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# Neuroimaging Manifestations and Classification of Congenital Muscular Dystrophies

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**BACKGROUND AND PURPOSE:** Recent work has shown that up to 50% of patients with congenital muscular dystrophies (CMDs) have abnormalities of the brain that can be detected by brain MR imaging. We attempted to determine whether brain MR imaging is useful for the diagnosis and classification of patients with CMDs.

**METHODS:** The brain MR studies of 12 patients with biopsy-proved CMDs were reviewed retrospectively. Using information available in the literature regarding associated brain anomalies as a guide, an attempt was made to classify the patients in terms of “pure” CMD, CMD with occipital agyria, Fukuyama CMD, muscle-eye-brain disease, or Walker-Warburg syndrome.

**RESULTS:** All the patients were easily classified into one of four groups: pure CMD (four patients), Fukuyama CMD (four patients), muscle-eye-brain disease (two patients), or Walker-Warburg syndrome (two patients). Patients with pure CMD had diffuse central cerebral hypomyelination with mild pontine and cerebellar hypoplasia. Patients with Fukuyama CMD had diffuse central cerebral hypomyelination, cerebellar polymicrogyria (with or without cysts), frontal polymicrogyria, a variable degree of hypoplasia of the pons and cerebellar vermis, and a variable occipital cobblestone cortex. Patients with muscle-eye-brain disease had cerebellar polymicrogyria (with or without cysts), absence of the septum pellucidum, diffuse cerebral cortical dysplasia, pontine and cerebellar vermian hypoplasia, patchy hypomyelination, and variable callosal hypogenesis and hydrocephalus. Patients with Walker-Warburg syndrome had diffuse cerebral cobblestone cortex, absence of cerebral and cerebellar myelin, cerebellar polymicrogyria (with or without cysts), pontine and cerebellar vermal hypoplasia, hydrocephalus, and variable callosal hypogenesis.

**CONCLUSION:** MR imaging shows distinctive brain anomalies that allows patients with CMD to be classified into four distinct groups that are consistent with known disorders.

The congenital muscular dystrophies (CMDs) are a heterogeneous group of disorders characterized by hypotonia, weakness, and, frequently, congenital contractures in conjunction with dystrophic changes of muscle as established by muscle biopsy (1). It has been known for several decades that some patients with CMDs have abnormalities primarily confined to muscle (so-called “pure” muscular dystrophies) (1), whereas others also have anomalies of the brain and eyes (2–8). Several years ago, it became apparent that many patients with pure CMDs have low intelligence quotients and low attenuation of white matter on X-ray CT studies of the brain (9–11). Therefore, it was suggested that pure muscular dystrophy be divided

into the “classic” form (without CNS involvement) and the “occidental” form (with CNS involvement). More recent analyses, however, have shown considerable overlap between even these groups (12).

A study by van der Knaap et al (13) suggested that imaging may have a role in classifying and understanding the disease processes in patients with CMDs. In this study, we report the brain MR imaging findings of 12 patients with CMDs. In addition, we attempt to determine whether the MR findings are useful in the classification of these patients and to explain the imaging findings by correlating them with known developmental events in this patient group.

## Methods

A review of our records revealed MR studies of the brains of 12 patients with CMDs who had been referred to our institution from 1986 through 1997. Eleven of the patients were imaged because of neurodevelopmental disorders; the 12th was imaged because her sibling, who also had CMD and was imaged after she had experienced a seizure, had a scan with

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abnormal findings. All patients had the diagnosis of CMD proved by muscle biopsy. The patients included four boys and eight girls who ranged in age from 8 months to 10 years at the time of their MR study. The cohort included two sets of siblings (patients 1 and 2 and patients 8 and 9). Before clinical records were reviewed, the MR studies were reviewed retrospectively, the imaging features were recorded, and the patients were classified according to the imaging findings. Subsequently, clinical data were extracted from patient records, and the patients were classified according to clinical manifestations.

Imaging studies included axial spin-echo (SE) T1-weighted images (500–650/11–20/2 [TR/TE/excitations]) and axial T2-weighted images (2500–3000/20–60, 80–120/1), which were available in all patients. Sagittal T1-weighted images (500–600/11–20/2) were available in 10 patients. Coronal T1-weighted images (500–650/11–20/2) were available in four patients.

The clinical records were evaluated specifically for any evidence of neurologic disease, including developmental delay, mental retardation, delayed motor milestones, asymmetric motor function, and seizures. Imaging studies were evaluated for any structural abnormalities, with particular attention directed at the cerebral and cerebellar cortices, myelination of the cerebral and cerebellar white matter, and contour of the brain stem. An attempt was made to classify each patient within one of the established categories of CMD (1–6, 13–16).

## Results

On the basis of neuroimaging results, the patients were confidently segregated into four established groups that correlated well with their classification based on clinical findings: four were classified as having pure cerebromuscular dystrophy, four as having Fukuyama CMD (2, 3), two as having muscle-eye-brain disease (4, 5), and two as having Walker-Warburg syndrome (6–8).

### Pure CMD

Our study included four patients classified as having pure CMD. These patients (two boys and two girls) were born at term and they were evaluated at an average age of 19 months (range, 15–25 months). Two of the patients were siblings. All were hypotonic from birth, had diminished deep tendon reflexes, and had elevated serum creatine kinase. All had delayed motor development, not being able to sit until an average age of 13 months; none were walking without assistance at the time of their evaluation. One child had amblyopia, and two had manifested febrile seizures. Cognitive development (interaction with the environment and development of speech) seemed normal.

Imaging studies in all these patients showed diffuse T1 and T2 prolongation of the cerebral white matter, interpreted as hypomyelination (Fig 1), mild hypogenesis of the cerebellar vermis, and a slightly small pons. The cerebral and cerebellar cortices and the white matter of the brain stem and cerebellum appeared normal.

### Fukuyama CMD

The four patients diagnosed as having Fukuyama CMDs were all girls, ranging in age from 6 to 20 months at the time of their evaluation. All were born at term and were very hypotonic from birth, with

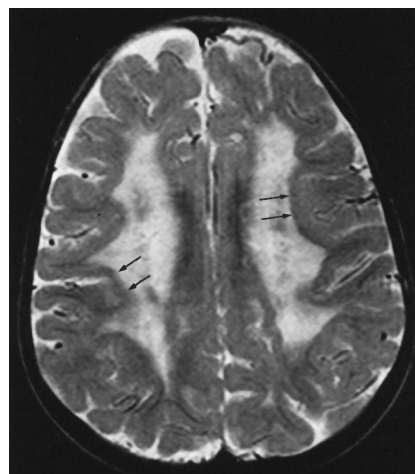


FIG 1. Axial SE (2500/90) image of 17-month-old girl with pure CMD shows abnormal T2-weighted prolongation in the central cerebral white matter. The subcortical white matter (arrows) is relatively spared.

diminished deep tendon reflexes. The 20-month-old patient had been sitting since age 14 months but was not yet standing unassisted. The 6-month-old and the two 10-month-old patients were not yet sitting unassisted. Two of the patients were microcephalic, one was normocephalic after being shunted for hydrocephalus (possibly caused by a documented intraventricular hemorrhage) at age 2 months, and the third had a normal-sized head but had severe plagiocephaly (probably caused by positional molding of the calvaria). One of the 10-month-old patients had had recent onset of generalized seizures. Two of the patients had normal serum creatine kinase, and the other two had elevated creatine kinase. The cognitive development of the 20-month-old patient was delayed.

MR studies of all four patients showed polymicrogyria in the medial anterior frontal lobes, cerebellar polymicrogyria, hypogenesis of the cerebellar vermis, T1 and T2 prolongation of the central cerebral hemispheric white matter, and a small pons that varied from mild to severe hypoplasia (Figs 2 and 3). The cerebellar white matter and the brain stem of all four patients had normal-appearing white matter; some normal T1 and T2 shortening was also seen in the subcortical white matter of the cerebral hemispheres. Patients 6 and 7 had a cobblestone lissencephaly in the occipital lobes bilaterally (Fig 3), whereas patient 8 appeared to have more diffuse microgyria, and patient 5 had a normal-appearing cerebral cortex other than the inferomedial frontal region (Fig 3). Patients 5 (Fig 2) and 7 had cerebellar cysts (17) associated with their cerebellar polymicrogyria, and patients 5, 7, and 8 had fusion of the superior and inferior colliculi (Fig 2).

### Santavuori Muscle-Eye-Brain Disease

Two male siblings were classified as having muscle-eye-brain disease. Both were born at term and were hypotonic at birth. The younger sibling was delivered by cesarean section because of breech presentation.

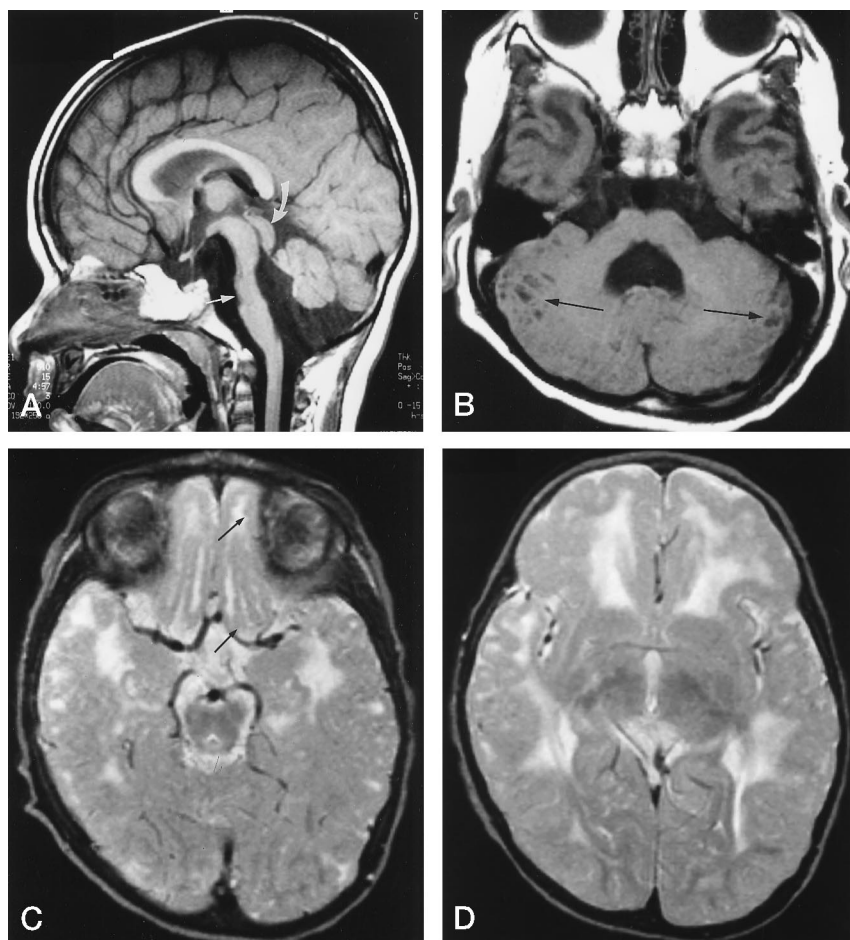


FIG 2. 20-month-old girl with Fukuyama CMD.

A, Sagittal SE (500/15) image shows marked pontine hypoplasia (*straight arrow*), fusion of the midbrain colliculi (*curved arrow*), and hypoplasia of the inferior cerebellar vermis lobules.

B, Axial SE (600/15) image shows low intensity in the temporal white matter, enlarged fourth ventricle associated with vermis hypoplasia, and the cystic type of cerebellar polymicrogyria, with the cysts (*arrows*) primarily in the lateral cerebellar cortex.

C and D, Axial (2500/90) images show T2-weighted prolongation of the central cerebral white matter and normal-appearing occipital and temporal gyral patterns. The subcortical white matter is better myelinated. Note that the inferomedial frontal cortex (*arrows*, C) has an irregular cortical-white matter junction, suggesting polymicrogyria.

The older sibling had a large head circumference from the time of birth (40.5 cm, >98th percentile) and was shunted at age 5 months because of increasing head circumference. The younger sibling had a normal-sized head at birth (50th percentile), but was

also shunted at age 5 months because of rapidly increasing head size. The younger child was also noted to have marked facial asymmetry and a high, arched palate. Ophthalmologic examination revealed pendular nystagmus, bilateral optic nerve hypoplasia, and

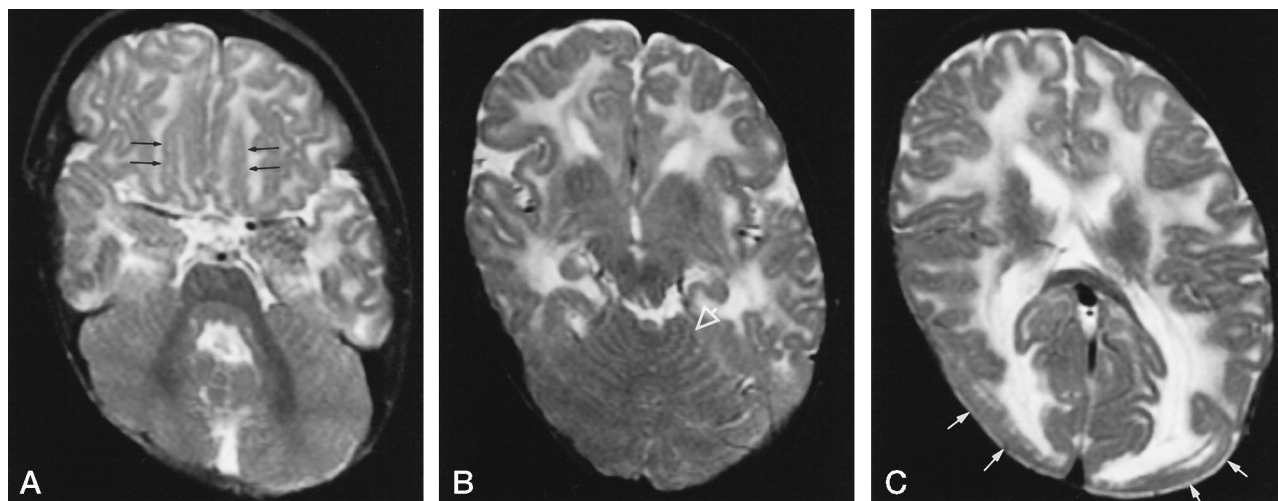


FIG 3. 8-month-old girl with Fukuyama CMD.

A, Axial SE (3000/120) image shows irregularity (*arrows*) of the inferomedial frontal cerebral cortex, suggestive of polymicrogyria.

B, Axial SE (3000/120) image of the superior cerebellum shows irregularity of the folia (*arrow*), suggesting cerebellar polymicrogyria. However, no cystic changes are seen (compare with Fig 2C).

C, Axial SE (3000/120) image at the level of the lateral ventricles shows occipital agyria (*arrows*) with a thick outer layer of gray matter and a thinner, irregular inner layer seen in type 2, or cobblestone lissencephaly.



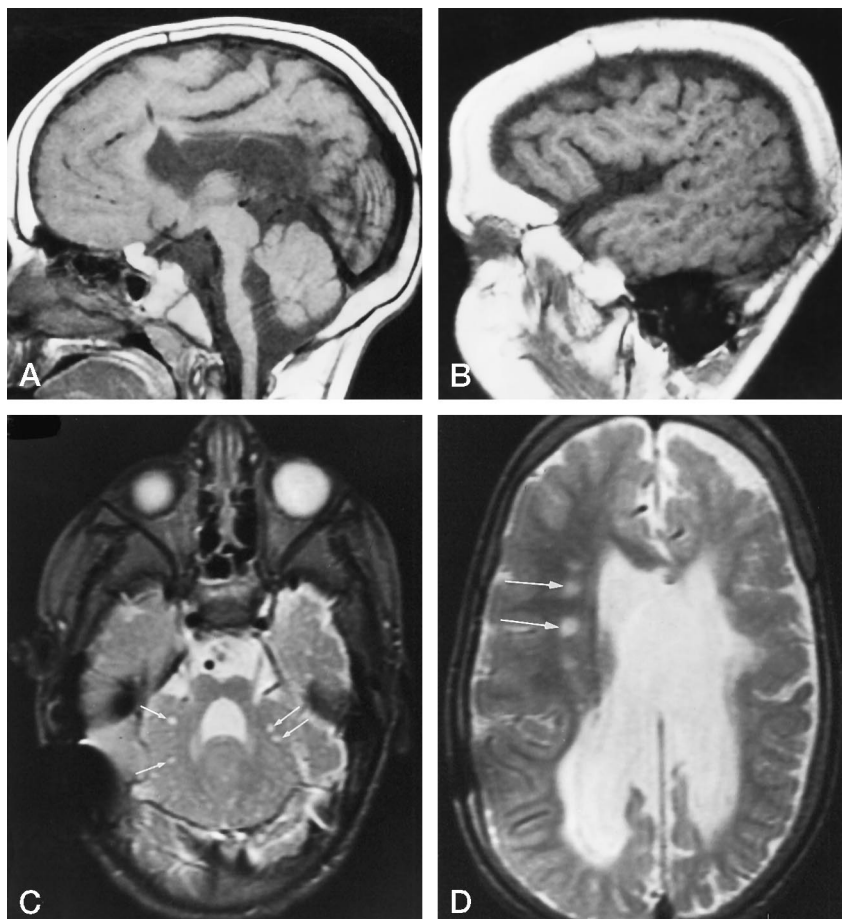
FIG 4. 10-year-old boy with muscle-eye-brain disease.

A, Sagittal SE (550/16) image shows callosal hypogenesis, hypoplastic pons, hypoplastic inferior vermis, and fused midbrain colliculi.

B, Parasagittal SE (550/16) image shows multiple areas of irregular, small gyri throughout the cortex. These were not well seen on axial images.

C, Axial SE (2500/80) image through the posterior fossa shows the hypoplasia of the pons and large fourth ventricle associated with hypoplasia of the cerebellar vermis. Cysts (arrows) are seen in the cerebellar hemispheres associated with the cerebellar polymicrogyria. The susceptibility artifact in the right temporooccipital region is from a ventriculoperitoneal shunt connector.

D, Axial SE (2500/80) image at the level of the lateral ventricles shows patchy T2 prolongation in the right hemisphere (arrows) and some T2 prolongation and volume loss in the left cerebral hemisphere.



retinal dysplasia in the older sibling. Ophthalmologic examination of the younger sibling revealed retinal pigmentary epithelial atrophy, optic nerve atrophy, congenital glaucoma, and buphthalmos in the right eye and subretinal fibrosis in the left eye. Serum creatine kinase levels were normal in both children.

MR studies of these two siblings were older and, therefore, of lower quality than those of the other patients in this study. Nonetheless, on the MR studies, one could detect a diffusely abnormal cerebral cortex in the cerebral hemispheres bilaterally, absence of the septum pellucidum, hypogenesis of the cerebellar vermis, cerebellar polymicrogyria (with cysts in the older sibling and without cysts in the younger), pontine hypoplasia, and fused colliculi in both patients. The cerebral cortical gyral patterns of both brothers looked like pachygyria on the axial images, but more like polymicrogyria (irregularity of the cortical-white matter junction, Fig 4) on the sagittal images of the older brother (the only one for whom a sagittal image was obtained). Abnormal cerebral white matter signal was seen in both children, but the pattern differed; in the younger brother, some abnormal T1 and T2 prolongation was present in the immediate periventricular frontal white matter only, whereas in the older brother a periventricular rim of T2 prolongation, possibly caused by astrogliosis from previous hydrocephalus, was seen in addition to several smaller foci of T2 prolongation (Fig 4D) in the

central portions of the cerebral white matter. The older sibling had hypogenesis of the corpus callosum, with only the genu being present; the corpus could not be accurately assessed in the younger sibling because of the presence of significant ventricular enlargement and the absence of a sagittal or coronal imaging sequence.

### *Walker-Warburg Syndrome*

Both infants with Walker-Warburg syndrome were girls who were delivered by cesarean section at term for congenital hydrocephalus. Both had severe hypotonia, weakness, and hyporeflexia at birth. Head circumferences at birth were normal, but both had progressive increases in head circumference and ventricular size that necessitated ventriculoperitoneal shunting by age 6 weeks. Ophthalmologic examination of one patient detected persistent hyperplastic primary vitreous and retinal dysplasia on the left with buphthalmos and a cataract on the right. In the second patient, ocular examination detected bilateral persistent hyperplastic primary vitreous with chronic retinal detachment on the right and a cataract on the left. One of the children had a generalized seizure at age 3 months. Neither child reached any developmental milestones. Serum creatine kinase levels were normal for both.

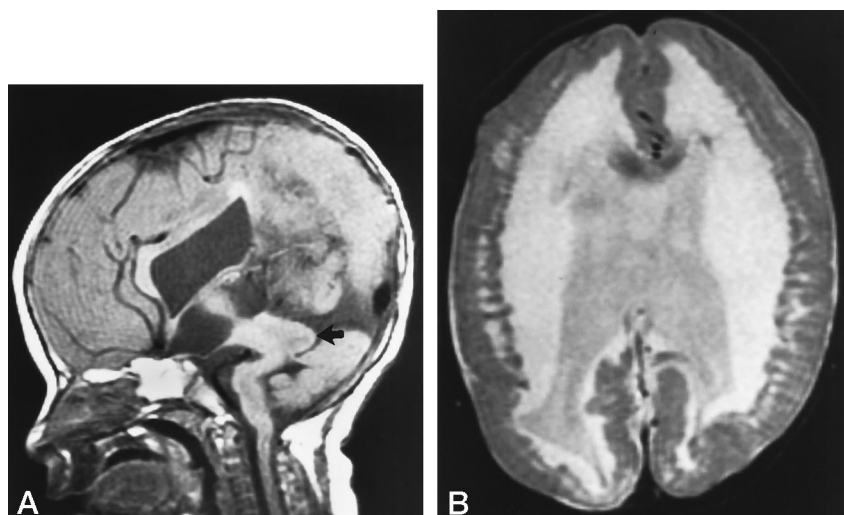


FIG 5. 8-month-old boy with Walker-Warburg syndrome.

A, Sagittal SE (600/20) image shows callosal hypogenesis, pontine hypoplasia, fused colliculi, and a dorsal pontomesencephalic kink (arrow). The cerebellum is dysplastic.

B, Axial (2800/80) image shows a complete lack of myelination and a diffuse cobblestone cortex. The lateral ventricles are enlarged.

MR studies of both children showed a diffusely abnormal cerebral cortex, with a thick, heterogeneous outer layer and a thinner inner layer, separated by a layer that appeared to represent unmyelinated white matter that was spanned by small strands of gray matter intensity (Fig 5). The outer surface of the cortex was nearly agyric. The cerebellar cortex showed apparent polymicrogyria with cysts. In addition, the cerebellar vermis and both cerebellar hemispheres were hypoplastic. The pons was hypoplastic and the brain stem was kinked posteriorly at the pontomesencephalic junction (Fig 5A). The colliculi appeared fused. No myelinated white matter was seen anywhere in the cerebral or cerebellar hemispheres.

### Discussion

Our findings suggest that patients with CMDs can be classified into four major groups based on radiologic features, which conform to the clinical groups of pure CMD, Fukuyama CMD, muscle-eye-brain disease, and Walker-Warburg syndrome (Tables 1 and 2). These are very similar to the groups defined by van der Knaap et al (13), with the exception that those authors excluded Fukuyama CMD from their classification and included an additional group, which they called CMD with occipital agyria (CMD-OA). They stated that their patients with CMD-OA differed from patients with Fukuyama CMD in that the former did not have the frontal polymicrogyria or the cerebellar cysts that are so common in the latter (both disorders have occipital agyria, diffuse or focal regions of T1 and T2 prolongation in the white matter,

and hypoplasia of the pons and cerebellar vermis) (13). Two of our patients classified as having Fukuyama CMD had very subtle inferomedial frontal and cerebellar polymicrogyria that might easily have been overlooked or missed entirely (Figs 2 and 3). If these lesions were not identified, patient 3 would have been better classified as having CMD-OA. This raises the possibility that at least some of the patients classified as having CMD-OA might in fact have subtle frontal and cerebellar polymicrogyria and might be reclassified as Fukuyama CMD. If so, this observation may call into question the inclusion of CMD-OA as a separate entity. More patients need to be examined with high-quality MR imaging to verify or contradict this conjecture. Chromosomal analysis might also be useful, since the gene for Fukuyama CMD has been identified (18).

On the basis of the findings in the patients in this study and those described in the literature (8, 9, 12, 13, 17, 19–28), we suggest the following patterns of MR abnormalities in CMD: 1) patients with pure CMDs (presumably with merosin deficiency [29], see below) have diffuse central cerebral hypomyelination with mild pontine and cerebellar vermal hypoplasia; 2) patients with Fukuyama CMDs seem to have diffuse central cerebral hypomyelination, cerebellar polymicrogyria (with or without cysts), frontal polymicrogyria, hypoplasia of the pons and cerebellar vermis, and, in some cases, occipital cobblestone cortex; 3) patients with muscle-eye-brain disease have cerebellar polymicrogyria (with or without cysts), absence of the septum pellucidum, diffuse cerebral cortical dysplasia, pontine and cerebellar vermian hypoplasia, patchy hypomyelination, and variable callosal hypogenesis and hydrocephalus; and 4) patients with Walker-Warburg syndrome have severe diffuse cobblestone cortex, complete absence of cerebral and cerebellar myelin, cerebellar polymicrogyria (with or without cysts), pontine and cerebellar vermal hypoplasia, hydrocephalus, and variable callosal hypogenesis. These features can be used, in conjunction

TABLE 1: Classification of congenital muscular dystrophies

1. "Pure" CMD
  - a. merosin-positive CMD
  - b. merosin-negative CMD
2. Fukuyama CMD
3. Muscle-eye-brain disease
4. Walker-Warburg syndrome

Note.—CMD indicates congenital muscular dystrophy.

TABLE 2: Characteristics of congenital muscular dystrophies

Disorder	Clinical Presentation	Cerebral Cortex	Cerebellar Cortex	White Matter	Brain Stem	Ocular Anomalies
Pure CMD (merosin-negative)	Hypotonia; delayed motor; high CK	Normal	Normal	Long T1, T2 in central cerebrum	Mild pontine hypoplasia	None
FCMD	Hypotonia; delayed motor; delayed cognition; +/- hydrocephalus; +/- seizures; variable CK	Frontal PMG; variable occipital cobblestone	PMG with or without cysts	Delayed myelination in cerebrum; peripheral white matter myelinate first	Variable pontine hypoplasia; +/- fused colliculi	Abnormal eye movements; myopia; cataracts; retinal "round" lesions
MEBD	Hypotonia; delayed motor; ocular anomalies; +/- hydrocephalus; +/- seizures; normal CK	Diffusely dysplastic	PMG with or without cysts; vermal hypogenesis	Patchy T1 and T2 prolongation; +/- callosal hypogenesis	Pontine hypoplasia; fused colliculi	Abnormal eye movements; myopia; glaucoma; cataracts; retinal dysplasia; hypoplastic nerve
WWS	Hypotonia; no motor milestones; no cognition; ocular anomalies; hydrocephalus; +/- seizures; normal CK	Diffuse cobblestone cortex	PMG with or without cysts; +/- cephalocele	No myelin in cerebrum or cerebellum; +/- callosal hypogenesis	Pontine hypoplasia; fused colliculi; pons-midbrain kink	Anterior chamber and iris anomalies; microphthalmos; cataracts; colobomas; retinal dysplasia and detachment

Note.—CMD indicates congenital muscular dystrophy; FCMD, Fukuyama CMD; MEBD, muscle-eye-brain disease; WWS, Walker-Warburg syndrome; CK, serum creatine kinase; +/-, variable; PMG, polymicrogyria.

with ocular and laboratory findings, to aid in the classification of affected patients.

Although Fukuyama CMD has traditionally been considered a disorder that primarily affects Japanese children, none of our four patients were of Japanese ancestry. We speculate that this disorder may be more common than is generally recognized and that the use of MR imaging will help to identify these patients more readily.

Another interesting observation in this series is the finding that the patients with pure CMDs had essentially no neurologic signs or symptoms (other than febrile seizures in two patients) despite their obvious white matter and subtle cerebellar abnormalities. This presence of white matter abnormality without associated neurologic signs and symptoms has also been noted by other investigators (9, 10, 12, 13, 19); in addition, some authors have pointed out that these patients also have normal to low-normal intelligence. Some studies have suggested that the presence of white matter abnormalities seen on imaging studies of patients with CMDs correlates with the absence of merosin on muscle biopsies (19, 29, 30) and have labeled these disorders as "merosin deficient" CMDs; this group of patients is likely the same as those identified previously as having "occidental" CMD. Merosin (also called laminin a-2) is an extracellular matrix protein that maps to chromosome 6q2; it is an important component for the linkage of the contractile elements of muscle with the muscle cell membrane, and is deficient in a subgroup of patients with CMDs (31, 32). Interestingly, merosin is also a permissive substrate for the migration of oligodendrocyte precursors (33); therefore, its deficiency may be directly related to the hypomyelination in these pa-

tients. Moreover, only weak staining for merosin is seen in muscles of patients with muscle-eye-brain disease (26) and Fukuyama CMD (34). The single patient tested for merosin in our group with pure CMD was merosin-negative.

Other molecules that are important in muscle contraction may also play a role in brain development; thus, their absence may be directly related to some of the other brain malformations that have been identified in patients with CMDs. Laminin 1 and laminin 2, which are components of the basal lamina of muscle, have been found to stimulate specifically and to guide migration of neurons (35, 36). Their absence may partly explain the cortical malformations in some affected patients; for example, patients with Walker-Warburg syndrome have deficiency in the laminin b-2 chain (37). Other proteins that have been identified in the muscle complexes are also present in the basal membranes of blood vessels, in the pia and arachnoid, and in the glial and retinal limiting membranes (26, 31, 32, 34, 37, 38). These glial and retinal limiting membranes, which are thought to be important for stopping neuronal migration and for normal cortical organization, are deficient in muscle-eye-brain disease and Fukuyama CMD (26, 39, 40); thus, the deficiency of these proteins may explain the overmigration of neurons into the subarachnoid space in patients with cobblestone lissencephalies (8, 21, 23, 26, 27).

Taking into account the large number of molecules that have already been found to be involved in the development and function of both skeletal muscle and the CNS, the high prevalence of brain anomalies in patients with CMDs is not surprising. It is also not surprising that substantial overlap of muscular, ocu-



lar, cerebral, and cerebellar anomalies is seen in these disorders; an overlap that has made classification difficult (13–16). Because all affected patients have CMD, classification has largely been based on severity of cognitive impairment, severity of superimposed neurologic impairment (such as development of seizures and mental retardation), and severity of ocular involvement. Although our study was limited by the small number of patients, our results seem to confirm those of van der Knaap et al (13), indicating that proper use of MR imaging, in conjunction with physical examination and laboratory studies, is very useful to properly classify patients with these disorders. This proper classification, in turn, is useful in aiding the physician to properly care for the child and counsel the parents as to prognosis.

### Conclusion

Although the number of patients in this study was small, our results suggest that information obtained from high-quality MR imaging of the brain is useful to properly classify children with CMDs. We have used MR imaging observations to classify 12 patients into four apparently distinct groups that correspond well with the clinical groupings of pure CMD, Fukuyama CMD, muscle-eye-brain disease, and Walker-Warburg syndrome. We speculate that high-quality imaging may show that some patients previously identified as having CMD with occipital agyria may, in fact, have Fukuyama CMD. The identification of specific chemicals that are important in both skeletal muscle contraction and in eye and brain development has greatly aided in the understanding of these complex disorders.

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Please see the Editorial on page 1383 in this issue.