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1q44 microdeletion syndrome: A new case with potential additional features

Elena-Silvia SHELBY[1], Tanser HUSEYINOGLU[2], Georgeta CARDOS[2], Liliana PADURE[1,3], Andrada MIREA[1,3], Madalina LEANCA[1], Mihaela BADINA[1], Nadejda BARLADEANU[4], Florina Mihaela NEDELEA[2,4]

[1] „Dr. Nicolae Robanescu" National Clinical Center for Children's Neurorecovery, Bucharest, Romania
[2] Filantropia Clinical Hospital of Obstetrics and Gynaecology, Bucharest, Romania
[3] Faculty of Midwifery and Nursing, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4] Medical Genetics Chair, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

1q44 microdeletion syndrome (1q44 monosomy) is a newly described genetic syndrome characterized by the haploinsufficiency of a 6 Mb locus on the long arm of chromosome 1. The main features are global developmental delay, seizures, hypotonia and craniofacial dysmorphism.

With a prevalence below one in a million cases, this syndrome is very rare and, hence, often passes undiagnosed. We present the case of a one year old girl admitted to our hospital with global developmental delay and several congenital abnormalities suggesting a plurimalformative syndrome. Microarray analysis detected a 967 kb deletion in the 1q44 region as well as a a 530 kb microduplication in the 14q31.1q31.2 region, the latter having unknown clinical significance as it contains no currently known OMIM genes. The patient's phenotype was in accordance to 1q44 microdeletion syndrome. Furthermore, after studying the 1q44 microdeletion syndrome cases reported so far in the literature, we have noticed that our patient presented previously undescribed features of this syndrome, namely prenatal hydronephrosis, bifid hallux and grey matter heterotopy. Based on the cerebral, renal and skeletal involvement in 1q44 microdeletion syndrome, we suspect these might be additional, previously unreported features of 1q44 microdeletion syndrome.

Keywords: 1q44 microdeletion syndrome, microarray, microduplication

INTRODUCTION

1q44 microdeletion syndrome (1q44 monosomy) is a newly described, very rare syndrome (according to Orphanet, the prevalence is below one in a million cases) characterized by global developmental delay, mainly of the expressive language, hypotonia, seizures and craniofacial dysmorphism (1-6). The 1q44 locus is a 6 Mb region located at the telomeric region of the long arm of chromosome 1 (1). Up to now, there are at least 230 reports in the literature about 1q43q44 or 1q44 deletion. Sometimes the condition may be reported as 1q43q44 deletion syndrome, although the main cause of the phenotype is the deletion of the 1q44 region (1).

The syndrome can be suspected prenatally in some cases based on non-specific findings such as choroid plexus cysts and single umbilical artery, visible at the second trimester ultrasound (22 weeks) (7).

Brain abnormalities are a common feature of 1q44 deletions. According to Boland et al. (8), these brain

Corresponding author:
Elena-Silvia Shelby
E-mail: silviajdx@yahoo.com

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abnormalities are caused by the haploinsufficiency of a critical region of 3,5 Mb containing one or more genes which, when deleted, lead to corpus callosum agenesis and microcephaly (8). About 90% of the patients diagnosed with this syndrome have absence or hypoplasia of the corpus callosum (1,3,5,6,9). More than 75% of the patients with 1q44 microdeletion syndrome have seizures (1,5,9).

There are several genes in the 1q44 locus known to be involved in the presence of microcephaly and seizures, their cumulative effect having an important role in the development of these features. Haploinsufficiency of AKT3 gene, coding a serine-threonine kinase has a very important contribution in the presence of microcephaly, agenesis of the corpus callosum and other brain development abnormalities (2,8,10), while the ZBTB18 gene (previously known as ZNF238) and HNRNPU play a significant role in the abnormalities of the corpus callosum (2). Heterozygous mutations in the HNRNPU gene are, also, the main cause of intellectual disability in this syndrome (1,7). Loss of function of the HNRNPU, C1orf199 and COX20 have been shown to be responsible of the phenotype with seizures (7). Moreover, the HNRNPU gene has been shown to mediate long range control of SHH gene (7q36.3) necessary for the development of the brain, limbs, eyes and other parts of the body (11,12).

Regarding the effect of the ZBTB18 haploinsufficiency on the 1q44 microdeletion syndrome phenotype, a study by Cohen et al. from 2016 (13) on five unrelated patients with intellectual disability and variable syndromic features showed that all patients with mutations in this gene had hypoplasia of the corpus callosum and global development delay or intellectual disability. In 2018, van der Schoot et al. (14) identified using whole exome sequencing four patients with pathogenic mutations in the ZBTB18 gene. All of them had either agenesia or hypoplasia of the corpus callosum, developmental delay, hypotonia or facial dysmorphism (13). ZBTB18 gene is known to play a very important role in cortical development, with effects on neural growth, differentiation and maturation (13-15).

There have also been reported cases with occipital encephalocele, Dandy-Walker malformation (haploinsufficiency of ZIC1 and ZIC4 genes), holoprosencephaly (haploinsufficiency of SHH, SIX3, TGIF and ZIC2 genes) (8), lissencephaly (haploinsufficiency of DCX and LIS1 genes) (8), as well as hypoplasia of the cerebellar vermis (3).

The clinical manifestations of the syndrome are very variable, and both interstitial and terminal deletions of various sizes have been reported (7). Terminal deletions have been shown to determine more severe malformations of the brain compared to the interstitial ones (7). There has also been reported a case of 1q43q44 deletion with loss of 6 Mb region and a ring chromosome (7).

Intellectual disability can range from moderate to severe, with absent or very limited speech (3), severe motor delay, seizures, hypotonia, autonomic dysfunctions, dysphagia (1,5,9).

The craniofacial dysmorphism is characteristic, consisting in microcephaly, a round face, thin upper lip with prominent cupid's bow, thin, downturned corners of the mouth, smooth philtrum, micrognathia, retrognathia, short nose with a broad root, epicanthus, upslanted palpebral fissure, strabismus, telecanthus, low-set ears, as well as, in some cases, biparietal narrowing with high forehead, frontal bossing, prominent metopic ridge, synorphis or widely spaced teeth (5,6,9,10,16-18). Abnormalities of the hands and feet can also occur (5,16). Growth retardation with short stature is a common feature (16,18). Moreover, up to 30% of the patients have hydrocephalus as well as heart defects, usually minor (1), such as abnormal cardiac septum morphology (5). Hypospadias, horseshoe kidney, vesicoureteral reflux, intestinal malrotation, optic disk hypoplasia or scoliosis are also relatively common features of this syndrome (1,5).

Moreover, midline defects such as bladder exstrophy, absent phallus, hypogenitalism or various gastrointestinal and cardiac abnormalities have also been reported (7,16). Furthermore, in 2014 a new case with previously unreported features such as supranumerary nipple, arachnoid cysts, polydactyly of the foot and auricular pits was described (16). In the same year, another group of researchers (5) described a 3-year-old girl with HHE syndrome (hemiconvulsion - hemiplegia - epilepsy) who had a 1.8 Mb deletion in the 1q44 region (11). The patient also presented global developmental delay, preaxial polydactyly and mild facial dysmorphism (11).

A large number of 1q44 microdeletion syndrome cases are the result of parental balanced translocations, therefore the analysis of the parental chromosomes is very important (1).

CASE PRESENTATION

We present the case of a one year old girl admitted in September 2019 to "Dr. Nicolae Robanescu" National Clinical Center for Children's Neurorehabilitation for medical recovery, as she had hypotonia and motor retardation.

She is the third child of a GIV P III mother (one miscarriage in the first trimester of pregnancy). She has a four year old sister and a ten year old brother, both healthy, with the same father. The parents denied consanguinity. According to the mother, there are no known genetic diseases in the family.

Antenatal ultrasound detected hydronephrosis, ventriculomegaly and partial corpus callosum agenesis. Testing at 23 weeks and 5 days for trisomies 13, 18 and 21 (karyotype and QF-PCR from amniotic fluid) was normal (46, XX, no aneuploidies of chromosomes 13, 18 or 21).

Hydronephrosis was remitted before birth, and postnatal abdominal ultrasound was normal, with normally positioned kidneys with a normal structure, as well as liver, spleen, pancreas and urinary bladder with normal structure and position.

Heart ultrasound revealed atrial septum defect.

The patient was born with bilateral bifid hallux, corrected postnatally after right hallux surgery.

She had hypotonia and motor retardation since birth.

The postnatal transfontanellar ultrasound revealed an important ventricle asymmetry with right hydrocephaly, a moderate dilation of the left lateral ventricle, a dilated right lateral ventricle - predominantly at the occipital horn level, which determined a decrease in the occipital parenchyma. A formation floating in the cerebrospinal fluid at the level of the choroid plexus, suspicioned to be a tumour derived from the choroid plexus, was also detected.

Brain MRI (at 2 months) revealed corpus callosum agenesis, white commissure agenesis, cerebral falx agenesis and an asymmetric ventricular system with the dilatation of the right ventricles. Also, the lateral ventricles were surrounded by a discretely hyperintense band of white substance, signalling a potential heterotopy of the grey substance.

The patient was diagnosed with positional talus varus.

The physical exam revealed microcephaly (head circumference was of 42,5 cm, on the third percentile), a relatively low weight and height (weight was of 9 kilograms, on the 25th percentile, and height was of 73 cm, on the 25 to 50 percentile).

The patient had craniofacial dysmorphism with hypertelorism, prominent forehead with two frontal prominences, midface hypoplasia, facial asymmetry, short nose, retrognathia, straight eyebrows, flat nasal bridge, short philtrum, epicanthus, anteverted nostrils, narrow bitemporal diameter and microcephaly (see figures 1 and 2).

Patient had a right bifid hallux (Fig. 1C), an eversed lower lip, generalised hypotonia. She had severe motor retardation and was able to hold her head without support or sit without support. She never gained walking ability. She had bilaterally absent patellar reflexes. She also had cognitive delay, being unable to pronounce simple words. According to the mother, she had no epileptic seizures. Anterior fontanelle was open (2/2 cm).

After obtaining the mother's written consent, two milliliters of whole blood were sent to the Genetics Laboratory of the Filantropia Clinical Hospital of Obstetrics and Gynaecology in Bucharest, Romania, for microarray analysis.

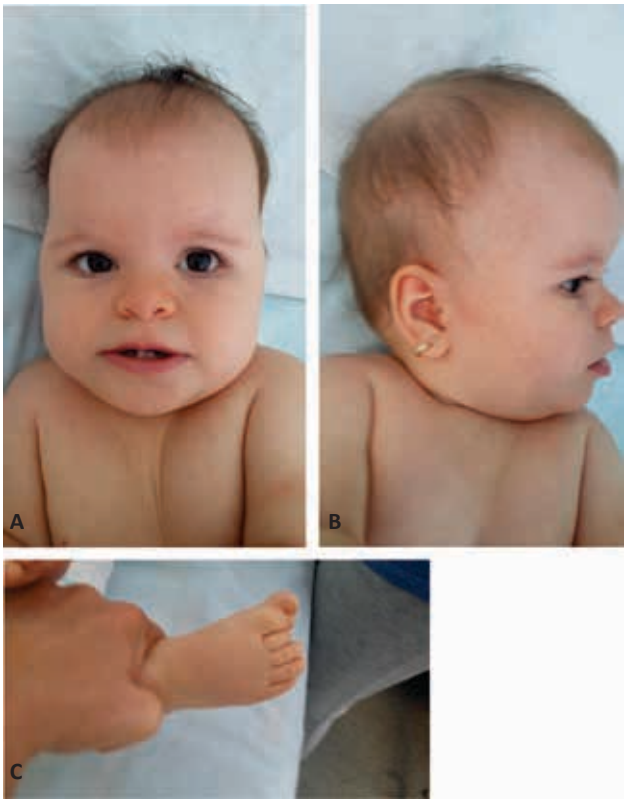
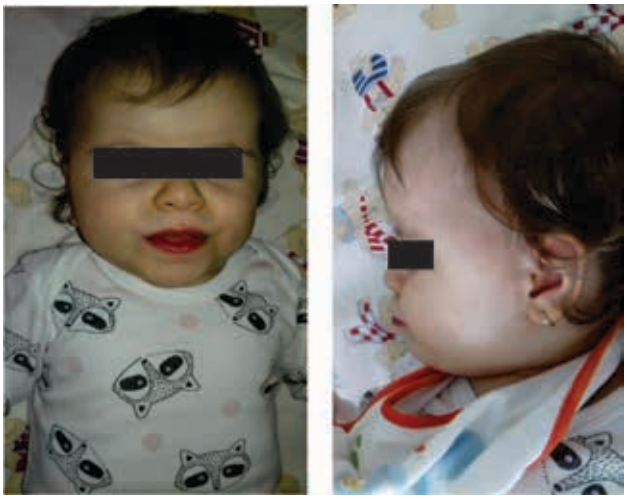


FIGURE 1. *Patient at the age of one. Notice the narrow bitemporal diameter, microcephaly, prominent forehead, smooth philtrum (A), straight eyebrows, short nose with flat bridge, retrognathia, midface hypoplasia (B), bifid hallux (C)*



A **B**

FIGURE 2. *Patient at the age of one year and eight months. Notice the prominent forehead with smooth philtrum, facial asymmetry, (A) midface hypoplasia and retrognathia (B)*

DNA was isolated from the blood and analysed using the HumanCytoSNP-12 v2.1 Analysis BeadChip Kit from Illumina. The scanning was made using the NextSeq550 equipment and the soft of the equipment (Illumina), using the databases: UCSC Genome Browser, DECIPHER, OMIM, ISCA, DGV, ClinGen and ClinVar.

The molecular karyotype (ISCN 2016) arr[GRCh37] 1q44(244161982 x 2, 244171992_245121226x1, 245128628x2), 14q31.1q31.2(83587297 x 2, 83587297 x2, 83589975_84119756 x 3, 84142036 x 2) was obtained.

A microdeletion of 967 kb in the 1q44 region was detected, this region being associated with the relatively recently described 1q44 microdeletion syndrome characterized by facial dysmorphism, development delay, seizures, hypotonia, agenesis/hypogenesis of corpus callosum.

Furthermore, a 530 kb microduplication was detected in the 14q31.1q31.2 region. This microduplication does not contain OMIM genes, and has, thus, an unknown clinical significance for the patient.

The parents received genetic counselling and they have been informed about the necessity of parental testing in order to establish the origin (inherited or de novo) of the genomic abnormalities detected in the patient.

DISCUSSIONS

Because of its rarity and the nonspecific features it presents, 1q44 microdeletion syndrome often passes undiagnosed.

In our case, this syndrome was detected following microarray analysis due to craniofacial dysmorphism, global developmental delay and congenital abnormalities of the heart, brain, skeleton and, prenatally, kidney. Genetic testing has established the diagnosis of 1q44 microdeletion syndrome and has revealed an additional microduplication of 530 kb in the 14q31.1q31.2 region with unknown clinical significance for the patient, as it contains no known OMIM genes.

The SNP-array method can detect microdeletions and microduplications like copy number variations, loss of heterozygosity, single nucleotide polymorphism variants, aneuploidies, imbalanced genomic rearrangements or mosaicism with a medium resolution of about 62-72 kb. Copy number variations under 400 kb are reported only if they are relevant for the patient or if they are classified as pathogenic or potentially pathogenic.

Microarray analysis does not allow the detection of balanced chromosomal rearrangements, polyploidies (such as 3n, 4n), mosaicisms in a low percentage or genetic mutations responsible of monogenic diseases.

Phenotypically, our patient presented the commonly reported features (global development delay, short stature, skeletal abnormalities, heart defects, brain abnormalities including agenesis of corpus callosum, kidney defects as well as craniofacial dysmorphism with high forehead, frontal bossing, biparietal narrowing, hypertelorism, smooth philtrum, everted lower lip, midface hypoplasia and retrognathia). It's important to say that facial asymmetry is a very rare feature of this syndrome, to our knowledge having been reported only once (16). Furthermore, after studying the literature, apart from preaxial polydactily, reported as a feature of this syndrome (7) we have not found so far any article reporting bifid hallux associated with this syndrome. Moreover, although one source reported the presence of congenital hydronephrosis (19), we have not found so far any article describing prenatal hydronephrosis which was before after birth. Also, we have not found so far any source describing heterotopy of the grey matter, having found only one article describing a patient with neuroglial migration defects in the periventricular and subcortical cerebral white matter (20).

It is not clear whether the previously undescribed features we have noticed in our patient (prenatal hydronephrosis remitted prior to birth, heterotopy of grey matter, bifid hallux) are additional features of 1q44 microdeletion syndrome or are the result of the 530 kb microduplication in the 14q31.1q31.2 region. Considering the brain, urinary and skeletal abnormalities present in the 1q44 microdeletion syndrome, we presume the first hypothesis to be true.

Moreover, although about 75% of the patient have seizures, our patient did not present epilepsy.

According to Orphanet, due to the rarity of the syndrome (prevalence below one in a million cases), the mode of inheritance is unknown. A large majority of the cases are the result of parental balanced translocations (21). The parents received genetic counselling and, in order to establish the mode of inheritance, parental testing was suggested. As they currently do not want any future pregnancies, they have decided not to be tested.

CONCLUSIONS

We believe our article might be important for clinicians from various specialties, and especially for paediatricians, pediatric neurologists and medical geneticists, as it could broaden the phenotype of 1q44 microdeletion syndrome, presenting potential new features associated with this disease.

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