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Merosin-Negative Congenital Muscular Dystrophy: Diffusion-Weighted Imaging Findings of Brain

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Merosin-negative congenital muscular dystrophy is a rare genetic disease of childhood involving the central and peripheral nervous system. There were high signal intensities throughout the centrum semiovale, periventricular, and subcortical white matters on T2-weighted images in a 4-year-old girl with merosin-negative congenital muscular dystrophy. An apparent diffusion coefficient map revealed increased signal intensity and apparent diffusion coefficient values in the periventricular and deep white matters. It may be attributable to increased water content in the white matter because of an abnormal blood-brain barrier rather than to decreased or abnormal myelination.

Keywords: muscular dystrophy; magnetic resonance imaging

Clinical manifestations of merosin-negative congenital muscular dystrophy occur at birth and consist of markedly delayed motor development, severe muscle hypotonia, weakness, severe and early joint contractures associated with joint deformities, elevated serum creatine kinase, and features of dystrophy on muscle biopsy.[1] A primary deficiency of merosin is caused by mutations of the laminin α2 chain gene. The merosin gene has been mapped to chromosome 6q2. Nonmuscular organs causing significant morbidity are the brain (white matter involvement and malformations), the peripheral nervous system (polyneuropathy), and the heart (congestive cardiomyopathy). Conventional magnetic resonance imaging findings of the white matter changes were interpreted as leukodystrophy-like demyelination, arrest in myelination, and dysfunction of blood brain barrier.[2-5] Diffusion-weighted imaging and apparent diffusion coefficient maps provide important structural information about tissues.[6,7] The random motion of water molecules, also known as Brownian motion, is restricted only by their local environment, such as cellular structures, cell walls, and orientation of the local tissue bundle. The findings of brain diffusion abnormalities in patients with merosin-negative congenital muscular dystrophy might represent evidence of microstructural abnormalities. In one study, diffusion-weighted imaging and magnetic resonance spectroscopy findings of merosin-negative congenital muscular dystrophy were reported.[7] To the best of our knowledge, in the literature, this is the second study reporting the diffusion-weighted imaging findings of merosin-negative congenital muscular dystrophy.

Case

A 4-year-old girl was admitted to our clinic because of muscle weakness. She was admitted to the hospital at 23 months because of hypotonia and delay in development. Her weight and height were below the third percentile. A neurological examination revealed symmetric muscular weakness, decreased motor activity and deep tendon reflexes, and negative Babinsky reflex. Marked joint contractures were noted. The Denver-II test revealed gross motor and fine motor-adaptive development abnormalities. Electromyography was concordant with myopathic features. In the laboratory examination, serum creatine kinase was 1063 U/L. Muscle biopsy revealed dystrophic changes, and merosin staining was deficient. Merosin-negative congenital muscular dystrophy was diagnosed by clinical examination, neurophysiological investigations, and muscle biopsy. Informed consent was obtained from the parent of the patient.

The magnetic resonance imaging examination consisted of routine imaging and diffusion-weighted imaging. Magnetic resonance imaging was performed on a 1.5-T system (Philips, Gyroscan Intera Master, Best, The Netherlands). T1-weighted images (repetition time, 560; echo time, 15 ms) were obtained in the axial and sagittal planes. T2-weighted images (repetition time, 4500; echo

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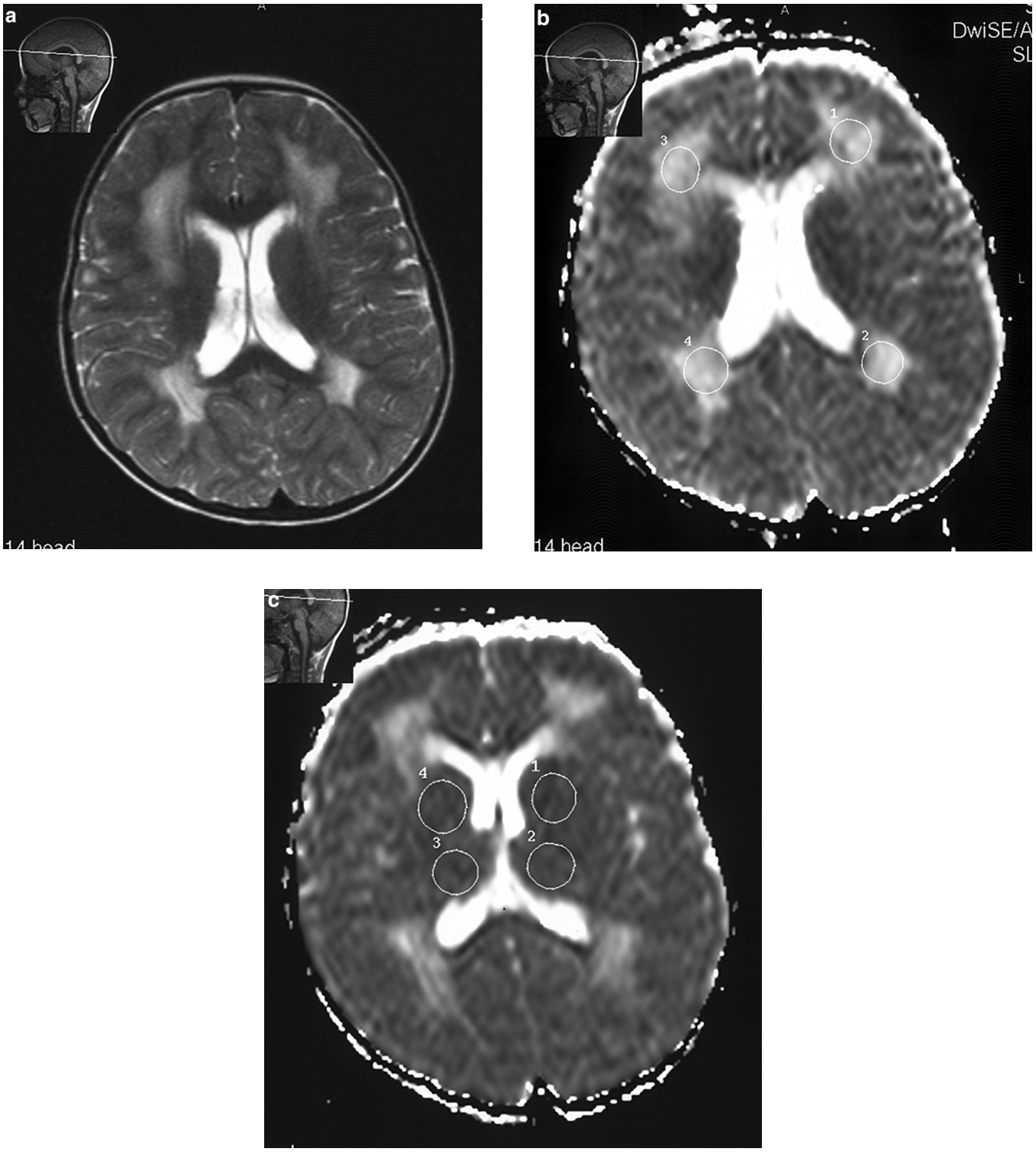

Figure 1. A 4-year-old girl with merosin-negative congenital muscular dystrophy. (a) Transverse T2-weighted (repetition time, 4500; echo time, 110 ms) images show high signal intensity in the frontal and parietooccipital white matters. (b) An apparent diffusion coefficient map reveals high signal intensity and apparent diffusion coefficient values in the frontal (1580 and 1600 $\times$ 10^{-6} mm^2/s) and parietooccipital white matters (1630 and 1602 $\times$ 10^{-6} mm^2/s). (c) Apparent diffusion coefficient maps reveal normal signal intensity and apparent diffusion coefficient values in the basal ganglia (724, and 748 $\times$ 10^{-6} mm^2/s) and thalamus (722 and 762 $\times$ 10^{-6} mm^2/s).

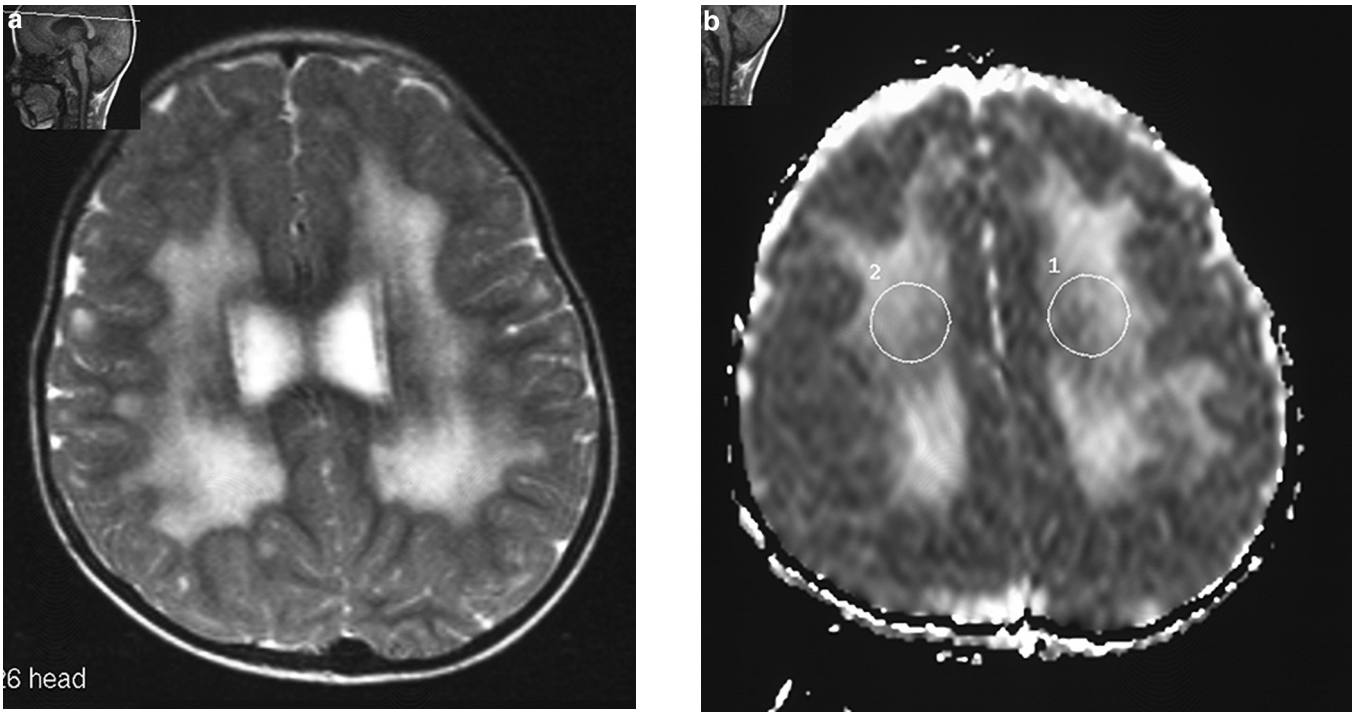

Figure 2. (a) Transverse T2-weighted (repetition time, 4500; echo time, 110 ms) images show high signal intensity in the deep white matter that extends to the arcuate fibers. (b) An apparent diffusion coefficient map reveals high signal intensity and apparent diffusion coefficient values in the deep white matter (1348 and 1308 × 10^{-6} mm^2/s).

Table 1. Mean Apparent Diffusion Coefficient Values of Children With Merosin-Negative Congenital Muscular Dystrophy

	Mean Apparent Diffusion Coefficient Values (× 10^{-6} mm^2/s)					
	Frontal White Matter	Parietooccipital White Matter	Deep White Matter	Cerebellar White Matter	Basal Ganglia	Thalamus
Case	1590	1616	1328	745	736	742
Control	786 ± 40	794 ± 30	780 ± 27	756 ± 33	723 ± 43	735 ± 40

time, 100 ms) were obtained in the axial and coronal planes. For the diffusion-weighted imaging, single-shot echo-planar pulse sequence (repetition time, 4832 ms; echo time, 81 ms; field of view, 230 mm; matrix size, 128 × 256; slice thickness, 7 mm; interslice gap, 1 mm) was used in the patient and controls with 2 different b values (0 and 1000 s/mm^2). We calculated directionally averaged apparent diffusion coefficient values from an apparent diffusion coefficient map, in circular or elliptical regions of interest drawn as the areas ranging between 50 to 150 mm^2. Six distinct locations (frontal, parietooccipital, cerebellar and deep white matter, thalamus, and basal ganglia) were selected for the analysis. Age-matched healthy children (n = 5) constituted the control group. T2-weighted images revealed a diffuse and symmetrical increase in signal intensity in the periventricular, subcortical, and deep white matters of the cerebral hemispheres in our case. The brainstem and cerebellum were structurally normal. The apparent diffusion coefficient values obtained from the periventricular and deep white matters were significantly increased compared with control subjects (Figures 1 and 2). Apparent diffusion coefficient values obtained from the patient and corresponding control group are presented in Table 1.

Discussion

Merosin (laminin α2) is a protein that links the extracellular matrix to the dystrophin-glycoprotein complex of muscle cells. Deficiency of this protein results in muscle degeneration and fibrosis, possibly as a result of disruption of the attachment of muscle cells to the extracellular matrix. Merosin is also implicated in the development of the nervous system and in particular in neurite outgrowth and Schwann-cell migration.[8] In merosin-negative congenital muscular dystrophy patients, laminin α2 is absent in the basement membrane of blood vessels of the brain.[9] Laminin α2 is also found in the basement membrane of Schwann cells and in blood vessels within the brain as well as in other tissues. This basal lamina constitutes part of the blood-brain barrier, which actively selects molecules that are allowed to reach the brain. Thus, merosin deficiency could lead to impaired selective filtration (vascular hyperpermeability), allowing normal plasma components or even toxic substances to reach the central nervous system.[9] Merosin deficiency, resulting in an abnormal basal lamina constriction and in a deficient extracellular matrix composition, may lead the myelin arrest in both the central and peripheral nervous systems.[10] It has been suggested that the cerebral white matter abnormalities are a result of this defective blood-brain barrier.[3,11,12] A defective blood-brain barrier is an associated phenomenon and that the white matter abnormalities are caused by a dysfunction of the oligodendrocytes, which are the myelin-producing cells.

Diffuse cerebral white matter changes, dilated lateral ventricles, and gyral abnormalities have been reported on magnetic resonance imaging in patients with merosin-negative congenital muscular dystrophy.[10,11,13] It is clear that only the cerebral areas that are the last to be myelinated in the developing brain (subcortical and periventricular regions) are affected, whereas the areas that are myelinated earlier in life (corpus callosum and internal capsule) are not affected.[10] The white matter changes may not be apparent until 6 months of age. There was no further progression of cerebral white matter changes with increasing age.[14] Caro et al[11] hypothesized that the hyperintense lesions on T2-weighted images observed in their study were attributable to increased water content caused by a defect in the blood-brain barrier rather than to decreased or abnormal myelination. In our case, there was high signal intensity throughout the periventricular and subcortical white matters on T2-weighted images and also in the centrum semiovale. The changes that were observed in the white matter in our case were similar to those described in the literature.[7,11,14]

Diffusion-weighted imaging is dependent on the random motion of water molecules and offers an opportunity to evaluate the structural characteristics of tissues. Diffusion of water molecules depends on tissue microstructure and microdynamics.[6] It is particularly sensitive for the detection of acute ischemic stroke. It may also provide unique information for other cerebral disorders, including neoplasms, traumatic brain injury, demyelinating diseases, and prion diseases. Besides true diffusion images (b, 1000 s/mm^2 images), calculation of apparent diffusion coefficient values is significant, as both provide information regarding tissue integrity in a variety of brain lesions. High apparent diffusion coefficient values are consistent with increased amounts of extracellular water associated with increased motion of water molecules in the affected white matter of patients with merosin-negative congenital muscular dystrophy.[7] In our case, the increased signal intensity and apparent diffusion coefficient values were revealed in the periventricular and deep white matter. It may be attributable to increased water content in the white matter because of an abnormal blood-brain barrier rather than to decreased or abnormal myelination.[11] Leite et al[7] hypothesized that white matter changes in patients with merosin-negative congenital muscular dystrophy are not related to the destruction of brain myelin but rather reflect the leakage of plasma into the brain. Gilhuis et al[3] reported that they did not find myelin-specific protein in the cerebrospinal fluid of patients with merosin deficiency; this is in contrast to findings in patients with demyelinating diseases. Villanova et al[9] reported an alteration in the blood-brain barrier, leading to vascular hyperpermeability and the penetration of substances into the central nervous system.

Conclusion

Apparent diffusion coefficient maps reveal abnormally high free-water concentrations in the white matter of patients with merosin-negative congenital muscular dystrophy.[7] Diffusion-weighted imaging appears to be a promising sequence to evaluate the changes in the brain tissue. Further diffusion-weighted imaging studies may provide increasing data and new conceptions into the mechanisms of merosin-negative congenital muscular dystrophy.

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