CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

Nancy Lee Harris, M.D., *Editor*
Jo-Anne O. Shepard, M.D., *Associate Editor*
Sally H. Ebeling, *Assistant Editor*
Eric S. Rosenberg, M.D., *Associate Editor*
Alice M. Cort, M.D., *Associate Editor*
Christine C. Peters, *Assistant Editor*

Case 35-2006: A Newborn Boy with Hypotonia

Robert H. Brown, Jr., M.D., D.Phil., P. Ellen Grant, M.D., and Christopher R. Pierson, M.D., Ph.D.

From the Departments of Neurology (R.H.B.) and Radiology (P.E.G.), Massachusetts General Hospital; the Department of Pathology, Children's Hospital (C.R.P.); and the Departments of Neurology (R.H.B.), Radiology (P.E.G.), and Pathology (C.R.P.), Harvard Medical School — all in Boston.

N Engl J Med 2006;355:2132-42.

PRESENTATION OF CASE

A 2-day-old boy was admitted to the special care nursery of this hospital because of hypotonia.

He was delivered at another hospital to a 40-year-old mother (gravida 2, para 2) at 38 weeks and 6 days of gestation by a scheduled cesarean section, which was the mother's second. The pregnancy was uneventful, and tests for rapid plasma reagin, hepatitis B surface antigen, and group B streptococcus were negative in the mother. Her blood type was A positive, with negative results on antibody screening, and she was immune to rubella. Fetal movements during the pregnancy were normal.

The delivery was uncomplicated, but the infant initially had a weak cry and decreased tone in his arms; the cry improved with the administration of blow-by oxygen. The Apgar scores were 8 at 1 minute and 9 at 5 minutes. The birth weight was 3815 g. During the first day, decreased muscle tone in the arms and legs and a high-pitched cry were noted. Six hours after birth, the infant had an episode of tachypnea, with an oxygen saturation of 87%; oxygen was administered, and the patient was weaned from supplemental oxygen and breathing ambient air by day 2 of life. The complete blood count and levels of serum electrolytes, calcium, phosphorus, and magnesium were normal. The total bilirubin level was 7.2 mg per deciliter (123 μmol per liter). The baby was initially breast-fed without difficulty but fed poorly on day 2 of life. The hypotonia worsened, and the high-pitched cry persisted. He was transferred to this hospital.

The patient's 14-year-old half-sister was well. The infant's father reported being told that he did not sit up until he was 10 months old and was spoon-fed as an infant because he was a "lazy feeder"; he was unable to walk or hold anything until he reached 2½ years of age. No explanation had been given for the father's weakness. His subsequent development was normal, and he was functioning normally at 35 years of age. The baby's mother had no medical problems. There was no other family history of neurologic or muscular diseases.

On admission, the patient's weight was 3440 g, the length 50.8 cm, and the head circumference 36 cm. He was not in acute distress. The blood pressure was 85/49 mm Hg, and the pulse 130 beats per minute; the respirations were 32 breaths per

minute; the temperature was 36.6°C. The skin was mildly jaundiced, with no lesions. The pupils were equal in size, round, and reactive to light. Extraocular movements were intact. There was no facial asymmetry or dysmorphism and the palate was normal. Examination of the neck and spine showed no sinus tracts or cysts. Cardiac examination revealed no murmurs, and the lungs were clear on auscultation. The abdomen was soft, with active bowel sounds and no hepatosplenomegaly. The abdominal wall muscles were decreased in tone. The genitalia were normal. The fingers were long and tapered without clubbing, cyanosis, or edema. The hips were stable, and the back was not dimpled. Neurologic examination showed diffuse hypotonia, with absent step and minimal Moro's reflexes. There were positive sucking and rooting reflexes and no tongue fasciculations. There was a marked head lag, and the arms and legs were held in a flaccid extensor posture.

Neurologic evaluation on the second hospital day revealed absent deep-tendon reflexes in the arms, trace reflexes at the knees, and bilateral ankle clonus. Laboratory evaluation revealed the following: total serum bilirubin level, 7.5 mg per deciliter (128 μmol per liter); direct bilirubin level, 0.3 mg per deciliter (5 μmol per liter); alanine aminotransferase level, 93 U per liter (normal range, 0 to 35); aspartate aminotransferase level, 187 U per liter (normal range, 0 to 35); and creatine kinase level, 14,528 U per liter (normal range, 60 to 400). Plasma levels of amino acids showed minor deviations from reference ranges that were deemed unlikely to be of clinical importance. A urine sample did not show a pattern suggestive of an organic acid disorder. Screening of the urine for metabolic disorders was positive (1+ for nitroprusside). A plasma acylcarnitine profile was normal, the lactate level was 0.9 mmol per liter, and the pyruvate level was 0.08 mmol per liter.

Magnetic resonance imaging (MRI) of the brain showed a region of polymicrogyria, 2 to 3 cm in diameter, involving the medial right temporal and occipital lobes. No other cerebral malformations were present. The size of the ventricles and cortical sulci and the degree of myelination were normal for the patient's age. The posterior fossa was structurally normal. Results of a chromosomal analysis with fluorescence in situ hybridization performed on the third hospital day were characteristic of a chromosomally normal male. Fluorescence in situ hybridization with the use of probes SNRPN/D15S10 in the domain associated with the Prader–Willi and Angelman syndromes (PWS/AS) at 15q11–q13 revealed disomy for this locus in 5 of 5 cells in metaphase examined per probe.

The infant remained in hemodynamically stable condition while breathing ambient air in an open crib. Attempts at oral feeding resulted in choking, oxygen desaturation, and bradycardia, which resolved when the bottle was removed from his mouth and he was held upright. Subsequent feedings were given by gavage, with no spitting or residual material in the stomach.

An evaluation of feeding and swallowing by speech pathologists on the fifth hospital day showed normal oral motor skills and an organized oral stage of swallowing. There was choking and coughing during the pharyngeal stage of swallowing. A barium swallow resulted in aspiration of a small amount of barium into the upper trachea. There was no evidence of abnormal communication between the esophagus and trachea. Gastric feedings were recommended.

The infant continued to be fed infant formula (Enfamil 20, Mead Johnson) by gavage, and by the eighth hospital day his weight had increased to 3785 g.

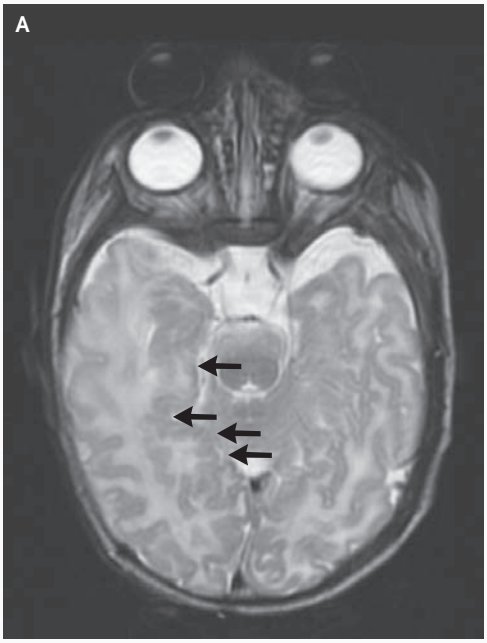
A nerve conduction and electromyographic study performed on the seventh hospital day revealed normal right median sensory and tibial motor responses. The sural response could not be recorded because of technical problems. The needle electromyographic study revealed fibrillation potentials with myopathic units in the right deltoid, rectus femoris, and tibialis anterior muscles.

A diagnostic test was performed on the eighth hospital day.

DIFFERENTIAL DIAGNOSIS

Dr. Robert H. Brown, Jr.: May we review the imaging studies?

Dr. P. Ellen Grant: The axial T_1- and T_2-weighted images show an abnormal gyral folding pattern on the medial aspect of the right temporal lobe (Fig. 1A). A large number of small gyri give the junction of the gray matter and white matter a saw-toothed appearance. These findings in the newborn's incompletely myelinated brain can be better appreciated on T_2-weighted images, which better demonstrate the contrast between gray and white matter.



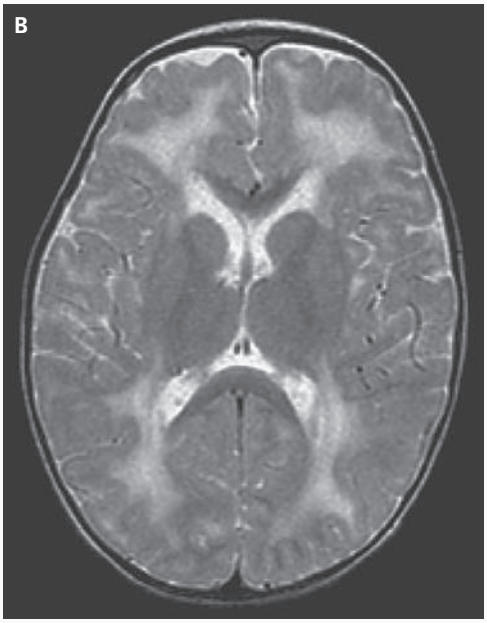


Figure 1. MRI of the Brain of the 2-Day-Old Patient under Discussion (Panel A) and a 2-Year-Old Patient with Merosin-Deficient Congenital Muscular Dystrophy (Panel B).

An axial T_2-weighted image at the level of the inferior temporal lobes in the patient shows polymicrogyria, with its characteristic abnormal serrated appearance (arrows, Panel A), in the medial portion of the right temporal lobe. The bright white matter and darker cortex are normal findings in an infant of this age. An axial T_2-weighted image at the level of the basal ganglia in a 2-year-old patient with merosin-deficient congenital muscular dystrophy shows an abnormally bright signal in the lobar white matter, with preserved myelin in the corpus callosum and internal capsule (Panel B).

The findings on axial T_1- and T_2-weighted images through the level of the basal ganglia are normal; there is normal myelination in the posterior limb of the internal capsule and the ventrolateral thalamus, as reflected by a decreased signal on T_2-weighted images and an increased signal on T_1-weighted images. On the remaining images, myelination is normal for a full-term newborn. The findings on diffusion-weighted imaging were also normal. Proton magnetic resonance spectroscopy with an echo time of 144 msec did not reveal a lactate peak. Levels of the standard metabolites, *N*-acetylaspartate, choline, and creatine were within normal ranges for newborns.

Dr. Brown: This floppy infant has a normal neurologic examination other than the weakness itself, a focus of polymicrogyria, and a markedly elevated serum creatine kinase level. A wide range of disorders can produce muscle hypotonia in the newborn. The first challenge in such a case is to identify the approximate location of the primary pathologic process. It is useful to consider four broad categories: the central nervous system (CNS), peripheral nerves (motor and sensory neurons), the neuromuscular junction, and the muscle itself (Table 1).

ABNORMALITIES OF THE CNS AND PERIPHERAL NERVOUS SYSTEM

Many disorders of the CNS that can cause hypotonia in newborns seem unlikely in this case. Other than the hypotonia, there are no findings on physical examination that suggest lesions of the CNS: there is no evidence of seizure or hemiparesis, and the ocular anatomy and visual function are normal. Chromosomal analysis rules out nearly all causes of the Prader–Willi syndrome. The single abnormality that can be traced to the CNS is a focus of polymicrogyria, but the marked elevation in creatine kinase argues strongly against a primary CNS process, as does the evidence of fibrillations on electromyography.

Involvement of the motor neurons or the pe-

ripheral nervous system is less easily dismissed. Spinal muscular atrophy type 1 (Werdnig–Hoffmann disease) can produce flaccid weakness as well as diffuse fibrillations in infants. However, many babies in whom that diagnosis has been made have tongue fasciculations, which were not described in the infant under discussion, as well as areflexia. Although the arm reflexes were absent in this baby, the knee and ankle reflexes were present, and ankle clonus was described. A sensory neuropathy is unlikely, since we were not told of any sensory deficits. The failure to record a sural nerve potential on the physiological testing was due to technical problems. The normal conduction velocities are not consistent with a diagnosis of a demyelinating peripheral neuropathy, although the peripheral myelin is not fully developed at birth, and thus, the results of this study may be misleading. The elevated creatine kinase level argues strongly against the presence of this category of neuromuscular disorder.

Table 1. Differential Diagnosis of the Floppy Infant Syndrome.

Central nervous system disorders
Congenital, nonprogressive encephalopathies
Ischemic encephalopathies
Infectious encephalopathies
Metabolic encephalopathies
Endocrine encephalopathies
Developmental encephalopathies (e.g., Prader–Willi syndrome)
Degenerative, progressive encephalopathies
Spinal cord disorders (anterior horn cell and peripheral nervous system)
Infections (e.g., poliomyelitis)
Motor neuron diseases (spinal muscular atrophy type 1)
Neurogenic arthrogryposis
Glycogen storage diseases (e.g., Pompe's disease)
Lysosomal storage abnormalities
Sensorimotor polyneuropathies
Demyelinating disorders
Axonal disorders
Disorders of the neuromuscular junction
Presynaptic disorders
Infantile botulism
Congenital myasthenia
Postsynaptic disorders
Neonatal myasthenia gravis
Congenital myasthenia
Muscle disorders
Infantile myotonic dystrophy
Congenital myopathies

THE NEUROMUSCULAR JUNCTION

Could this baby's floppiness result from a disturbance in transmission at the neuromuscular junction? If so, three entities should be considered: congenital myasthenia, neonatal myasthenia gravis, and infantile botulism. The history does not suggest exposure to foods that might cause botulism; pupillary reactivity, which is often abnormal in infants with botulism, was normal in this patient. Infantile myasthenia gravis, usually acquired through passive acquisition of maternal antibodies, is unlikely without a history of this disease in the mother. An inborn defect that alters the proteins that make up either the presynaptic or the postsynaptic junctional apparatus can also lead to floppiness at birth, but babies with such conditions typically have profound ptosis and normal creatine kinase levels. For these reasons, I would rule out junctional disorders.

CONGENITAL ABNORMALITIES OF THE SKELETAL MUSCLE

Three types of skeletal muscle diseases merit consideration — congenital myopathies, congenital muscular dystrophy, and a form of neonatal myotonic dystrophy with floppiness (Table 2). Babies born to mothers with myotonic dystrophy are prone to hypotonicity; in most instances, there is a family history of this disease, which is dominantly inherited. The mother may have undiagnosed myotonic dystrophy; however, in that circumstance, the baby would not be expected to have a markedly elevated serum creatine kinase level.

The congenital myopathies are a diverse group of muscle diseases that are inherited as autosomal dominant or recessive traits and share several common features, including distinctive histologic abnormalities and features such as a high arched palate or abnormal arches in the feet — neither of which was seen in this patient. Affected patients may be extremely weak at birth, but the condition may improve over time. A marked elevation in the level of creatine kinase, such as in this patient, is unusual in these disorders.

Table 2. Congenital Diseases of Skeletal Muscle.

Disease	Mechanism
Congenital myopathies	
Nemaline myopathy	Abnormalities in α-tropomyosin, β-tropomyosin, troponin 1, nebulin, α-actin
Central core disease	Defective ryanodine receptor
Myotubular (centronuclear) myopathy	Defective myotubularin
Desmin myofibrillar myopathy	Defects in αB-crystallin, desmin
Congenital muscular dystrophies	
Duchenne's muscular dystrophy	
Congenital muscular dystrophies with abnormal development of the nervous system	
Fukuyama-type congenital muscular dystrophy	Fukutin deficiency
Muscle–eye–brain disease	Defects in protein O-mannose beta-1,2-*N*-acetylglucosaminyltransferase 1 (glycosyltransferase)
Walker–Warburg syndrome	Defects in protein O-mannosyltransferase 1 (glycosyltransferase)
Fukutin-related peptide congenital muscular dystrophy	Defective fukutin-related peptide
Congenital muscular dystrophies with normal development of the nervous system	
Rigid spine syndrome	*SEPN1* mutation encoding selenoprotein N1
Ullrich congenital muscular dystrophy	*COL6A1, COL6A2, COL6A3* mutations
α_7 Integrin deficiency	
Normal levels of merosin α_2 and merosin	
Primary merosin α_2 and merosin deficiency	Mutations in the *LAMA2* gene
Secondary merosin α_2 and merosin deficiency	No mutations in the *LAMA2* gene; mutations in the *FKRP* gene or in other genes

CONGENITAL MUSCULAR DYSTROPHY

The hallmark of the congenital muscular dystrophies is the presence of clinically significant muscle weakness at birth, elevated serum creatine kinase levels, and histologic features of dystrophy on muscle biopsy.[1] These disorders are often characterized by abnormal development of the nervous system[2,3] (Table 2). A third entity, Duchenne's muscular dystrophy, the most common muscular dystrophy, is less likely in this patient. It is caused by the absence of the submembrane protein dystrophin, which connects two complexes of transmembrane proteins, the sarcoglycans and the dystroglycans (Fig. 2).[5] Most cases of Duchenne's muscular dystrophy become clinically evident 6 to 9 months after birth or later. Although a congenital presentation may occur, because of its rarity, it is not a major consideration in this case. However, several disorders involving proteins associated with dystrophin typically present as congenital muscular dystrophies.

Congenital Muscular Dystrophy with Markedly Abnormal CNS Development

There are four disorders in which congenital muscular dystrophy is associated with developmental disturbances in the eyes, brain stem, cerebellum, and forebrain[6]: Fukuyama-type congenital muscular dystrophy, muscle–eye–brain disease, Walker–Warburg syndrome, and a disorder recently defined by mutations in a protein called fukutin-related peptide (Table 2). In these disorders, defects in proteins that are involved in the glycosylation of α-dystroglycan impair its interaction with the cell membrane.[7-10] There is considerable phenotypic overlap among these disorders. In this patient, the only brain abnormality is the focus of polymicrogyria; the major structural defects of the brain typical of these disease entities are absent.

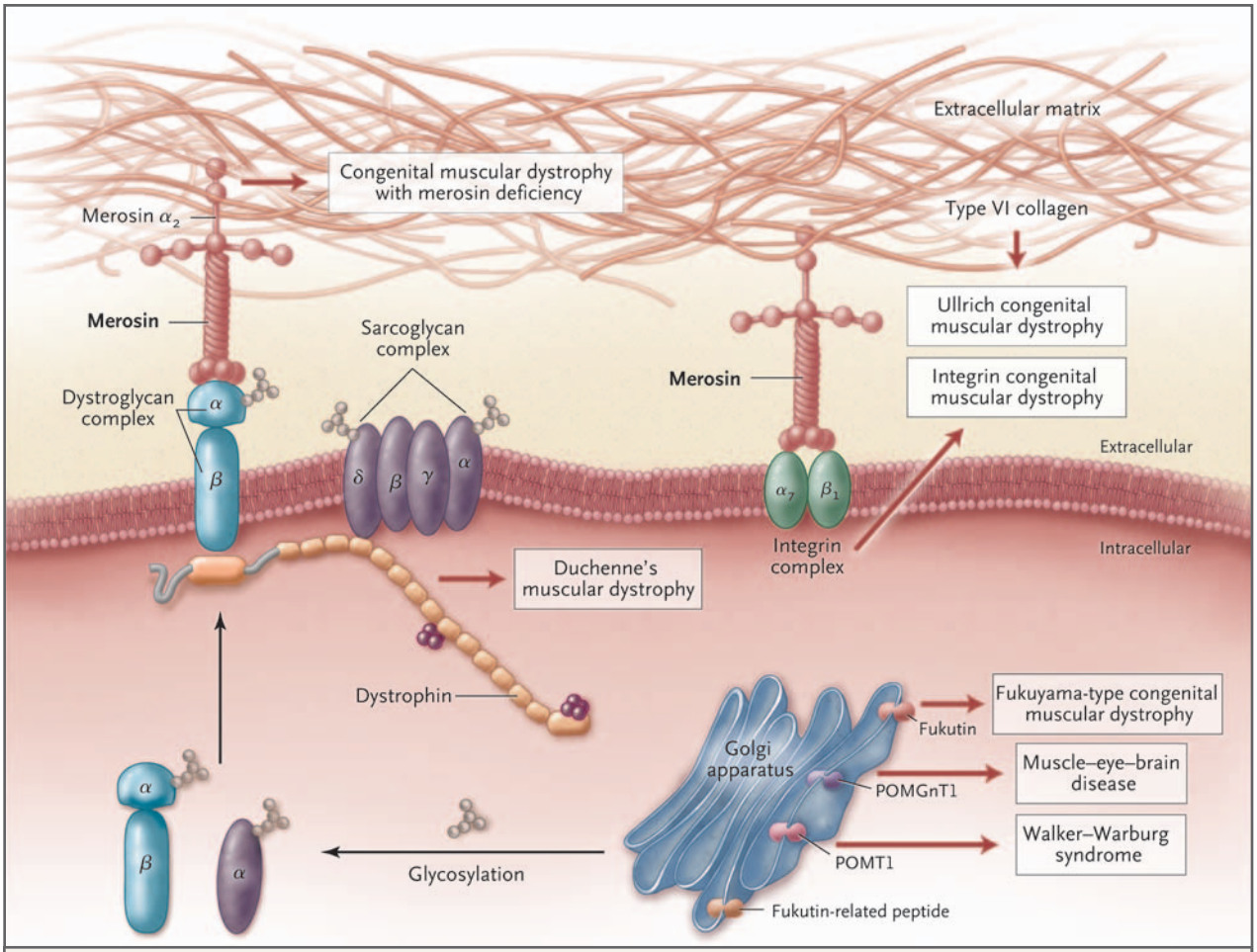


Figure 2. Structure and Function of the Dystrophin–Glycoprotein Complex.

Dystroglycan and dystrophin form the core of the dystrophin–glycoprotein complex. Dystroglycan is transcribed from one gene and cleaved after translation into α- and β-dystroglycan.[4] β-Dystroglycan is a transmembrane protein whose intracellular portion binds dystrophin, which in turn binds to the actin cytoskeleton. Extracellularly, β-dystroglycan binds α-dystroglycan, which is linked to the merosin α_2 chain of merosin and other constituents of the extracellular matrix.[5] Dystroglycan most likely functions as a link between intracellular and extracellular components of muscle through the dystrophin–glycoprotein complex. Closely associated with dystrophin is a complex of four membrane-spanning proteins (δ-, β-, γ-, and α-sarcoglycan). Also embedded in the membrane is the $\alpha_7\beta_1$ integrin dimer that, like dystroglycan, serves as a receptor for merosin. Inside the muscle cell, multiple enzymes within the Golgi apparatus are essential for the correct glycosylation and membrane localization of nascent peptides. Primary gene defects in diverse proteins in the cell lead to muscular dystrophies: mutations in merosin α_2 (encoded by the *LAMA2* gene) lead to merosin-deficient congenital muscular dystrophy, mutations in dystrophin to Duchenne's muscular dystrophy, mutations in type VI collagen to Ullrich congenital muscular dystrophy, mutations in α_7 integrin to integrin congenital muscular dystrophy, mutations in fukutin to Fukuyama-type congenital muscular dystrophy, mutations in protein O-mannose beta-1,2-*N*-acetylglucosaminyltransferase 1 (POMGnT1) to muscle–eye–brain disease, mutations in protein O-mannosyltransferase 1 (POMT1) to Walker–Warburg syndrome, and mutations in fukutin-related peptide to various forms of congenital muscular dystrophy, ranging from mild to severe.

Congenital Muscular Dystrophy with Minimally Abnormal CNS Development

The congenital muscular dystrophies without major CNS abnormalities may be usefully subdivided into those with abnormal expression and levels of the skeletal muscle extracellular matrix protein merosin, also known as laminin-2, and those with normal levels of merosin (Table 2). Merosin is a trimeric protein composed of three subunits: the α_2, β_1, and γ_1 chains (Fig. 2). In congenital muscular dystrophy in which the level of expression of merosin is normal or nearly normal, the disease-

causing mutations typically affect genes that anchor skeletal muscle merosin (e.g., collagen or the integrin that is a receptor for the protein in the cell membrane). Less frequently, some mutations affecting the *LAMA2* gene, which encodes the merosin α_2 chain, may cause only a partial loss of expression of merosin and merosin α_2. These mutations tend to produce milder symptoms than those in the patient under discussion, and active myonecrosis, whose presence is suggested by the very high levels of serum creatine kinase in this patient, is not present.

Merosin-Deficient Congenital Muscular Dystrophy

The remaining entity in the differential diagnosis is congenital muscular dystrophy arising because of severe deficiency in merosin expression. This type has two categories: one in which the defect is the consequence of a mutation in the *LAMA2* gene and one in which the *LAMA2* gene is normal but mutations in other genes affect the expression of merosin. Merosin is expressed in skeletal muscle, heart muscle, skin, brain, and peripheral nerves. It helps maintain the stability of the relationship between the cell membrane and the extracellular matrix, normal cell–cell interactions during development and differentiation, and tissue integrity after differentiation.[11] Thus, patients with merosin deficiency have profound weakness and atrophy of the skeletal musculature, as well as secondary effects such as scoliosis.[6]

Although mental development is usually normal in such patients, they may have a range of CNS abnormalities, including mental retardation, epilepsy, and abnormalities of gyration, similar to the polymicrogyria seen in the brain in this patient. Abnormalities in the signal intensity of white matter on MRI typically develop in the brain over time but are not present at birth; thus, their absence in this patient does not rule out the diagnosis.

In summary, I believe the most likely diagnosis in this case is a congenital muscular dystrophy, probably caused by severe merosin deficiency that is either primary (i.e., associated with mutations in the *LAMA2* gene that lead to reduced levels of merosin α_2) or secondary. The diagnostic procedure that was performed was probably a muscle biopsy, which I expect showed dystrophic disease and subnormal levels of merosin.

Dr. Grant: The combination of a clinical finding of hypotonia and a finding of polymicrogyria on MRI is highly suggestive of a congenital muscular dystrophy. Polymicrogyria is part of the spectrum of abnormalities seen in Fukuyama-type congenital muscular dystrophy and muscle–eye–brain disease, but it can be seen in both merosin-negative and merosin-positive congenital muscular dystrophy. Merosin is thought to enhance the formation of myelin in membrane by oligodendrocytes, and merosin deficiency is associated with deficient development of myelin; for this reason, MRI shows an abnormally bright T_2-weighted signal in the white matter in older infants and children (Fig. 1B). However, the abnormality would not be present in a newborn with the disorder, since myelin formation is not sufficiently advanced during the first 6 months of life.

Dr. Nancy Lee Harris (Pathology): Dr. Krishnamoorthy, will you give us your clinical impressions at the time of the diagnostic procedure, and tell us what the procedure was?

Dr. Kalpathy S. Krishnamoorthy (Pediatric Neurology): In a case of profound hypotonia like this one, the clinical examination typically does not provide a specific diagnosis. We quickly screen for metabolic disorders and inborn errors of metabolism; then we proceed to molecular studies, specifically for spinal muscular atrophy, Prader–Willi syndrome, and congenital myotonic dystrophy, followed by MRI of the brain. If there is no obvious abnormality on MRI, we perform a muscle biopsy. Early muscle biopsy, even in the newborn period, is extremely helpful. In this case, our thinking is similar to that of Dr. Brown. Since the creatine kinase level was so high, we suspected a congenital muscular dystrophy, so we proceeded with a muscle biopsy.

Dr. Harris: How do you interpret the father's early history?

Dr. Brown: The question is whether he is a carrier of the disease who has had some of its symptoms. Although I find that an attractive hypothesis, I could not find such a case reported in the literature.

CLINICAL DIAGNOSIS

Congenital muscular dystrophy.

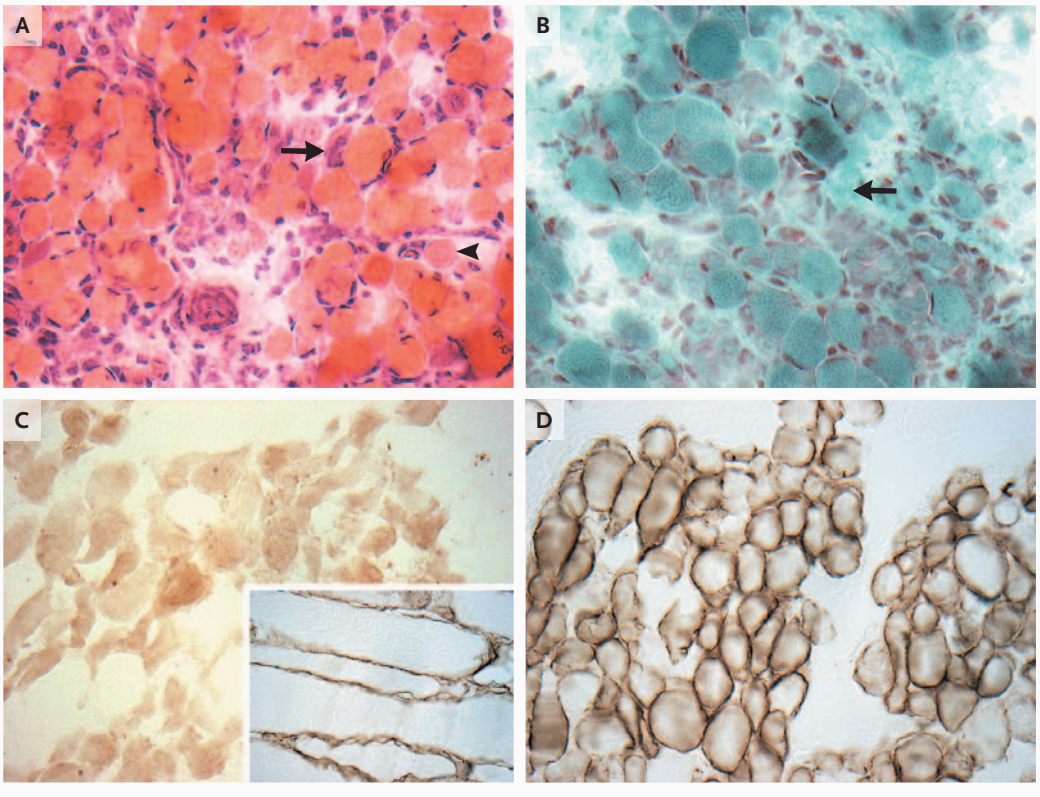


Figure 3. Muscle-Biopsy Specimen.

Frozen sections stained with hematoxylin and eosin (Panel A) and modified Gomori's trichrome (Panel B) show marked variation in the size of myofibers and necrotic myofibers (arrow, Panel A), as well as scattered ring fibers (arrowhead, Panel A), with myofibrils abnormally arranged in a circle at the periphery of the myofiber rather than appearing parallel to the long axis. Endomysial connective tissue is increased (arrow, Panel B). Immunohistochemical staining with antimerosin antibody (Panel C) shows no membranous merosin immunoreactivity; the inset shows a normal muscle for comparison. In contrast, a section stained with antidystrophin antibody (Panel D) shows appropriate dystrophin expression.

DR. ROBERT H. BROWN, JR.'S DIAGNOSIS

Congenital muscular dystrophy caused by merosin deficiency, either primary (*LAMA2* gene mutation) or secondary.

PATHOLOGICAL DISCUSSION

Dr. Christopher R. Pierson: A portion of grossly normal quadriceps muscle, 1.5 cm in greatest dimension, was snap-frozen, and frozen sections were prepared. Sections stained with hematoxylin and eosin showed variation in the size of myofibers, with both small and hypertrophic myofibers (Fig. 3A), scattered basophilic fibers suggestive of regeneration, myophagocytosis with scattered endomysial macrophages and inflammatory cells, and increased endomysial connective tissue (Fig. 3B). Staining with periodic acid–Schiff and oil red O showed appropriate levels of glycogen and lipid, respectively. Histochemical staining with nicotinamide adenine dinucleotide–terazolium reductase showed some coarsening of the intermyofibrillar network and rare, scattered myofibers with aberrant, circumferentially oriented myofibrils (called ringbinden). ATPase histochemical analysis revealed poor distinction of fiber types and small

Table 3. Clinical, Radiologic, and Pathological Features of Established Congenital Muscular Dystrophies.*

Congenital Muscular Dystrophy	Gene and Locus	Important Clinical Findings and Disease Characteristics	CNS Findings	Results of Testing
Congenital muscular dystrophy with primary merosin α_2 deficiency	6q22–q23, *LAMA2*	Patients able to sit and stand with support; motor skills not affected by complete deficiency; neuropathy; epilepsy in 30%; subclinical cardiomyopathy possible; mental development generally normal	Abnormal white-matter signal intensity on T_2-weighted MRI; occipital pachygyria or agyria in 5% of patients	Most often complete merosin α_2 deficiency on IHC and WB; α_7 integrin levels may be reduced
Congenital muscular dystrophy with partial merosin deficiency	1q42, unknown	Rare; variable severity; delayed onset possible; proximal girdle weakness; generalized muscle hypertrophy; early respiratory failure pos-sible	Abnormal white matter and structural changes possible	Partial merosin α_2 deficiency on IHC and WB; α-dystroglycan levels reduced on IHC
Fukutin-related proteinopathy	19q13.3, *FKRP*	Often similar to those of congenital muscular dystrophy with primary merosin α_2 deficiency, but more variable in severity; generally normal mental development; rare cases with brain-structure anomalies and mental retardation	Generally normal; structural abnormalities with cerebellar cysts possible	Molecular weight of α-dystroglycan reduced on WB; secondary reductions in merosin α_2 on IHC and WB
Ullrich congenital muscular dystrophy	21q22.3 and 2q37, *COL6A1, COL6A2, COL6A3*	Hyperextensibility of distal joints; proximal contracture; motor abilities variable; no independent ambulation in severe cases; soft palmar skin	Normal	Mild-to-severe deficiency of type VI collagen on IHC
Congenital muscular dystrophy with early spine rigidity	1p36–p35, *SEPN1*	Delayed walking; mostly axial weakness and early development of spinal rigidity; restrictive respiratory syndrome	Normal	Normal merosin α_2 levels
Fukuyama-type congenital muscular dystrophy	9q31, fukutin gene	Most common in Japan or in persons of Japanese descent; neonatal or infantile onset; marked hypotonia; hypokinesis; most patients never walk; hydrocephalus often present initially; microcephaly common; severe mental retardation; epilepsy common; ocular involvement	Lissencephaly type II; polymicrogyria; increased white-matter signal intensity on T_2-weighted MRI with peripheral sparing; brain-stem and cerebellar abnormalities; hydrocephalus often present initially	Molecular weight of α-dystroglycan reduced on WB; secondary reductions in merosin α_2 on IHC and WB
Muscle–eye–brain disease	1q32–q34, *POMGnT1*	Most common in Finland or in persons of Finnish descent; severe disease with onset in neonatal period or early infancy; severe hypotonia and poor visual contact, weakness, severe mental retardation, some hydrocephalus and large head, prominent forehead, flat midface, rarely walk, visual failure due to ocular involvement (severe myopia, retinal hypoplasia), deterioration due to spasticity	Lissencephaly type II; variable degrees of cortical dysplasia; variable degrees of white-matter involvement; eye malformations; brain-stem and cerebellar abnormalities; variable degrees of ventricular enlargement	Molecular weight of α-dystroglycan reduced on WB; secondary reductions in merosin α_2 on IHC and WB
Walker–Warburg syndrome	9q34.1, *POMT1*	Severe, profound hypotonia at birth, contractures, typically lethal in first years of life due to severe central nervous system involvement, hydrocephalus	Lissencephaly type II; polymicrogyria; hydrocephalus; diffusely bright white matter on T_2-weighted MRI; severe hydrocephalus; encephalocele; eye malformations	Molecular weight of α-dystroglycan reduced on WB; secondary reductions in merosin α_2 on IHC and WB
α_7 Integrin congenital muscular dystrophy	12q13, α_7 integrin	Rare; motor milestones delayed; patients walk at 2 to 3 yr of age	Normal	Absence of integrin α_7 on IHC

* Adapted from Kirschner and Bönnemann.[2] IHC denotes immunohistochemical analysis, WB Western blotting, POMGnT1 protein O-mannose beta-1,2-*N*-acetylglucosaminyltransferase 1, and POMT1 protein O-mannosyltransferase 1.

and large fibers of both histochemical types. The histopathological findings in this clinical setting are highly suggestive of congenital muscular dystrophy.

The classification of congenital muscular dystrophy is based primarily on the immunohistochemical detection of merosin and the presence of abnormal CNS development, although CNS malformations can occur whether or not merosin is deficient. A summary of the currently recognized types, with their genetic, clinical, and pathological features, is provided in Table 3.[2,3]

Merosin is found in the skeletal muscle basal lamina and is a critical component of the dystrophin–glycoprotein complex (Fig. 2).[5] This complex[4] binds intracellularly through dystrophin to the actin cytoskeleton, and it binds extracellularly to merosin and other constituents of the extracellular matrix.[5] The dystrophin–glycoprotein complex helps maintain the structural stability and integrity of the muscle membrane during contraction and relaxation cycles.[10] In the absence of merosin, the muscle membrane becomes unstable, and muscle necrosis results.

A number of nonsense and splice-site mutations in the *LAMA2* gene have been described that are predicted to yield a truncated protein; in these cases, a total lack of merosin α_2 and thus a lack of merosin expression result, leading to merosin-deficient congenital muscular dystrophy.[12,13] Other *LAMA2* missense mutations are associated with partial merosin expression, or so-called merosin-positive congenital muscular dystrophy.[5,14] Because of the large size of the *LAMA2* gene, sequencing for diagnostic purposes is impractical and is not routinely performed.

Merosin immunohistochemical analysis in this patient revealed a lack of membranous staining in all myofibers (Fig. 3C). β-Dystroglycan staining appeared to be slightly decreased in some myofibers. Dystrophin (Fig. 3D) and α-, β-, γ-, and δ-sarcoglycans all had a normal pattern of immunoreactivity. This immunohistochemical profile confirms the diagnosis of merosin-deficient congenital muscular dystrophy.

Dr. Harris: Dr. Krishnamoorthy, would you tell us how the patient is doing?

Dr. Krishnamoorthy: In the newborn nursery, the child had increasing respiratory distress, necessitating intubation. Eventually, tracheostomy and gastrostomy were performed. At approximately 8 weeks of age, he was transferred to a rehabilitation facility, where he stayed for several months. When I last saw him at 7 months of age, he was alert, smiling, and behaving normally for a child of that age, such as reaching for things and recognizing his mother. His head circumference was normal for his age. He still had hypotonia, but his head control had improved and he was able to sit up with some support. Dr. Callahan is now the patient's primary care physician.

Dr. Jeanette Callahan (Pediatrics, Cambridge Hospital): The patient is now 2½ years old and being followed at Children's Hospital in Boston. He has been hospitalized several times for pneumonia but is generally doing well at home, with a permanent tracheostomy and gastrostomy. He requires continuous positive airway pressure for all but 2 hours daily and receives pressure-assisted ventilation at night. His cognitive development is normal.

Dr. Harris: What is the prognosis for these children?

Dr. Krishnamoorthy: Most are never able to walk, but they have reasonably normal mental development. They may live for 20 or 30 years with proper care.

ANATOMICAL DIAGNOSIS

Merosin-deficient congenital muscular dystrophy.

Dr. Brown reports receiving consulting fees from Cytrx, Biogen-Idec, and Acceleron and research funding from Cytrx and holding equity in Avit Therapeutics (AviTx). No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Batten FE. Case of myositis fibrosa, with pathological examination. Brain 1903;26:147-8.
2. Kirschner J, Bönnemann CG. The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. Arch Neurol 2004;61:189-99.
3. Congenital muscular dystrophies. In: Carpenter S, Karpati G. Pathology of skeletal muscle. 2nd ed. New York: Oxford University Press, 2001:406-11.
4. Michele DE, Campbell KP. Dystrophin-glycoprotein complex: post-translational processing and dystroglycan function. J Biol Chem 2003;278:15457-60.
5. Voit T, Tome FMS. The congenital muscular dystrophies. In: Engel AG, Franzini-Armstrong C, eds. Myology. 3rd ed. Vol. 2. New York: McGraw-Hill, 2004:1203-38.
6. Kano H, Kobayashi K, Herrmann R, et al. Deficiency of α-dystroglycan in muscle-eye-brain disease. Biochem Biophys Res Commun 2002;291:1283-6. [Erratum, Bio-

chem Biophys Res Commun 2002;293:1579.]
7. Hayashi YK, Ogawa M, Tagawa K, et al. Selective deficiency of α-dystroglycan in Fukuyama-type congenital muscular dystrophy. Neurology 2001;57:115-21.
8. Ervasti JM, Campbell KP. A role for the dystrophin-glycoprotein complex as a transmembrane linker between laminin and actin. J Cell Biol 1993;122:809-23.
9. Michele DE, Barresi R, Kanagawa M, et al. Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. Nature 2002;418:417-21.
10. Campbell KP. Three muscular dystrophies: loss of cytoskeleton-extracellular matrix linkage. Cell 1995;80:675-9.
11. Ibraghimov-Beskrovnaya O, Ervasti JM, Leveille CJ, Slaughter CA, Sernett SW, Campbell KP. Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. Nature 1992;355:696-702.
12. Guicheney P, Vignier N, Helbling-Leclerc A, et al. Genetics of laminin alpha 2 chain (or merosin) deficient congenital muscular dystrophy: from identification of mutations to prenatal diagnosis. Neuromuscul Disord 1997;7:180-6.
13. Helbling-Leclerc A, Zhang X, Topaloglu H, et al. Mutations in the laminin α 2-chain gene (LAMA2) cause merosin deficient congenital muscular dystrophy. Nat Genet 1995;11:216-8.
14. Nissinen M, Helbling-Leclerc A, Zhang X, et al. Substitution of a conserved cysteine-996 in a cysteine-rich motif of the laminin α2 chain in congenital muscular dystrophy with partial deficiency of the protein. Am J Hum Genet 1996;58:1177-84.