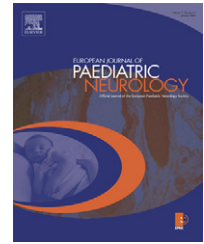




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Case study

LAMA2 stop-codon mutation: Merosin-deficient congenital muscular dystrophy with occipital polymicrogyria, epilepsy and psychomotor regression

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ABSTRACT

Merosin-deficient congenital muscular dystrophy (MD) type 1A (MDC1A) is one of the most frequent forms of CMD in Western countries.

The classical form, characterized by a total lack of laminin $\alpha 2$ chain expression, usually shows severe clinical features; cases with complete laminin $\alpha 2$ deficiency and mild phenotype have also been reported, although the mechanisms underlying the lack of genotype–phenotype correlation have not been elucidated. Epilepsy and focal cortical dysplasia—in addition to the classical diffuse white matter abnormalities—have been described in some of these patients associated with cognitive deterioration.

We report on a patient with total laminin $\alpha 2$ deficiency due to a homozygous stop-codon mutation in the LAMA2 gene, with mild evolution. When 6.9 years old, she developed focal occipital seizures and absence-like status when awake, with probable relation to an extensive bilateral occipital micropolygyria. Soon afterwards she lost ambulation and developed cognitive deterioration.

Our case confirms that the clinical spectrum of MDC1A is more heterogeneous than previously thought.

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1. Introduction

Merosin-deficient congenital muscular dystrophy (CMD) type 1A (MDC1A) is one of the most frequent forms of CMD in Western countries. It is an autosomal recessive neuromuscular disorder caused by mutations in the LAMA2 gene on chromosome 6q2, resulting in deficiency of the laminin $\alpha 2$ chain, a component of the skeletal muscle extracellular matrix laminin-2 (merosin).¹ Mutations in the LAMA2 gene are usually responsible for severe phenotypes and (in most cases) for a total lack of laminin $\alpha 2$ chain; however, it is

becoming clear, as cases are being characterized at the molecular level, that the clinical spectrum of primary merosin deficiency is more heterogeneous than previously thought.

The classical form is characterized by the absence of laminin $\alpha 2$ expression and severe hypotonia at birth, associated with the inability to walk unsupported, delayed motor development, high CK levels and a clinically asymptomatic abnormality of the central white matter on MRI; partial laminin $\alpha 2$ expression frequently results in milder phenotypes with acquisition of independent walking.¹

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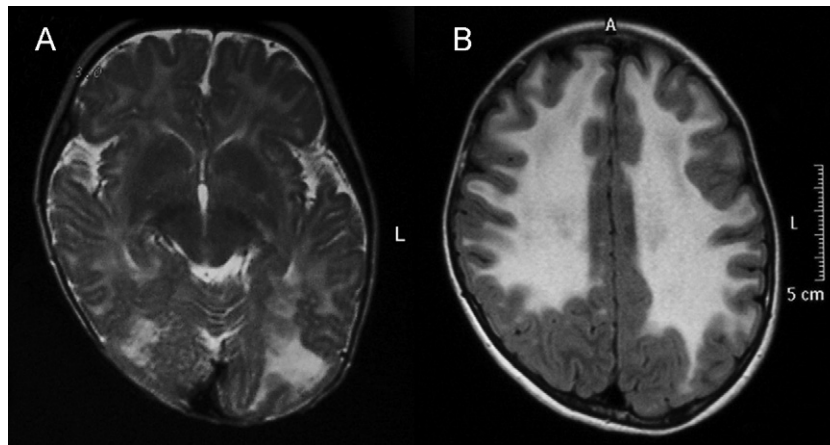


Fig. 1 – MRI T2 weighted images at 5 months (A) and at 6.9 years (B) of age, showing the classical white matter hyperintensity. The features evidence an extension of the white matter alteration and areas of cortical dysplasia (polymicrogyria) in the occipital lobes, involving occipital pole and occipito-basal cortex.

However, some exceptions have been reported in the literature: Pegoraro et al.² described a patient with an unusually severe phenotype, although partially expressing a mutated laminin $\alpha 2$ isoform generated by an alternative splicing; Prandini et al.³ reported on a girl with a total lack of laminin $\alpha 2$ chain and mild clinical features. In a recent paper Di Blasi et al.⁴ described two patients (3 and 4) that were able to walk although laminin $\alpha 2$ was absent in their muscle.

Epilepsy and focal cortical dysplasia—in addition to diffuse white matter abnormalities—have been reported in some of these patients^{5–7}; epileptic features are not well detailed—seizures are described as complex partial—except in three cases, which presented a homogeneous occurrence of partial seizures with periodic spasms.⁶

We will now detail the clinical features of a patient described in the Di Blasi study (no. 3), owing to the particularly mild development of the clinical findings. When 6.9 years old she began having drug-resistant polymorphic seizures, associated with motor and cognitive deterioration, secondary to an extensive bilateral occipital micropolygyria.

2. Case report

Our patient, now 8 years old, is the first daughter of healthy unrelated parents. She was seen at our department when 5 months old; she had severe hypotonia and marked proximal weakness since birth, congenital ankle contractures and absent tendon reflexes. This was followed by delayed motor development. At 3.8 years of age she achieved her best motor performance—ability to walk unsupported for about 10 m in restricted areas, with a waddling gait.

When the patient was first seen, CK levels were 1173 mU/mL, EMG showed myogenic potentials, and a quadriceps muscle biopsy revealed myopathic changes: fiber diameter variability, perimysial and endomysial connective tissue proliferation and mononuclear cells infiltration. Laminin $\alpha 2$, analyzed by immunohistochemistry on 6- μ m-thick cryosections using the two commercially available

antibodies against the 80 kDa carboxyl-terminus and the 320 kDa amino-terminal fragments, was absent.

Cardiac and pulmonary functions were unaffected. Ocular examination and visual evoked potentials were normal. Brain MRI showed normal cortical organization and, in T2 weighted images (Fig. 1A), white matter hyperintensity in the posterior regions.

The DNA analysis, performed as previously described revealed a homozygous mutation in the LAMA2 gene, in exon 21—a C>A change in nucleotide 2901—resulting in a stop codon (Cys967 stop).⁴ This finding allowed the prenatal diagnosis on the fetus of a second pregnancy.

When the patient was 4.6 years old, she was brought to the hospital by her parents, who described a possible accidental fall; they were not present at the episode but running to her soon afterwards, found the girl in a post-ictal confusional state which lasted a few hours. Transient right hemiplegia with loss of postural tone was evident.

Coagulation, inflammatory and immunological tests were normal; serum CK level was 643 mU/mL. The electroencephalogram (EEG), recorded 3 days after the episode, showed a bilateral posterior slow activity; the MRI showed an extension of the white matter hyperintensity to the frontal regions.

She recommenced walking in a few months with the aid of physiotherapy. The ambulation was limited to restricted surroundings, with a waddling gait, bilateral steppage and external rotation of the right foot. The patient was submitted to a motor and sensory conduction study. The results were within the normal range (right peroneal motor conduction velocity: 40.2 m/s and left: 41.3 m/s; right sural sensory conduction velocity: 47.6 m/s and left: 49.5 m/s).

Her cognitive development, evaluated at 6 years of age, before the beginning of primary school, was within the low range of normality, with a total IQ = 75, and an important deficit in visuo-spatial organization.

When 6.9 years old she had her first observed epileptic seizure: psychomotor arrest, staring with visual hallucinations, described as bright red moving phosphenes in the left visual field. Later the patient reported a seizure with

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