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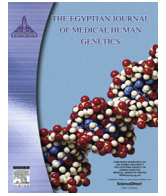


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Contents lists available at ScienceDirect

The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com



Case Report

First report of microcephaly-capillary malformations syndrome in Russia

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ARTICLE INFO

Article history:

Received 8 July 2017

Accepted 22 August 2017

Available online xxx

Keywords:

Microcephaly

Capillary malformations

Epilepsy

Deep developmental delay

STAMBP gene

ABSTRACT

Background: Microcephaly-capillary malformation (MIC-CAP) syndrome is a newly described autosomal recessive syndrome characterized by microcephaly, multiple cutaneous capillary malformations, intractable epilepsy and profound developmental delay. We present the first description of MIC-CAP syndrome in Russia.

Patient: We describe a 6-month-old girl with severe congenital microcephaly, intractable epilepsy (infantile spasms), multiple cutaneous capillary malformations and facial abnormalities. Genetic studies revealed the presence of new *STAMBP* gene mutations in the compound heterozygous state: c.273delA and the intron replacement c.204-5 C > G.

Conclusions: This report presents a case of MIC-CAP syndrome with earlier unreported new mutations of the *STAMBP* gene.

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1. Introduction

Microcephaly-capillary malformations (MIC-CAP) syndrome is a newly described syndrome with an autosomal recessive mode of inheritance. The primary manifestations of the syndrome are congenital microcephaly, intractable epilepsy, multiple cutaneous capillary malformations, facial abnormalities and substantial delays in psychomotor development. This syndrome was first described by Carter MT et al. in 2011 [1]. Currently, there are 14 patients known to have MIC-CAP syndrome. Mutations in the *STAMBP* gene responsible for disease development have been identified in these patients. This paper presents the first report of MIC-CAP syndrome in Russia.

2. Clinical report

Our patient is a 6-month-old girl born from the fourth pregnancy to unrelated healthy Russian parents. The couple's first pregnancy ended in a medical abortion, the second pregnancy ended in a miscarriage at 6 weeks, and a healthy boy was born from their third pregnancy. The parents' fourth pregnancy was complicated by a threatened miscarriage at 20 weeks of gestation. Intrauterine

growth retardation was diagnosed at 30 weeks of gestation. A normal vaginal delivery occurred at 38 weeks of gestation. Apgar scores for the infant were 8 at 1 min and 9 at 5 min. Her birth weight was 2550 g (below 15th percentile), the birth length was 48 cm (below 50th percentile), and the head circumference was 30 cm (below 3rd percentile). At birth, the girl was noted to have multiple flat vascular stains on the trunk and on the extremities. She was discharged from the hospital 5 days after birth. The girl started to hold her head up at the age of 1 month, started to roll over at 3 months, and did not sit up or crawl.

At 1 month of life, the infant showed failure to thrive with frequent vomiting. At 2 months, she developed paroxysmal events consisting of a sudden stiffening of the body with arms and head bending forward for a second (infantile spasms). At the same age, she became less emotional, she stopped looking after objects and her head control became worse. At 4 months of life, the frequency of epileptic seizures increased. The girl stopped holding her head up, stopped fixing her eyes on objects and stopped smiling.

At 6 months, the girl was admitted to our hospital. On admission, the child's condition was critical due to neurological symptoms and frequent epileptic seizures. The following phenotypic features were observed: hypertelorism, a wide nasal bridge, a short nose, thin lips with drooping mouth corners, a long philtrum, gum hyperplasia, low-set ears, a short neck, short fingers due to hypoplasia of distal phalanges, hypoplastic nails and toe malposi-

Peer review under responsibility of Ain Shams University.

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<http://dx.doi.org/10.1016/j.ejmhg.2017.08.011>

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Please cite this article in press as: Demikova NS et al. First report of microcephaly-capillary malformations syndrome in Russia. Egypt J Med Hum Genet (2017), <http://dx.doi.org/10.1016/j.ejmhg.2017.08.011>

tion on feet. Her head circumference was 35 cm (4 SD below the mean for her age). Her hair was sparse and had an unusual pattern of growth with long hair along the sagittal suture forming a “Mohawk” (Fig. 1). Multiple flat capillary malformations of irregular shape, measuring 4–15 mm in diameter, were noted on the scalp, the skin of the trunk and the extremities (Fig. 2). The child was seriously retarded in psychomotor development: unable to hold her head, roll, or sit without support. She had roving eye movements without fixation, myoclonus of eyelids, bulbar syndrome, and spastic tetraparesis. On examination, epileptic seizures in the form of tonic spasms and oculotonic seizures were observed.

Considering the observed features, diagnosis of MIC-CAP syndrome was suspected.

A CT brain scan at the age of 3.5 months showed the growing size of the outer cerebrospinal fluid spaces, which can indicate an increase in cortical atrophy.

Brain MRI, performed at the age of 5 months, revealed diffuse cortical atrophy, atrophic ventriculomegaly, and a delay in white matter myelination (Fig. 3).

An EEG showed abnormally slow background activity, multifocal epileptiform spike-and-wave activity, and a burst suppression pattern. At the age of 5 months valproic acid was prescribed in dose 40 mg for each kg of body weight per day, but the frequency of epileptic seizures did not change.

Her blood amino acids and acyl carnitines, urine organic acids, lactate level, and TORCH titers were normal. ECG and abdominal ultrasound examination were unremarkable. Her karyotype was identified as normal (46,XX).

To establish the genetic cause of MIC-CAP syndrome, we performed a search of mutations by means of direct automated sequencing of the gene responsible for the disease. Two mutations were observed in our patient. One mutation was the heterozygous deletion c.273delA, leading to a frameshift and stop codon formation in the next triplet.

This deletion is probably highly pathogenic, although it is not described in the international HGMD database or polymorphisms database (dbSNP). The intron replacement c.204-5 C > G in the heterozygous state was also detected in our patient. This intron replacement has not been described in the international HGMD database, but according to the data of Human Splicing Finder pathogenicity program, it can be a splice site mutation and can be considered to be pathogenic. Thus, the child’s mutations are in the compound heterozygous state, which results in the formation of a MIC-CAP syndrome phenotype.

3. Discussion

Since this disease has been described quite recently, and there are only 14 published cases to date, we want to focus on the characteristics of these cases.



Fig. 1. Note unusual hair growth into a “Mohawk” pattern.



Fig. 2. The multiple capillary malformations on the trunk.

The first publication of Canadian pediatricians described two boys from unrelated families who had similar clinical manifestations [1]. A unique feature of both children was the presence of congenital multiple randomly placed red spots (“port-wine stains”) on the skin, which were the result of abnormal capillary development (or capillary malformations). Both patients had progressive microcephaly, neonatal resistant seizures, psychomotor retardation, similar craniofacial anomalies, short fingers, and toes with nail hypoplasia. Brain MRI detected diffuse cortical atrophy, thinning of the corpus callosum, and delayed myelination of the white matter of the brain in both children. Such a high level of similarities of the phenotypic manifestations in two patients allowed the authors to classify this condition as a new syndrome. However, the cause of the syndrome was not clear.

The other case reports from France and the United States appeared almost simultaneously in the same year. Isidor B. et al. described the third case with similar symptoms in a girl who had been observed for 5 years [2]. Mirzaa G.M. et al. from the United States reported three more cases of the disease from two families [3]. As there were two children with the same disease within one family, autosomal recessive inheritance of the disease was assumed. The syndrome was called microcephaly-capillary malformation syndrome (MIC-CAP, OMIM 614261).

In all cases, the children showed congenital microcephaly and multiple capillary malformations on the skin of the trunk, head and extremities, which increased in size with the growth of the child. The onset of epileptic seizures in the majority of cases occurred in the neonatal period. Epileptic seizures were polymorphic (focal, tonic, hemiclonic, secondary generalized seizures, infantile spasms) and were resistant to anticonvulsant therapy and ketogenic dieting.

All of the children showed a prominent neurological impairment, a rough psychomotor retardation, as well as dysmorphic facial features, including a receding forehead, low hairline, a round face, hypertelorism, epicanthal folds, elongated palpebral fissures, ptosis, a short nose with a broad nasal bridge, low set rotated ears, high palate, drooping mouth corners, and micrognathia. Several patients had abnormal hair growth in the form of a “Mohawk”

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