Pictorial Essay

Brain MR findings in a patient with merosin-negative congenital muscular dystrophy

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Abstract We report a case of a Japanese patient with merosin-negative congenital muscular dystrophy (MNCMD), with a particular emphasis on the neuroradiologic findings. Brain MR at 4 years of age revealed diffuse T1 and T2 prolongation of the white matter, which was bilateral, symmetrical, and conspicuous in the anterior lobes. The internal and external capsules, basal ganglia, and corpus callosum were normal. There was no evidence of cerebral atrophy, ventricular dilatation, or abnormal cortical gyral formation. The cerebellum and brain stem were unremarkable. The extensive dysmyelination was incomparable to the neurologic symptoms. The pathogenesis of dysmyelination of the white matter has not yet been elucidated. Merosin is an important component of the laminin-glycoprotein complex-cytoskeletal linkage in the muscle, also expressed in Schwann cells. Merosin deficiency disrupts this linkage, resulting in muscle degeneration, and presumably, in dysmyelination of the white matter. Marked merosin reduction has been known in Fukuyama congenital muscular dystrophy (FCMD). The different amount of merosin expression between MNCMD and FCMD may account for the different evolution of the white matter changes between both entities.

Key words *Magnetic resonance, Merosin, White matter change, Leukodystrophy, Dystrophin-associated glycoprotein*

INTRODUCTION

Congenital muscular dystrophy (CMD) is a heterogeneous group of neuromuscular disorders inherited as an autosomal recessive trait. Muscle weakness, delayed motor development, and joint contractures as a result of dystrophic muscular changes manifest in the neonatal period. CMD is divided into several forms, including Fukuyama-type CMD (FCMD), Walker-Warburg syndrome (WWS),

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muscle-eye-brain syndrome (MEB), pure or classical CMDs[1], and miscellaneous undefined entities, such as CMD with mitochondrial structural abnormalities proposed by Nishino et al.[2]. Although Duchenne-type muscular dystrophy (DMD), myotonic dystrophy, facioscapulohumeral muscular dystrophy, and adhalin-deficient muscular dystrophy occasionally presents clinical symptoms within the first few months after birth, these entities are distinguishable from CMD on the basis of their clinical and pathological features[3].

Pure CMD is divided into two groups, comprising merosin-negative CMD (MNCMD) and merosin-positive CMD (MPCMD). Merosin deficiency in pure CMD was first discovered by Tome et al. in 1994[4]. Since then, it has been elucidated that MNCMD is responsible for approximately half cases of pure CMD in Western countries[5]. In Japan, however, MNCMD is uncommon: Kobayashi et al. found only 3 cases with MNCMD in 53 cases with pure CMD based on an immunohistochemical technique[5]. To date, 6 patients with MNCMD have been reported in Japan[6~13]. Here, we report an additional case of a Japanese patient with MNCMD, with a particular emphasis on the neuroradiologic findings that helped to diagnose this rare disorder.

CASE REPORT

The patient was a Japanese girl, who was the first child of a consanguineous couple. The parents of the patient, the 30-year-old father and 24-year-old mother, were first-degree cousins. The family history was not noteworthy for neuromuscular diseases. Pregnancy was unremarkable except for mild toxemia that did not require particular medical intervention. The patient was delivered normally at 39 weeks of gestational age. Birth weight was 2,458g (−1.5 SD), and the Apgar score was 8 at 1 minute. For a while after birth, the patient was well with normal muscular tone. However, poor sucking and weakness of activity ensued soon after. At 12 days of age, muscle hypotonia became obvious without deep tendon reflexes. Laboratory findings are summarized in **Table 1**. Serum creatine kinase (CK) level and other muscle origin enzymes were significantly elevated. Chest radiographs and electrocardiogram (ECG) were normal. Electromyographic findings were consistent with active myopathy. Ophthalmological findings were unremarkable. Neither intracranial hemorrhage nor ventriculomegaly was noted on brain ultrasonography. Electroencephalo-

Table 1 Laboratory Findings at 1 day of age

WBC	18,800/mm³	TP	6.9g/dℓ	CK	65,900IU/ℓ
RBC	602/mm³	ALB	3.4g/dℓ	BB	0 %
Hb	21.6g/dℓ	BUN	17mg/dℓ	MB	4 %
Hct	64.7%	Cr	0.8mg/dℓ	MM	96%
PLT	28.6/mm³	AST	488 IU/ℓ	LDH	3152 IU/ℓ
		ALT	116 IU/ℓ	Aldorase	342.3 IU/ℓ
CRP	4.2mg/dℓ	T-BIL	6.1mg/dℓ	Lactate	11.3mg/dℓ
IgM	29mg/dℓ	Na	139mEq/ℓ	Pyruvate	0.6mg/dℓ
Hapt	16.2mg/dℓ	K	3.9mEq/ℓ	Myoglobin	3610ng/mℓ
α1AG	8.5mg/dℓ	Cl	102mEq/ℓ		
pH	7.406	Ca	9.6mg/dℓ		
PCO_2	44.6mmHg	Glu	79mg/dℓ		
HCO_3	27.7mmHg	NH_3	58	chromosome	46,XX

Serum creatine kinase (CK) level and other muscle origin enzymes were significantly elevated.

graphy (EEG) revealed no epileptic discharge or other abnormal findings. The patient underwent muscle biopsy of the right rectus femoris muscle at 22 days of age. Histologic findings comprised marked variation in muscle fiber size with numerous internal nuclei, focal increase of dense fibrous connective tissues, and admixture of necrotic with redegenerating muscle fibers. Immunohistochemical analysis of the muscular specimens for merosin antibody revealed complete merosin deficiency, but that for dystrophin, dystrophin-associated glycoproteins(DAGs), and laminin alpha 1 and beta chains did not yield abnormal findings. The details of the muscle pathology were previously reported by S. Osari et al. (case 1)[8]. Chromosomal analysis by high resolution technique revealed a normal female karyotype without microdeletion including chromosome 6q. PCR-RFLP analysis of the LAMA2 gene showed homozygosity in the patient and heterozygosity in her parents and younger healthy brother. The clinical, laboratory, and pathological findings of the patient fulfilled the diagnostic criteria of MNCMD. The patient is currently 6 years of age with severe muscle weakness. However, she does not require ventilation support. She is able to sit unaided and is mentally normal. Despite physical disability, she has started school life. She has had no episode of seizure, and sequential EEG examinations have yielded normal findings.

BRAIN MR FINDINGS

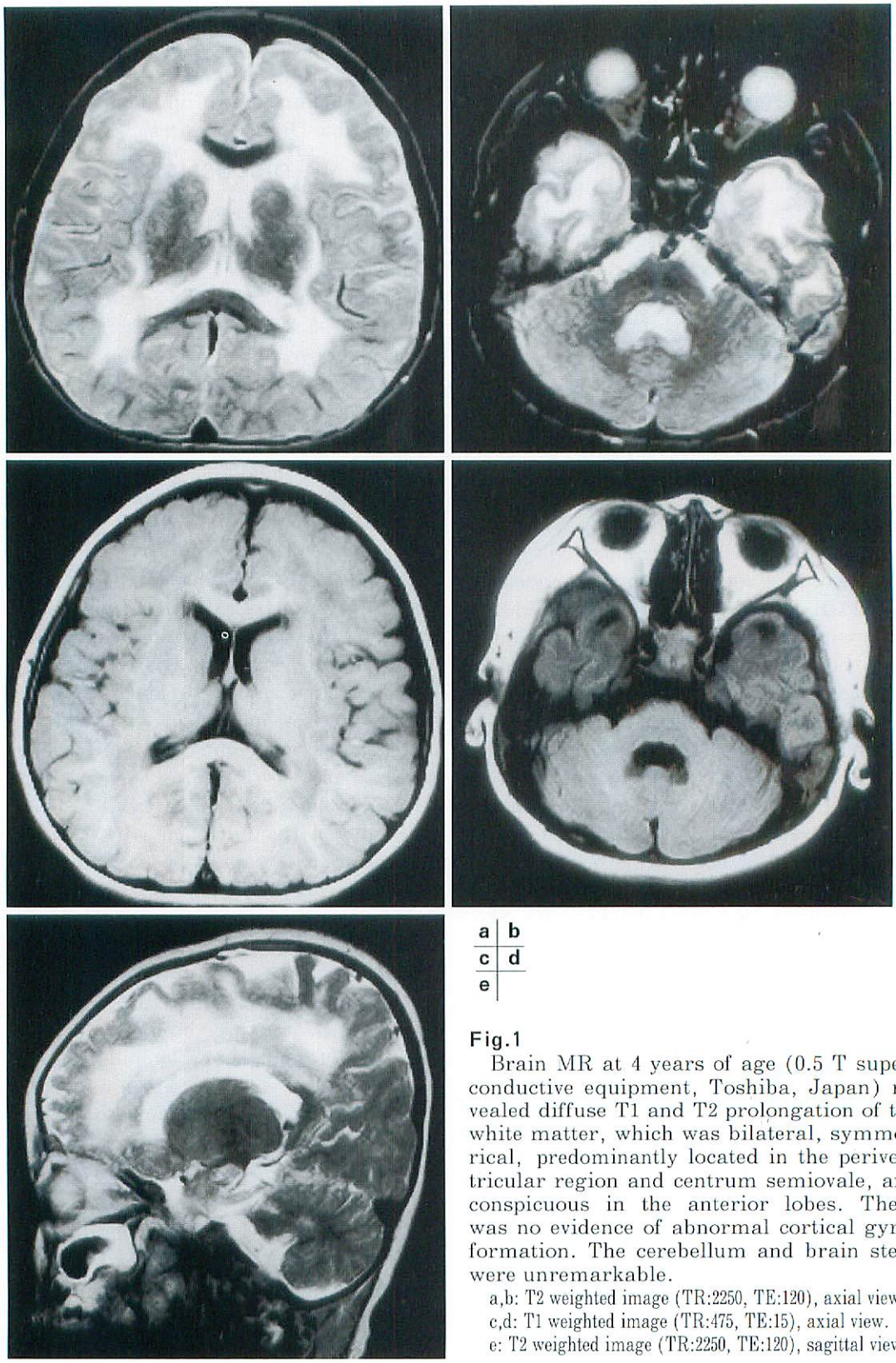
The patient underwent brain MR at 4 years of age, using a 0.5 T superconductive equipment (Toshiba, Japan). MR revealed diffuse T1 and T2 prolongation of the white matter, which was bilateral, symmetrical, predominantly located in the periventricular region and centrum semiovale, and conspicuous in the anterior lobes. The internal and external capsules, basal ganglia, and corpus callosum were normal. There was no evidence of cerebral atrophy, ventricular dilatation, nor abnormal cortical gyral formation. The cerebellum and brain stem were unremarkable (**Figure 1** - **a**~**e**).

DISCUSSION

Based on the current well-accepted classification of CMD that was proposed by Dubowitz et al.[1,14] at the 22nd European Neuromuscular Consortium-Sponsored Workshop in 1993, CMDs comprise three common subtypes, type 1 without severe impairment of intellectual development, type 2 with severe impairment of intellectual development including FCMD, and type 3 including all "muscle-eye-brain syndromes", and a number of uncommon forms (e.g., congenital atonic-sclerotic or Ullrich disease).

Type 1 CMD is further subdivided into MNCMD and MPCMD, based on the absence or presence of merosin expression, respectively. The hallmarks of MNCMD include severe muscle weakness of early neonatal onset, normal or subnormal intellectual development, and white matter changes that are discernible on CT and MR. The definitive diagnosis rests on muscular merosin deficiency by immunohistochemical staining technique. The merosin gene has not been discovered, but the gene locus has been mapped to the region near the LAMA2 gene (6q22~23)[15].

Brain MR findings of MNCMD have been reported to be bilateral, symmetrical, diffuse, and predominantly periventricular T1 and T2 prolongation of the white matter[16~21]. This white matter lesion is described by some to be more conspicuous in the anterior rather than the posterior lobes. Subcortical U fibers are less severely affected, and the internal capsule, external capsule, and the white matter of the cerebellum and brain stem are spared. Consequently, the present patient radiologically met the MR characteristics of MNCMD. Although unilateral



a	b
c	d
e	

Fig.1

Brain MR at 4 years of age (0.5 T superconductive equipment, Toshiba, Japan) revealed diffuse T1 and T2 prolongation of the white matter, which was bilateral, symmetrical, predominantly located in the periventricular region and centrum semiovale, and conspicuous in the anterior lobes. There was no evidence of abnormal cortical gyral formation. The cerebellum and brain stem were unremarkable.

a,b: T2 weighted image (TR:2250, TE:120), axial view.
c,d: T1 weighted image (TR:475, TE:15), axial view.
e: T2 weighted image (TR:2250, TE:120), sagittal view.

or bilateral ventricular enlargement and shrinkage of the corpus callosum are seldom found, these findings are attributable to brain atrophy secondary to general malaise or ischemic brain changes due to respiratory compromise. Abnormal cortical gyral formation is not generally considered to be a constituent of MNCMD, although three cases of MNCMD with brain malformations, including polymicrogyria, hamartomas, migration errors, and double cortex, have been reported[5,22]. Brain stem malformation such as pontine hypoplasia has rarely been observed[21].

Differential diagnosis of white matter alteration of the children includes Pelizaeus-Merzbacher disease, Krabbe's disease, peroxisomal disorders, metachromatic leukodystrophy, phenylketonuria, maple syrup urine disease, Lowe's disease and other metabolic diseases. Analysis of the thalami and specific tracts (the corticospinal tracts, in paticular)may contribute to the differentiation, however, diagnosis can be comfirmed by the clinical manifestations in most cases.

Brain MR can play a substantial role in distinguishing MNCMD from MPCMD and other CMDs. MPCMD does not show white matter involvement[21]. Types 2 and 3 CMD are commonly associated with migration anomalies, including polymicrogyria, pachygyria, lissencephalic findings, and heterotopia[3]. White matter changes are common in FCMD. Thus, MNCMD is neuroradiologically distinguishable from MPCMD by the presence or absence of white matter involvement, and from types 2 and 3 CMDs by the migration pattern. Based on sequential MR studies by Mercuri at al., who proposed the failure in the physiological maturation process of myelination as the cause of the white matter aberration[23], the white matter changes in FCMD are intriguingly less conspicuous with age[24], while the white matter aberrations in MNCMD become evident at 6 months and subsequently are invariable.

The pathogenesis of dysmyelination of the white matter in CMDs has not been elucidated, but a theoretical clue to the development of muscular dystrophy may be given by recent investigations on the relationship of dystrophin-associated glycoproteins(DAGs)and laminins. In Duchenne-type muscular dystrophy(DMD)and Becker-type muscular dystrophy (BMD), the lack of dystrophin disrupts the linkage between the extracellular matrix and cytoskeleton (laminin-glycoprotein complex-cytoskeletal linkage), resulting in muscular weakness and damage to the muscular fibers[25]. The laminin-glycoprotein complex-cytoskeletal linkage consists of laminin, DAGs, and dystrophin, from the outside to the inside of the sarcolemma in the muscle cells, and maintains the structural stability of the muscular unit; thus its disintegrity causes muscle degeneration.

Laminin is a diverse group of cell adhesion molecules, and merosin, previously termed laminin-M, is a subtype of the laminins[28]. Thus, merosin is also an important component of the laminin-glycoprotein complex-cytoskeletal linkage[25]. As in dystrophin deficiency, deficiency or severe reduction of merosin can give rise to muscle degeneration. Merosin is expressed not only in the striated muscle, but also in the placenta[15,26~27], thymus[28] and, more noticeably, Schwann cells[26,29]. Consequently, merosin deficiency can cause both muscle degeneration and abnormal myelination.

Marked merosin reduction has been known in FCMD[30]. However, the presence of severe brain malformations in FCMD indicates that the merosin reduction in FCMD represents a secondary consequence of a still undefined gene product. The different amount of merosin expression between MNCMD and FCMD may account for the different evolution of the white matter changes between both entities cited above.

Of interest is the fact that the extensive

dysmyelination in MNCMD is not comparable to the neurologic symptoms: most affected individuals do not have overt sensory disturbance or pathologic reflex, although Merculi et al.[31] reported abnormal somatosensory evoked potential (SEP). Thus, the white matter changes do not aggravate neurologic symptoms of affected individuals. However, the question of whether or not the seriousness of the white matter changes is related to the severity of muscular dystrophy has now been raised. Further case documentation is required to resolve this issue.

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