Merosin-Deficient Congenital Muscular Dystrophy with Polymicrogyria and Subcortical Heterotopia: A Case Report

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ABSTRACT

This paper reports the brain magnetic resonance imaging (MRI) findings of a case of merosin-deficient congenital muscular dystrophy (MDCMD) in a neonate and discusses the spectrum of brain involvement in MDCMD. A neonate presented hypotonia, increased serum creatine kinase levels, and polymicrogyria and subcortical heterotopia on brain MRI involving both posterior temporal and occipital lobes. Although these findings suggested Fukuyama muscular dystrophy, muscle biopsy showed dystrophic changes and an absence of merosin staining. We found that compound heterozygous mutation for c.2049_2050delAG (p.R683fs) and c.5866-2A>G in the LAMA2 gene which encodes Laminin-α2. To our knowledge, this is the second Korean case of MDCMD with polymicrogyria and subcortical heterotopias. This case shows that a range of brain structural malformations can be found in children with MDCMD and that the classification of congenital muscular dystrophy (CMD) is not complete yet, as indicated previously in reports suggesting other unclassified forms of CMD.

Key Words: Merosin-deficient congenital muscular dystrophy, Polymicrogyria, Subcortical band heterotopias, Laminin-2

INTRODUCTION

Congenital muscular dystrophies (CMDs) are a heterogeneous group of neuromuscular disorder with dystrophic findings in a muscle biopsy. Major clinical manifestations are early-onset hypotonia, muscle weakness, and joint contractures. The clinical course is static or slowly progressive and few children become ambulatory. CMD is classified into two general categories, depending on brain and eye involvement: classic CMD without brain malformations and CMD associated with brain malformations and severe mental retardation (Fukuyama type, Walker-Warburg syndrome, and muscle-eye-brain disease).

However, recent studies have demonstrated the involvement of the brain in infants with merosin-deficient congenital muscular dystrophy (MDCMD), which is categorized...
under classic CMD. MDCMD is a rare disease, especially in non-Caucasians. We present a case of neonatal MDCMD with neuronal migration disorder. To our knowledge, this is the second description of MDCMD with polymicrogyria and subcortical heterotopia in Korea. Additionally, we review reported cases of MDCMD with cortical abnormalities, which suggest that MDCMD might be more complex than originally thought.

CASE REPORT

A 13-day-old male infant, born by cesarean section at 41 weeks gestation and weighing 3,250 g, was referred to a neonatology clinic because of muscle weakness and recurrent feeding cyanosis. The pregnancy and delivery were uneventful. There was no family history of neuromuscular or metabolic disease. His height, weight, and head circumference were within normal ranges. Neurological examination revealed a generalized decreased motor activity and symmetric muscular weakness without muscular hypertrophy. Thus, we planned evaluations for hypotonia, including chromosomal and genetic screening for dystrophia myotonica protein kinase (DMPK), spinal muscular atrophy (SMA) multiplex ligation-dependent probe amplification (MLPA), and Prader-Willi syndrome methylation polymerase chain reaction (PCR). We also conducted magnetic resonance imaging (MRI) of the brain. Biochemical tests results were normal except for elevated serum creatine kinase (CK) levels up to 4,813 U/L. MRI showed polymicrogyria and subcortical heterotopia involving both posterior temporal and occipital lobes. Collectively, his findings suggested CMD, specifically Fukuyama muscular dystrophy (Figure 1). To confirm CMD we conducted a muscle biopsy of the left vastus lateralis at the 7th day of his stay in the hospital. In addition, we performed ocular examination, and evaluated cardiac and brain functions. The optic disc and fundus oculi were normal and the echocardiogram showed no structural anomalies and good left ventricle contractility. However, electroencephalogram (EEG) findings suggested focal brain dysfunction and indicated subcortical structural lesions. At hospital day 22, feeding cyanosis improved and he no longer needed supplementary oxygen, and was discharged.

The muscle biopsy showed dystrophic changes. There was variation in fiber size, fiber loss, and endomysial fibrosis but no evidence of significant inflammation or abnormal dystrophin or dysferlin expression (Figure 2). Merosin was completely absent from the sarcolemma (Figure 3). However, chromosomal and checked genetic tests were normal. By analyzing the gene test we found that compound heterozygous mutation for c.2049_2050delAG (p.R683fs) and c.5866-2A>G in the LAMA2 gene (Figure 4). MDCMD was confirmed as the final diagnosis.

Figure 1. Axial brain magnetic resonance image (MRI; T2-weighted) of subcortical and deep white matter shows an abnormally high signal (A) and an abnormally low signal in MRI (T1-weighted) (B). Irregular heterotopic tissue of the corticomedullary junction involving both posterior temporal and occipital lobes suggests polymicrogyria and subcortical heterotopias.
DISCUSSION

CMDs, described in 1903, are a heterogeneous group of neuromuscular disorders characterized by the early onset of hypotonia and dystrophic findings in a muscle biopsy\(^1\). Clinical features range from early fatal disorders to mild conditions with survival into adult life. In 1993, an International Consortium on CMD identified a classical form of CMD without structural brain changes, which is subdivided into merosin-positive and merosin-negative subtypes, separate from other forms of CMD which are all associated with structural brain changes\(^3\). Thus, in patients presenting with features of CMD, MRI can help further differentiate the various CMD subtypes.

MDCMD was initially identified in 1994 as a variant of classic CMD\(^5\). It is an autosomal recessive CMD caused by a deficiency in laminin-\(\alpha\)2, also known as merosin. MDCMD varies by region and is most common in Caucasians, accounting for 50% of classic CMD cases in that ethnic group\(^3\). In Asian countries, the disease is very rare, with frequencies ranging from 1% to 6% of classic CMD cases\(^4\).

Laminin is an abundant protein in the extracellular matrix with a cross-shaped heterotrimeric form through the association of \(\alpha\), \(\beta\) and \(\gamma\) chain. Laminin-\(\alpha\)2 is expressed in skeletal muscle, the basal lamina of the neural vasculature, developing white

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**Figure 2.** The muscle specimen staining were from the patient. (A) Hematoxylin and eosin stain (\(\times 200\)) shows variation in muscle fiber size, fiber loss, and replacing endomysial fibrosis. The other panels (B-D) show normal expression. (B) Dystrophin Related Protein 2 (DRP2) (\(\times 200\)); (C) ATPase reaction (pH 4.3; \(\times 200\)); (D) alpha dystroglycan, glycosilated (\(\times 200\)).

**Figure 3.** Immunohistochemical staining was performed with a primary antibody against merosin. All muscle fibers stained positively at the muscle surface membrane in normal control (A), compared to the absence of staining of muscle fibers in the patient’s left vastus lateralis muscle (B) (\(\times 200\)).
matter tracts, and Schwann cells. Its molecules are secreted into the extracellular matrix and bind at the cell surface to both dystroglycan and integrin where they serve as part of the structural scaffold. They also function as an active part of signaling cascades, cell differentiation, and tissue survival. Merosin in particular, plays a role in myogenesis, promoting myotube stability by preventing apoptosis. Therefore merosin deficiency disturbs the assembly and stability of the laminin-network, resulting in the typical clinical-pathologic manifestations of CMD. Children with MDCMD usually present at birth with hypotonia and joint contractures. Other frequent complications include respiratory insufficiency, feeding problems and failure to thrive.

Brain MRI represents a powerful tool in the study of patients with CMD because the MRI generally shows typical findings. After the age of 6 months, patients with MDCMD show a specific pattern of white matter changes in MRI, with increased signal intensity on T2-weighted images. In other words, classic phenotype of MDCMD has no migration anomaly. Pachygyria and polymicrogyria are all the results of abnormal cell migration. The abnormal migration is typically associated with a disorganized cellular architecture, failure to form six layers of cortical neurons, and functional problems. In the current case, MRI showed polymicrogyria and subcortical heterotopia involving both posterior temporal and occipital lobes. Although this finding has been described in Fukuyama CMD and is rare in MDCMD, it has been recently described as a feature of this condition. Like this, in addition to the white matter abnormalities, structural brain changes have been reported in some patients with laminin-α2 deficiency. These included occipital polymicrogyria/agyria and hypoplasia of the pons and/or the cerebellum. In Korea, there were two reports of a large case-series of MDCMD. All of the patients had typical white matter signal change in T2-weighted images on brain MRI. But just in one patient, migration anomaly was noted on both frontal and right occipital area. Therefore to the best of our knowledge, this is the second Korean case report of MDCMD with migration anomaly. Normal intelligence is found in a majority of patients, although some present with seizures and mental retardation. In particular, occipital agyria has been associated with mental retardation and epilepsy.

Cardiac failure seems to be a rare feature of this disorder, although echocardiographic evidence of left ventricular hypokinesia has been observed. Autopsy showed that, despite the lack of heart dilatation or histological alterations, laminin-α2 was also absent in the myocardium. In the current case, initial ocular and cardiac functions were normal and feeding cyanosis disappeared without oxygen supply. We will follow up the patient with repeat echocardiography, and assess feeding, growth, and development over the next few years.

Diagnosis of MDCMD is made by muscle biopsy and genetic testing. Skeletal muscle abnormalities include typical dystrophic changes such as muscle fiber necrosis, with signs of ongoing degeneration and regeneration. Immunohistochemical studies focus on the expression pattern of the C- and N-terminal of laminin-α2. Laminin-α2 is also expressed at the junction of the dermis and epidermis. Therefore, skin biopsy can be an assistive diagnostic tool to check laminin-α2 expression.

Laminin-α2 is encoded by the LAMA2 gene, which is composed of 64 exons. Various mutations in the LAMA2 gene have been found to cause a deficiency in merosin quantity or function. And phenotype severity is highly dependent on the type of mutation.

In this case, MRI showed polymicrogyria and subcortical heterotopia with early-onset hypotonia and increased CK le-
vel. Although we suspected Fukuyama muscular dystrophy, MDCMD was diagnosed by muscle biopsy, which showed dystrophic changes and an absence of merosin staining. Identification of the compound heterozygous mutation for c.2049-2050delAG (p.R683fs) and c.5866-2A>G in the LAMA2 gene clarified the diagnosis. This case suggests that, although structural brain anomalies are rare in children with MDCMD, the spectrum of brain involvement is wider than previously thought. Recent advances in molecular technologies and the genetic basis of CMD have allowed an improved understanding of CMD pathogenesis and clinical diversity. Therefore, classification of CMD should consider clinical features along with the identification of genetic and biochemical defects. We suggested evaluations and predictions of the clinical course of the disease include muscle biopsy, DNA testing, and eye examination along with cranial MRI.

ACKNOWLEDGMENTS

The authors are grateful to Bo-Ram Kang (Department of Neurology, Pusan National University Yangsan Hospital, Yangsan, Korea) for technical help with staining.

REFERENCES

1) Batten FE. Three cases of myopathy, infantile type. Brain 1903; 26:147-8.