Marinesco-Sjögren syndrome occurrence in family (case of a rare syndrome in siblings)

Rodzinne występowanie zespołu Marinesco – Sjögrena (opis przypadku występowania rzadkiego zespołu u rodzeństwa)

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ABSTRACT

Marinesco-Sjögren syndrome (MSS) is a rare malformation syndrome inherited in an autosomal recessive manner. The most typical features are cerebellar ataxia with cerebellar atrophy, dysarthria, nystagmus, early-onset cataract, myopathy, hypotonia and muscle weakness. Additional symptoms often include psychomotor delay, hypergonadotropic hypogonadism and short stature. We present a case of a 6-year-old boy admitted to the Department due to psychomotor developmental retardation for completion of further diagnostics. Initial diagnostics led to a preliminary diagnosis of Marinesco-Sjögren syndrome, ultimately confirmed by genetic testing. When the patient's younger brother was born, he presented with similar symptoms. Knowledge of his older sibling's diagnosis aided in immediately using single-gene testing to confirm the presence of two mutated copies of the SIL1 gene. This finding allowed to establish a proper diagnosis in the younger brother, leading to immediate multi-specialist intervention..

Key words: Marinesco-Sjögren syndrome, psychomotor delay, rare diseases in families

STRESZCZENIE

Zespół Marinesco-Sjögrena (ang. Marinesco-Sjögren syndrome - MSS) jest rzadkim zespołem wad wrodzonych, dziedziczonym autosomalnie recesywnie. Do najbardziej charakterystycznych jego cech zalicza się ataksję móżdżkową z zanikiem móżdżku, dyzartrię, oczopląs, wczesną zaćmę, miopatię oraz osłabienie siły i napięcia mięśniowego. Dodatkowo często występuje opóźnienie rozwoju psychomotorycznego, hipogonadyzm hipergonadotropowy oraz niskorosłość. Przedstawiamy przypadek obecnie 6-letniego chłopca, który został po raz pierwszy przyjęty do Kliniki z powodu opóźnienie rozwoju psychomotorycznego. Etapowa, wielokierunkowa diagnostyka doprowadziła do postawienia wstępnego rozpoznania zespołu Marinesco-Sjögrena, co zostało ostatecznie potwierdzone badaniem genetycznym, w którym wykryto obecność mutacji w obu kopiach genu SIL1. Młodszy brat chłopca od urodzenia prezentował objawy MSS. Rozpoznanie choroby u tego dziecka nastąpiło szybko, co umożliwiło wczesne wdrożenie wielospecjalistycznej opieki nad chłopcem..

Słowa kluczowe: zespół Marinesco-Sjögrena, opóźnienie psychomotoryczne, rodzinne występowanie chorób rzadkich

INTRODUCTION

Marinesco-Sjögren syndrome (MSS) is a rare malformation syndrome, primarily characterized by cerebellar atrophy with cerebellar ataxia and other parallel signs of cerebellar dysfunction like dysarthria, nystagmus, hypotonia and muscle weakness. Other typical symptoms are myopathy and early-onset (not necessarily congenital) cataract [1-7]. Other features often common with MSS include psychomotor delay, hypergonadotropic hypogonadism, short stature and various skeletal malformations [1-3, 7]. MSS is inherited in an autosomal recessive manner. Usually, the first symptom observed in children is muscular hypotonia. Later, signs of cerebellar dysfunction like ataxia, dysdiadochokinesis, nystagmus or ataxia become apparent. Motor function deteriorates progressively for an unspecified amount of time, then stabilizes at an unpredictable age and degree of severity. A cataract usually occurs very early and requires lens extraction in the first decade of life [4]. Life span seems to be unscathed, even though many adults have severe disabilities. Diagnosis is usually established in an individual with typical symptoms and biallelic pathogenic variants of the SIL1 gene. Treatment is symptomatic, conducted by pediatric or adult neurologists, physiatrists and /or physical therapists. Patients usually undergo individual education programs adjusted to their developmental needs. Hormone replacement therapy is used when needed at the expected time of puberty [1].

CASE STUDY

A one-year-old boy was admitted to the Department of Infectious Diseases and Child Neurology with a case of psychomotor development delay. Parents reported that the patient had difficulties with breastfeeding and his developmental milestones were delayed – he could not sit by himself at twelve months of age. From the age of five months, the patient was under intense Vojta therapy. Genetic counseling revealed a normal karyotype. The boy was born by

cesarean section due to a lack of progressive birth action. Apart from that, there were no complications in the prenatal or early postnatal period.

When admitted to the Department, the boy presented muscular hypotonia. In laboratory tests, elevated serum creatine kinase levels with accompanying elevated AST levels were observed. On EMG, myopathic changes in efferent conduction from the motor cortex to the L5-S1 center were found. MRI showed a broadened fourth ventricle, a general reduction of cerebellar volume with secondarily broadened sulci and hemosiderin deposits in the caudothalamic groove, described as state after 1-st level IVH. MRI of the spinal cord did not show any abnormalities. Samples for diagnosis of metabolic pathway disorders were taken and later revealed to be within reference values.

During his second visit to the Department half a year later, cerebrospinal fluid was taken for further tests and proved to be without abnormalities. Results of MRI and EMG examinations were similar to the ones from the first visit. An ophthalmological consult was conducted – esotropia and farsightedness were present. More detailed genetic testing proved no mutations in SMN1, ATXN1, ATXN2, ATXN3 and CACNA1A genes. No abnormalities were found during EEG examination. Screening for lysosomal storage disorders was also done, but no abnormalities were found.

At 4 years of age the patient underwent a surgical vitrectomy due to the development of a cataract in the right eye. After ruling out other potential disorders, the boy underwent genetic testing for the presence of mutated alleles in the SIL1 gene. A positive result along with the typical clinical findings allowed for the successful identification of MSS.

When the patient was 3-years old his younger brother was born with similar clinical symptoms to his elder sibling. Following the identification of MSS in our patient, the younger brother had rapidly undergone single gene-testing, leading to the diagnosis of MSS.

METHODS

Venous blood was collected from the patient as well as from all affected and unaffected available family members (parents and sibling). Genomic DNA was isolated from peripheral blood using standard protocols for salting out procedure. Polymerase chain reactions were designed and performed to amplify all coding exons of the SIL1 gene together with the flanking regions (app. 20 bp) [8].

DISCUSSION

In its typical phenotype, MSS diagnosis can be established relatively easily by just connecting classical clinical findings such as cerebellar dysfunction symptoms, early-onset cataracts, myopathy, muscle weakness and hypotonia with the identification of biallelic pathogenic variants in SIL1 on molecular genetic testing. In such a scenario, gene-targeted testing is usually enough. However, in a situation suggestive of an atypical phenotype, where there are more clinical findings, establishing a proper diagnosis is much more complicated and it requires multiple different examinations and laboratory tests [1]. In our patient's case, there were numerous characteristic features of MSS presented, such as cerebellar dysfunction symptoms. MRI demonstrated changes in cerebellar structure, including reduced general cerebellar volume due to atrophy [2, 5]. The boy presented muscular hypotonia during early infancy. Myopathic features were found on EMG examination, and an elevated serum creatine kinase level was also present. There are some specific MSS findings on muscle biopsy by electron microscopy (autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei), however, in this case, a biopsy was not taken [6-7]. The patient rapidly developed a cataract in his right eye and in his 4th year of life underwent a surgical vitrectomy. Aside from the early-onset cataracts which required lens extraction, the boy also presented strabismus, an ophthalmologic issue described in more than half of patients [4, 7]. Developmental milestones were severely delayed – in this case the patient could not sit without help until his second year of life and in his third year of life he was able to walk only with the help of his parents. Intellectual abilities described in MSS may vary from normal to severe intellectual disability and are still under evaluation in the described patient. Other clinical findings associated with MSS such as hypergonadotropic hypogonadism or skeletal malformations were not found in the presented individual [2-3, 7, 9]. A wide range of clinical findings in MSS makes a list of potential disorders considered in differential diagnosis very long. In the presented case, neurological disorders such as spinal muscular atrophy, spinocerebellar ataxia types 1-3, or acute disseminated encephalomyelitis were taken into consideration. Inherited metabolic disorders and lysosomal storage diseases such as Pompe disease also needed to be evaluated. In the presented individual, the early-onset of cataracts with coexisting clinical findings made the initial diagnosis more clear and highlighted some potential genes that should be evaluated by molecular gene-testing [6]. Otherwise, even more disorders, including some extremely rare ones, should be taken into consideration in the differential diagnosis. Since MSS is inherited in an autosomal recessive manner and only recessive homozygotes are affected by the disease, it is obvious that the proband's parents are obligate heterozygotes. This also gives us the ability to predict the chances of further generations inheriting the mutated alleles [1]. In the described case, the patient's younger brother presented similar clinical findings soon after his birth. Knowing his older siblings diagnosis, he underwent molecular gene-testing focused on the SIL1 gene almost immediately and proved to be another member of the family affected by MSS. Quick diagnosis allowed for early intervention of specialists and, ultimately, a better quality of life for the patient. The presented patient is still under intense Vojta therapy. Additionally, he is under regular follow-up with a child neurologist, as is his younger sibling.

REFERENCES:

[1] Venkatesan A., Tunkel A.R., Bloch K.C. et al.: International Encephalitis [1] Anttonen A.K.: Marinesco-Sjögren Syndrome. GeneReviews® 2006 [updated 2019], [13 screen pages] Address: https://www.ncbi.nlm.nih.gov/books/NBK1192/

[2] Anttonen A.K., Mahjneh I., Hamalainen R.H., et al.: The gene disrupted in Marinesco-Sjogren syndrome encodes SIL1, an HSPA5 cochaperone. Nat Genet. 2005; 37: 1309–1311.

[3] Anttonen A.K., Siintola E., Tranebjaerg L., et al.: Novel SIL1 mutations and exclusion of functional candidate genes in Marinesco-Sjogren syndrome. Eur J Hum Genet. 2008; 16: 961–969.

[4] Goto M., Okada M., Komaki H., et al.: A nationwide survey on Marinesco-Sjögren syndrome in Japan. Orphanet J Rare Dis. 2014; 9: 58.

[5] Harting I., Blaschek A., Wolf N.I., et al: T2-hyperintense cerebellar cortex in Marinesco-Sjogren syndrome. Neurology 2004; 63: 2448–2449.

[6] Herva R., von Wendt L., von Wendt G., et al.: A syndrome with juvenile cataract, cerebellar atrophy, mental retardation and myopathy. Neuropediatrics 1987; 18:164–169.

[7] Krieger M., Roos A., Stendel C., et al.: SIL1 mutations and clinical spectrum in patients with Marinesco-Sjogren syndrome. Brain 2013; 136: 3634–3644.

[8] Lahiri D.K., Bye S., Nurnberger J.I., et al.: A non-organic and non-enzymatic extraction method gives higher yields of genomic DNA from whole-blood samples than do nine other methods tested. J. Biochem. Biophys. Methods 1992; 25: 193-205.

[9] Mahjneh I., Anttonen A.K., Somer M., et al.: Myopathy is a prominent feature in Marinesco-Sjogren syndrome: a muscle computed tomography study. J Neurol. 2006; 253: 301–306.

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