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CASE REPORT

SEVERE FORM OF SALIH MYOPATHY CAUSED BY COMBINATION OF TWO HETEROZYGOUS TTN MUTATIONS

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ABSTRACT

Salih myopathy is autosomal recessive hereditary early-onset myopathy with fatal cardiomyopathy. It is a rare and heterogeneous form of congenital titinopathies (TTN). Affected children have delayed motor development, normal mental development, and in further course dilated cardiomyopathy. Motor functions have a tendency to improve, but death occurs most often before 20 years of age due to arrhythmias.

Our patient is a 2-year-old girl, born in severe perinatal asphyxia, with global hypotonia and poor spontaneous movements. She required immediate endotracheal intubation and mechanical ventilation was initiated without the possibility of cessation. Improvement in her neurological status was not observed. Due to her clinical presentation, we performed genetic testing and a diagnosis of Salih myopathy caused by combination of two heterozygous TTN mutations was confirmed.

This case illustrates that Salih myopathy may have severe presentation from birth, with continuous necessity for mechanical ventilation, without any motor improvement.

Keywords: cardiomyopathies, congenital hypotonia, exome sequencing, muscular diseases, Salih myopathy, titinopathy

INTRODUCTION

Salih myopathy is also known as early-onset myopathy with fatal cardiomyopathy, which is a rare and heterogeneous form of congenital titinopathies (TTN). It is an autosomal recessive hereditary neuromuscular disorder with early onset of its clinical manifestations in the neonatal period or in early childhood (1,2). Affected children have delayed motor development, with joint contractures and scoliosis at a later age. Most cases have normal mental development. Further progression of the disease leads to the development of dilated cardiomyopathy. Death occurs due to arrhythmias, most often between 8 and 20 years of age (3,4).

Salih myopathy is ultra-rare disease. It was first described in two Arab families, in 2007 (5). The prevalence of Salih myopathy is unknown, as it occurs in a small number of families of Moroccan and Sudanese origin.

The diagnosis is made in the proband by identifying biallelic pathogenic variants in the first three exons encoding the M-line (*Mex1*, *Mex2*, and *Mex3*) of TTN, the only gene for which pathogenic variants are known to cause Salih myopathy (6).

Treatment requires a multidisciplinary approach (3).

CASE REPORT

In this manuscript we describe a 2-year-old Roma origin girl who was diagnosed with Salih myopathy. She is the fourth child of nonconsanguineous parents. The second child from the same parents was born in severe perinatal asphyxia, with hypotonia, congenital heart defect (partial anomalous inflow of the pulmonary veins) and multiple joint contractures and died in the 5th month of life before a definitive diagnosis was made. Our patient is from a regularly monitored pregnancy, but oligohydramnios was noted near the end of the pregnancy which was terminated by caesarean section at 38+ 5/7 weeks of gestation. The baby was born in severe perinatal asphyxia (Apgar score 2/2). The somatometric parameters at birth were as follows: BW 3090 g (50.p), BL 50 cm (50.p), HC 37 cm (>99.p). After birth she was cyanotic, bradycardic, without spontaneous breaths and movement, with global hypoto-

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nia and hypermobility of the elbows, hips and ankles and deformity of foot (equinovarus). Upon first examination, the following was observed: macrocephaly, short nose, low set ears, low set hairline, up-slanting palpebral fissures, excess skin at the back of the neck. On the radiographic image of the locomotor system, multiple fractures of the long bones were established (fracture of the body of the left humerus, the body of both femurs and the right tibia in the proximal part). She was referred to the Department of Intensive Care and Therapy immediately after birth due to respiratory failure. She required endotracheal intubation and since then the child has been on mechanical ventilation without the possibility of cessation, while maintaining a neurological finding dominated by global hypotonia and poor spontaneous movements. Fractures of long bones were treated with immobilization. No new fractures were registered during further hospitalization.

Due to signs of global muscular hypotonia and a positive family history of congenital hypotonia, a laboratory, metabolic, neuroradiological and genetic evaluation have been conducted. The findings are shown in Table 1.

According to clinical manifestations, conducted examinations, including genetic testing, a diagnosis of Salih myopathy was made. A segregation analysis was done for the parents and a heterozygous genetic variant c.15218-2A>G in the TTN gene was detected in the child's mother, and a heterozygous genetic variant c.56572C>T (p.Arg18858Ter) in the TTN gene was detected in the child's father.

DISCUSSION

Salih myopathy is relatively new entity, so it is difficult for clinicians to distinguish congenital titinopathies from congenital myopathies associated with other genes (7,8). With that in mind, the diagnostic approach excluded some of the more common causes of hypotonia in children and suspected a rare cause.

Salih myopathy is characterized by muscle weakness, hypotonia that manifests itself in the neonatal period or early childhood. According to Hackam et al., affected children walk between the ages of 20 months and 4 years, with a tendency for motor functions to improve (3). In contrast, our reported child is 2 years old, without spontaneous movements, with the same motor functions as at birth, and is dependent on invasive respiratory support.

Contractures and deformities of the foot are common in patients with titinopathies, localized distally and affecting more than two joints, appearing in the first decade of life (7, 9). Unlike joint contractures and foot deformities, multiple fractures are rare. According to data from the literature, fractures were described only in two patients until now (10). So far, there are no reported multiple fractures in the neonatal period as our patient had.

Cases are described where mechanical support was needed only at birth and with further progression of the disease. This was performed intermittently only during the night (10). Unlike patients found in the literature, our patient has been on invasive respiratory support from birth.

Table 1.

Diagnostics	Results
Creatine kinase	13.69 μkat/l (reference range 0.72-7.9 μkat/l)
Karyotype	46,XX Normal female karyotype
Plasma and urine amino acid concentration	Normal finding
Organic acids in urine	Normal finding
Genetic testing for SMA	Negative
TORCH	Normal finding
Echocardiography	Normal finding
MRI of the head	Volume reduction of brain parenchyma at the expense of white matter and corpus callosum and diffuse hyperintensity of supratentorial white matter periventricularly.
EMNG	The finding indicates myopathically altered pattern, slightly prolonged and polyphasic. Denervation potentials were not registered. Neurographic parameters are obtained as expected for age.
Muscle biopsy	Examination of muscle biopsy sample showed the presence of small, oval muscle fibers of abnormal size with accentuated interfascicular fibrous weft. Signs of necrosis and inflammation were not observed. The presence of centrally located nuclei and perinuclear halo was not observed. Neurofibrillary tangle with myelinated nerve fibers was clearly observed. Mitochondria were normal. Small groups of type 2 atrophic fibers was observed.
Psychologist	Gross delay of psychomotor development.
Genetic testing	Two heterozygous pathogenic genetic variants c.56572C>T (p.Arg18858Ter) and c.15218-2A>G in the TTN gene were detected.

SMA - Spinal muscular atrophy; TORCH - Toxoplasma, Rubella, Cytomegalovirus, Herpes simplex; EMNG – Electromyoneurography

According to data from the literature, dilated cardiomyopathy can occur in patients at the age of 4 months, but most often between 5 and 16 years of age (11,12,13). The echocardiographic examination of our patient is still normal.

There are no specific laboratory and radiological findings that can be used to diagnose Salih myopathy. Creatine kinase may be at the upper limit of normal or elevated (generally 1.5-7x elevated) (3). Similarly, creatine kinase in our case was initially elevated, 1.7x above the upper limit, and later normal. In the literature, EMNG findings of patients are reported, indicating a polyphasic potential of low amplitude of short duration (3). The same finding was obtained in our patient.

The findings of muscle biopsies in patients with titinopathies are pathological. The changes that can be observed are increased fiber size variation, centrally placed cores and cores with additional structural abnormalities (10). In Salih myopathy, electron microscopy of skeletal muscles reveals multiple foci of sarcomere disruption and mitochondrial depletion (3). In our patient's muscle biopsy, no pathognomonic changes were registered to the extent that they were diagnostic.

The intellectual development of children with Salih myopathy is usually normal (3). Our patient is conscious, establishes social contact, and a psychological examination shows gross retardation in psychomotor development, most likely because of severe perinatal asphyxia (MRI), most likely due to severe congenital hypotonia.

CONCLUSION

Congenital titinopathies are increasingly recognized as a potentially severe form of congenital myopathies. In case of congenital hypotonia, it is necessary to think about Salih myopathy as a possible underlying cause. By establishing an earlier diagnosis, it is possible to improve the development of motor functions with early habilitation treatment, regular monitoring and treatment of cardiac and respiratory disorders. Prenatal diagnosis is possible, including preimplantation genetic testing for monogenic gene defects (PGT-M) in some centers.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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