CASE REPORT

Merosin-deficient congenital muscular dystrophy type 1A

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Abstract

Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) is the most common form of congenital muscular dystrophy. MDC1A is caused by mutation of the laminin alpha-2 gene (LAMA2), localized to chromosome 6q22–23. The diagnosis of merosin-deficient CMD is based on the clinical findings of severe congenital hypotonia, weakness, with high blood levels of creatine kinase, WM abnormalities, and dystrophy associated with negative immunostaining of biopsied muscle for merosin. We investigated clinical and laboratory a patient: a girl with merosin-deficient congenital muscular dystrophy type 1A. Clinically the particularity of the case is the association of merosin-negative congenital muscular dystrophy (MN-CMD) with congenital feet deformity. The level of serum creatine kinase is elevated 1045 U/L. Immunohistochemistry show presence of dystrophin, lack of merosin, also the utrophin is normally expressed. Nerve conduction studies are normally, while electromyography suggested a myopathic process with early recruitment and decreased amplitude and duration of response. Magnetic resonance imaging: MRI T1 and MRI T2 show hypointensity and diffuse hyperintensity respectively in the white matter. Supratentorial MRI images showed hypotrophy of the corpus callosum and almost absent cingulate gyrus. In addition, hypophysis is reduced size.

***Keywords*:** congenital dystrophy, LAMA2 gene, merosin, white matter.

Merosin-deficient congenital muscular dystrophy type 1a

Congenital muscular dystrophies (CMDs) are a heterogeneous group of disorders that are characterized by the early onset of hypotonia, muscular weakness, and dystrophic findings at muscle biopsy [1, 2].

CMDs can be limited to the muscle or can be associated with central nervous system and eye abnormalities. Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) is the most common form of congenital muscular dystrophy. MDC1A is caused by mutation of the laminin alpha-2 gene (LAMA2), localized to chromosome 6q22–23 [3, 4].

This gene encodes the alpha 2 chain, which constitutes one of the subunits of the laminin 2 (merosin). Laminin-2 (merosin) is a heterotrimer composed of laminin subunits alpha-2, beta-1, and gamma-1 [5].

Mutations in the LAMA2 gene lead to a primary deficiency in the laminin alpha-2 chain of merosin [6]. Expression of laminin-alpha2 is related to disease severity. Complete lack of expression is always associated with a severe phenotype [7].

Partial loss of expression is often associated with a mild phenotype, but severe phenotypes have also been described [8, 9].

MDC1A is a severe form characterized by an absence of merosin around muscle fibers, elevated serum creatine kinase (CK), especially in the early months of life, no independent ambulation due to weakness and contractures, respiratory insufficiency [10].

Clinically MDC1A patients present: severe hypotonia, weakness, feeding difficulty, and respiratory insufficiency, contractures are common. Weakness is static or minimally progressive. External ophthalmoplegia may occur late. Most infants eventually sit unsupported, but standing is rare. A sensory motor demyelinating neuropathy is present in many patients, but it may be not clinically relevant. May occur mild mental retardation, perceptual-motor difficulties or seizures in up to 30% of patients [11–13].

The patients with primary laminin-2 deficiency have abnormalities of the central white matter on magnetic resonance imaging (MRI) that, however, are usually asymptomatic [7].

The diagnosis of merosin-deficient CMD is based on the clinical findings of severe congenital hypotonia, weakness with high blood levels of creatine kinase, WM abnormalities, and dystrophy associated with negative immunostaining of biopsied muscle for merosin.

Patient and methods

The patient was a 6-year-old girl, born by full-term, first born from a pair of non-identical dizygotic female twins, cesarean delivered (because the lack of progression), mild perinatal acute hypoxia, APGAR 7, low birth weight (2200 grams), moderate severe

jaundice (Rh incompatibility: child Rh positive, blood group A II, mother Rh negative, A II) for that she necessitated intermittent phototherapy for a 3-days period with a favorable evolution, congenital bilateral idiopathic talipes equinovarus.

Family history revealed that her parents were non-consanguineous and there were no family cases of neuromuscular diseases, her twin sister healthy and without deformity.

By the age one month she had just 2660 grams, PC 35 cm, PT 44 cm, L 47 cm, she was not breastfed with negative sucking reflex and she was noted to be mild hypotonic with primitives reflexes presented, with no other modifications on the cardiovascular and pulmonary systems.

Her developmental milestones had been delayed and by age one year she presented an axial and peripheral severe hypotonic syndrome, she did not hold head up, did not roll over or sit alone, and she was suspected of infantile cerebral palsy.

By the age 2, she realized the rolling and at the age of 4 she was sitting without support, intellectual and speech, development was normal.

Results

Clinical assessment

Actual physical examination revealed severe axial hypotonia syndrome with bilateral upper and lower extremity weakness, non-progressive, more proximal than distal, predominantly at shoulder and pelvic girdle, facial weakness, global areflexia, generalized symmetric amyotrophia, anterior axillary folds sloped down and out as a result of wasting of the pectoral muscles (Figure 1).

Cranial nerves were normal, with no difficulties on sensory examination and coordination. The triceps surae muscle and tendon of Achilles was bilaterally shortened and tight with fixed bilateral equine-varus feet deformity (Figure 2), plantar reflexes were flexor and Babinski sign was absent.

She showed impossibility to crawl or stand and bear weight on her legs but she could sit unaided. She could not rise from the floor in to sit position. Ankle angle during passive or active movement was 0^0, active knee flexion was 40°, hip extension 0^0, hip active flexion 70^0.

Muscle strength of flexo-extensor lower limb muscles, manually assessed using the standard *Medical Research Council* (MRC) scale, was 1/5 for tibialis anterior, 1/5 quadriceps, and 0/5 for glutei muscles. Upper limb proximal muscle power was determined to be at grade 2/5.

The cardiac assessment was normal. Clinical findings, generalized amyotrophy, muscle weakness (present at birth) and deep tendon areflexia, indicated a non-progressive congenital muscular dystrophy (CMD).

Laboratory examinations

The level of serum CK is elevated: 1045 U/L (normal value <160 U/L).

Muscle biopsy

Biopsy of left gastrocnemius muscle: muscle fragment with a pronounced variability size of muscular fibers: from very small fibers to mild hypertrophy, with atrophy predominance.

It is an important proliferation of endomysium and perimysium collagen. Very rare fibers split are present.

The distribution of histoenzymatically types is without specific modifications. The internal structure of muscular fibers is normally.

Immunohistochemistry: presence of dystrophin, lack of merosin, utrophin is normally expressed.

The biopsy shows merosin-deficient congenital muscular dystrophy.

Electrophysiological study

Electromyography (EMG) was used to help differentiate whether the patient's deficits were myogenic or neurogenic.

Needle EMG of the left tibialis anterior muscle suggested a myopathic process with early recruitment, decreased amplitude and duration (<5) of response, appearance of variable small amplitudes, short duration polyphasic myogenic 100% waves.

Nerve conduction studies (NCS) were done on the left tibial and left deep peroneal nerves using conventional methods. They revealed normal conduction velocity: tibial posterior 46.5 m/sec and deep peroneal 41 m/sec (normal range 42–47 m/sec in the legs).

Magnetic resonance imaging (MRI)

On MRI T2 weighted and fluid-attenuated inversion recovery (FLAIR) images, patient had a diffuse and symmetrical increase in signal (diffuse hyperintensity) in the white matter of the cerebral hemispheres, subcortical and centrum ovale, in the external capsule and periependymal (Figure 3).

MRI T1 weighted showed hypointensity in the white matter. These findings revealed extensive demyelination changes of white matter. Ventricles, cerebellum, basal ganglia, pons were normal.

Supratentorial MRI images showed hypotrophy of the corpus callosum and almost absent cingulate gyrus. Pituitary fossa and stalk were normal on MRI but with reduced size of hypophysis (pituitary volume hypotrophy to 60% of the sella).

Discussions

The inheritance of this disease is autosomal recesive. This means that both parents are carriers of the mutation (clinically unaffected) and they have risk of 25%, or a one in four chance in each pregnancy, of passing the condition on their children.

The gene responsible for this disease spans some 633 kb of genomic DNA and contains 64 exons. The exons 44 and exon 53 are very small measuring 6 and respectively 12 base pairs. Substitutions, small deletions, or insertions in the LAMA2 induce complete merosin-deficiency, most localized between 1–31 exons, in the N-terminal domain [14].

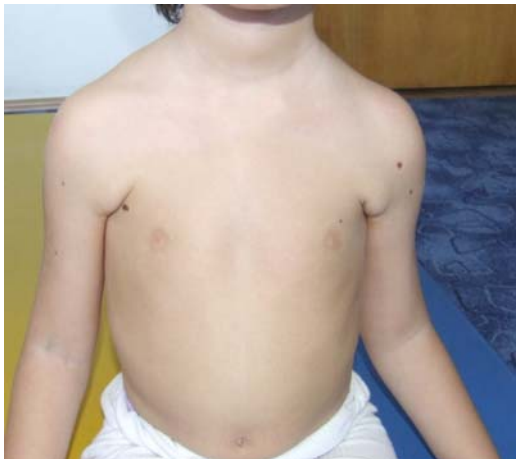

Figure 1 – ***Anterior axillary folds sloped down and out as a result of wasting of the pectoral muscles***

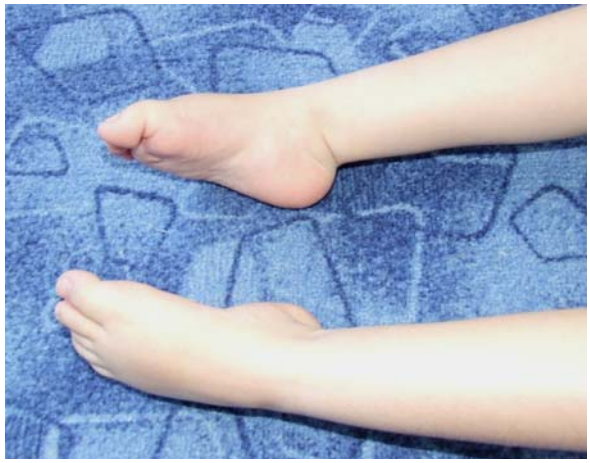

Figure 2 – ***Congenital bilateral equine-varus feet deformity***

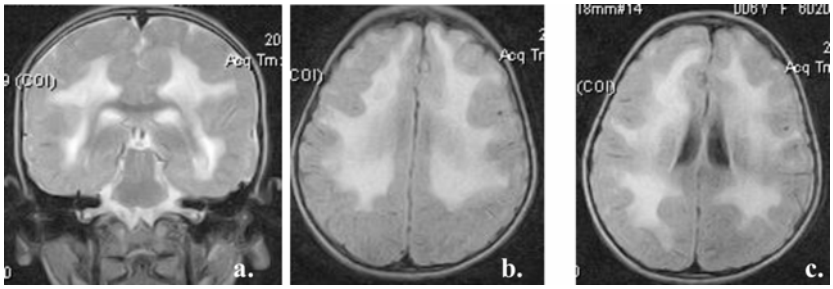

Figure 3 – ***Coronal cerebral MRI T2 weighted (a) and axial FLAIR (b, c) image of case showing widespread T2 hyperintensity of white matter***

More than 90 different missense, nonsense, splice-site, and deletion mutations have been described. The laminin 2 chain gene codes for a protein of 390 kd and, under reducing conditions, laminin 2 chain migrates as an N-terminal fragment of 300 kd and a C-terminal fragment of 80 kd. The LAMA2 protein consists of 3110 amino acids; a 22-residue signal peptide, amino acids 1–22, and a 3 088 amino acid mature protein [15].

Merosin is specifically found in the basement membranes of the striated muscle and Schwann cells. Laminin-2 is the isoform of laminin present in the basal lamina of the skeletal muscle [13, 16].

Laminin alpha 2-chain has been shown to be a native ligand for alpha-dystroglycan, an extracellular component of the dystrophin-associated glycoprotein complex (DGC). This complex constitutes a link between the subsarcolemmal skeleton and the extracellular matrix [17, 18].

A number of components of the DGC have now been shown to be involved in muscular dystrophies suggesting a crucial role of laminin-2 and the components of the DGC in maintaining the integrity of muscle cell function [19–21].

Clinically, particularity of this case is the association of merosin-negative congenital muscular dystrophy (MN-CMD) with congenital feet deformity, also the presence of Rh incompatibility: child Rh positive, blood group A II, mother Rh negative, A II. The absence of merosin with evocative clinical features, MRI abnormalities and high level of CK strongly suggests the diagnosis of MDC1A. The level of muscle enzyme CK is mildly to markedly elevated (2–150 times normal) in persons with CMD1C or any other CMD due to abnormal glycosylation.

Muscle biopsy is indicated in all cases of suspected CMD to help confirm the diagnosis and exclude other causes of weakness. Patients may have severe dystrophic pathology with muscle-fiber degeneration and regeneration, fiber necrosis, and endomysial and perimysial fibrosis [22].

Mononuclear cell infiltrates may be present in biopsy samples obtained from infants. Muscle biopsy shows a great variation and some of these fibers are replaced by fat and fibrous tissue.

Immunohistochemical studies show complete loss of staining for laminin-alpha 2. Antibodies must be used against both the 300- and 80-kd subunits [23]. Alpha-dystroglycan and beta-laminin staining is also absent. Approximately 95% of biopsy samples with absent laminin-alpha 2 staining have a mutation in the LAMA2 gene.

In our case, merosin is absent, but dystrophin and utrophin is normally expressed. In MDC1A a skin biopsy rather than a muscle biopsy may also be used. This followed the discovery that the protein merosin, normally present in both skin and muscle, is absent in both tissues in patients with MDC1.

Electromyography (EMG) and nerve conduction study (NCS) should be performed in all patients with suspected CMD to confirm myopathy and to exclude other diseases. NCS results are normal except in some cases of MDC1A, in which mild neuropathic changes may be seen (some with demyelinating features). EMG changes were typical and early found in all types of CMD. EMG usually shows typical small-amplitude,

narrow-duration motor-unit potentials with early recruitment. An associated neuropathy was detected in most patients with merosin-deficient CMD [24].

In our case, the NCS is normally, while EMG suggested a myopathic process with early recruitment and decreased amplitude and duration of response.

Patients with this type of CMD have abnormal findings at cranial MR imaging. The brain involvement in these patients manifests as abnormal signal intensity in the supratentorial WM and external capsules [25, 26]. The extent of WM involvement at MR imaging in these patients does not appear to correlate with the clinical phenotype or the degree of merosin expression [27].

In our case, MRI T1 and MRI T2 show hypointensity and respectively diffuse hyperintensity in the white matter. Remarkably is the presence of hypotrophy of the corpus callosum and almost absent cingulate gyrus, also reduced size of hypophysis. The WM involvement has been described as diffuse and symmetric in the cerebral hemispheres. The WM lesions are hypointense on T1-weighted images, hyperintense on T2-weighted and fluid-attenuated inversion recovery images [28].

Conclusions

Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) is an autosomal recessive inherited form of congenital muscular dystrophy.

The prognosis depends on the type of CMD and the other features association.

No specific treatment is available but the clinical and laboratory investigations can differentiate between merosin-deficient CMD and other muscular dystrophy forms.

Prenatal diagnosis and genetic counseling is often helpful to patients and their families.

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