nuclei were seen among the debris of myofibrils, mitochondria, sarcotubules, and Z bands. Central nuclei were seen occasionally.

A striking feature in these biopsies was the abundance of dense collagen either between the

muscle fibres (Fig. 7) or continuous with the sarcolemma. Vascular changes were not seen, and an occasional neuromuscular junction found appeared normal.

DISCUSSION

Our own light microscopic findings in congenital muscular dystrophy are in agreement with published observations (Table III), and point to a number of common morphological features (central nuclei; variation in fibre size, hyaline changes, adipose infiltration) between congenital muscular dystrophy and other types of dystrophy, particularly Duchenne muscular dystrophy. Thus, in the absence of clear-cut, qualitative, histological differences between congenital muscular dystrophy and the other dystrophies, an attempt was made to single out discrete quantitative characteristics that might distinguish congenital muscular dystrophy.

Surveying our cases (Table II), we were impressed by the relative uniformity of the findings in different cases as to the degree of fibrosis and variation in size of muscle fibres. Similar observations have been made in cases reported in the literature (Table III). The degree of fibrosis in our material was generally more marked in the biopsies from the clinically severe cases. Attempts at regeneration were conspicuously absent in all but one patient (case 4) in whom an occasional regenerating myofibre was seen. This is in marked contrast with the active regenerative attempts seen in most of the other dystrophies. Infiltration of muscle with adipose tissue was minimal to moderate in amount in most biopsies, and did not correlate with the degree of fibrosis. A marked degree of infiltration with adipose tissue was seen in a second biopsy in only one case

TABLE III

CONGENITAL MUSCULAR DYSTROPHY LIGHT MICROSCOPIC PATHOLOGY

Author	Cases (no.)	Fibrosis	Adipose infiltration	Central nuclei	Sarcolemmal nuclei in rows	Hyaline and floccular changes in fibre	Variation in fibre size	Neuromuscular junction
Howard (1908)	1	A	++	—	—	P	P	N
Collier and Holmes (1909)	1	+++	+++	P	P	P	P	—
Lereboullet and Baudouin (1909)	1	+++	—	—	P	—	P	—
Councilman and Dunn (1911)	1	+++	++	P	P	—	P	—
Haushalter (1920)	1	+++	+	—	—	—	P	—
Silberberg (1923)	1	++	+	—	P	—	P	—
Ullrich (1930)	1	+++	—	—	P	P	—	—
Menges (1931)	1	++	+	—	P	P	P	—
DeLange (1937)	1	+	—	—	P	P	P	—
Brandt (1950)	1	+++	+	—	P	P	P	—
	2	+++	A	P	—	P	P	—
	3	+++	+	—	—	P	P	—
Richter and Humphreys (1955)	1	—	++	—	P	P	—	—
Banker <i>et al.</i> (1957)	1	+++	+++	P	P	P	P	—
	2	—	—	P	P	P	P	—
Greenfield <i>et al.</i> (1958)	1	+++	+++	—	—	P	P	—
Lewis and Besant (1962)	2	—	—	P	—	—	P	—
Lelong <i>et al.</i> (1962)	1	—	—	—	—	P	P	—
Turner and Lees (1962)	1	—	+++	P	P	P	P	—
O'Brien (1962)	1	+	++	P	—	P	—	—
Pearson and Fowler (1963)	2	+++	++	P	P	P	P	—
Short (1963)	1	+++	+	P	P	P	P	—
Fontaine <i>et al.</i> (1965)	1	+++	++	—	—	P	P	—
Wharton (1965)	1	++	—	—	P	P	—	N

+ = minimal, ++ = moderate, +++ = marked, A = absent, P = present, — = no data available, N = normal.

FIG. 6. *Quadriceps femoris* (case 3, at age 4 years). An intact fibre showing fusion of collagen with sarcolemma (arrow). $\times 1,450$.

(case 6). Paradoxically, fatty infiltration was more prominent in the clinically benign cases. This pattern of fatty infiltration is different from that seen in the usual case of pseudohypertrophic progressive muscular dystrophy. A significant degree of floccular and hyaline changes in muscle fibres was found in half of the cases, while phagocytosis was generally rare or absent. Central nuclei and arrangement of nuclei in rows were seen in some cases.

FIG. 7. *Quadriceps femoris* (case 3, at age 4 years). Abundance of collagen fibres (c) is seen between muscle fibres. Fusion of external collagen with the sarcolemma is seen at arrow. $\times 2,400$.

TABLE IV
CONGENITAL MUSCULAR DYSTROPHY ELECTRON MICROSCOPIC PATHOLOGY

Author ¹		Myofilament	Sarcoplasmic reticulum	Sarcolemma	Collagen	Mitochondria	Nuclei
Pearce (1963)	(2)	Loss	Prominent		Excessive		
Pearce (1965)	(1)			Defective			
Gubbay <i>et al.</i> (1966)	(1)	Fusion	Dilated	Defective	Excessive. Fusion with sarcolemma	Loss of cristae	Central
Afifi and Zellweger (1968)	(6)	Loss	Dilated	Tortuous	Excessive. Fusion with sarcolemma	Aggregates	Central

¹Number of cases in parentheses.

Thus, it seems to us that at the light microscope level, congenital muscular dystrophy presents a morphological picture akin to that of other dystrophies, but from which it may be differentiated by: (1) the marked fibrous tissue proliferation, out of proportion to the degree of fibre necrosis and greater than that generally observed in cases of Duchenne muscular dystrophy; (2) the essential lack of significant regenerative attempts; (3) the essential absence of significant phagocytic activity.

Electron microscopic studies on congenital muscular dystrophy in the literature are very few. The findings in four reported cases (Pearce, 1963, 1965; Gubbay *et al.*, 1966) consisted of evident loss of myofilaments; prominence of sarcotubular system; enlargement of mitochondria with separation of their cristae; defects of sarcolemmal membrane; and excessive collagen (Table IV).

The ultrastructural findings in the muscle from our six patients showed two basic patterns. One, seen chiefly in the clinically benign cases (cases 4, 5, 6), was characterized by saccular dilatation of the sarcoplasmic reticulum, increase in number of subsarcolemmal and perinuclear mitochondria, central nuclei, and marked increase in collagen between muscle fibres. While changes in contractile elements were noted in this group of cases, they were by no means prominent. The second pattern, seen in the clinically severe cases (cases 1, 2, 3), was characterized by disarray and dissolution of myofilaments, disintegration of myofibrils, increase in number of sarcolemmal nuclei, centralization of nuclei, and some phagocytosis. Atrophic ghost fibres with intact sarcolemma and rows of central nuclei were commonly seen. Fibrous tissue replacement was abundant in this group. Mitochondrial and sarcotubular changes were present, but were much less prominent. The loss and disarray of myofilaments seen in our cases are consistent with those reported by Pearce (1963) in two cases of congenital muscular dystrophy. The fusion of myofibrils reported by Gubbay *et al.* (1966) was

not seen in any of our cases. Myofilaments are delicate structures highly vulnerable to injury, and seem to respond uniformly to different types and aetiologies of insults. Myofilamentous alterations similar to those described in congenital muscular dystrophy have been reported in other dystrophies as well as in neurogenic muscular atrophy (Pearce, 1963; Aleu and Afifi, 1964; Van Breemen, 1960; Mair, 1965; Mölbert, 1960; Afifi, Aleu, Goodgold, and McKay, 1966).

Dilatation of sarcotubular system occurred in our cases and in those of Pearce (1963) and Gubbay *et al.* (1966). In our cases, sarcotubular system changes occurred in the absence of any other significant morphological abnormality in the fibres and involved the longitudinal component of the system which is concerned with metabolic functions (Bergman, 1958; Price, Pease, and Pearson, 1962; Pearce, 1963). Early involvement of the sarcotubular system in other types of dystrophy (Van Breemen, 1960; Pearce, 1963) led Van Breemen to suggest that this might mark the primary site of abnormality in muscular dystrophy.

Alterations in mitochondria occurred early in our material, and were not necessarily associated with any changes in the contractile elements. Mitochondrial aggregates underneath the sarcolemma have been described in other dystrophies (Pearce, 1963; Mair, 1965), in neurogenic muscular atrophy (Afifi *et al.*, 1966), and in chloroquine myopathy (Mair, 1965). The occurrence of mitochondrial aggregates in relatively intact fibres and their paucity in severely affected and ghost fibres suggest that this organelle is active in the response of a fibre to injury.

The relative intactness of sarcolemmal membrane is consistent with known resistance of the sarcolemma to injury. The occasional defects in continuity of sarcolemma described by Pearce (1965) and Gubbay *et al.* (1966) were not seen in our cases. Similar sarcolemmal defects have been described in Erb dystrophy (Mölbert, 1960), their functional

significance in relation to enzyme leakage in dystrophy cannot be adequately assessed at our present stage of knowledge.

Excessive collagen accumulation seen in our cases confirms similar observations by Pearce (1963) and Gubbay *et al.* (1966). As in Gubbay's case, collagen in our material was fused with the surface of the muscle fibre and did not invade any other component of the fibre. The marked increase in collagen in congenital muscular dystrophy raises the possibility that it might be the primary event in this type of dystrophy. Golarz and Bourne (1960) demonstrated that the endomysium in human muscular dystrophy possesses a strong dephosphorylating activity. Although this possibility cannot be completely dismissed, we tend to agree with Gubbay *et al.* (1966) that the changes observed in the muscle fibre itself (myofilamentous loss, sarcotubular changes, mitochondrial changes) are sufficient to indicate that the disease is due primarily to a dystrophic process involving the muscle fibre itself. We would like to suggest, in addition, that in this primary dystrophic process, the sarcotubular system and mitochondria comprise the first line of defence. Our view is based on the observations that changes in these organelles occur early, and seem to be prominent in the milder cases before any significant changes in myofilaments are seen.

The number of normal neuromuscular junctions seen in the present study is too small for any definite conclusions to be drawn. Cazzato and Walton (1968) have described marked atrophy of the intrafusal fibres and thickening in the capsule of the spindle in severe cases of congenital muscular dystrophy.

SUMMARY

The light and electron microscopic findings in six cases of congenital muscular dystrophy are described. Congenital muscular dystrophy differs from the more common types of dystrophy by excessive collagen proliferation, out of proportion to the degree of fibre degeneration, and by relative paucity of regenerative attempts. Our electron microscopic findings are compared with similar observations in the literature. The possible primary abnormality in congenital muscular dystrophy is discussed.

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