TRISOMY 8 MOSAICISM WITH ATYPICAL PHENOTYPIC FEATURES

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Abstract

Mosaic trisomy 8 is a relatively common chromosomal abnormality, which shows a great variability in clinical expression, however cases with phenotypic abnormalities tend to present with a distinct, recognizable clinical syndrome with a characteristic facial appearance, a long, slender trunk, limitation of movement in multiple joints, and mild-to-moderate mental retardation; the deep plantar furrows are a typical finding, the agenesis of the corpus callosum occurs frequently. We report a case, which in addition to certain characteristic features of mosaic trisomy 8, presented with craniofacial midline defects, including notched nasal tip, cleft maxillary alveolar ridge, bifid tip of tongue, grooved uvula and left choanal atresia, previously not described in this chromosomal disorder and a severe delay in psychomotor development, uncommon in trisomy 8 mosaicism.

Keywords: mosaic trisomy 8, atypical findings, midline defects

Introduction

Mosaic trisomy 8 is a relatively common chromosomal abnormality, with a distinct, recognizable phenotype in most cases. Characteristic of the clinical picture are: normal birth weight, normal or advanced growth, mild-to-moderate mental retardation, dysmorphic facies with a myopathic appearance, with prominent forehead, down slanted palpebral fissures, a coarse, pear-shaped nose, everted lower lip and low-set, large ears with a protruding lower segment; a long, slender trunk, limitation of movement in multiple joints [1, 2]. Particularly typical are the deep plantar furrows; agenesis of the corpus callosum is a frequent finding, internal organ malformations are uncommon. We report a case, which in addition to certain characteristic features of mosaic trisomy 8, presented with several signs including craniofacial midline defects, previously not described in this chromosomal disorder.

Case report

The proposita is the first child of an unrelated, healthy couple, a 21-year-old mother and 28-year-old father. Fetal ultrasounds scan at 20 week of gestation revealed ventriculomegaly. The baby was delivered by cesarean section at 37 weeks of gestation with a birth weight of 3010 g, length 50 cm and head circumference of 34 cm. At birth she was noted to have a particular facial appearance (Fig.1A) with telecanthus, upslanting palpebral fissures, notched nasal tip, cleft upper alveolar ridge, bifid tip of tongue, grooved uvula and low-set, dysplastic ears.

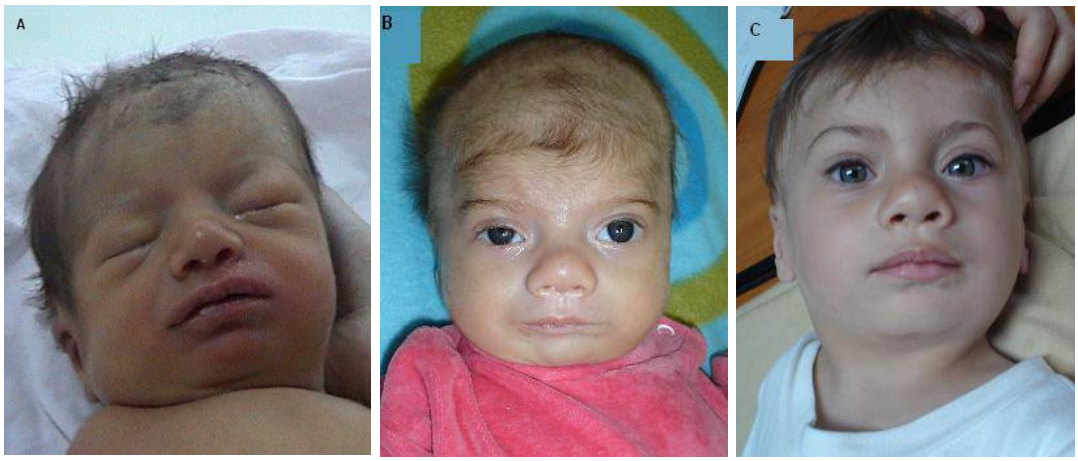

Fig. 1: Facial appearance of the patient: (A) the neonatal period, (B) at the age of six weeks, (C) age of 14 months.

On both hands deep palmar creases were observed (Fig. 2 A), a single transverse palmar crease and a single flexion crease on the fifth fingers; the thumbs were proximally inserted bilaterally (Fig. 2 B). The feet were in equinovarus position, with a wide space between the first and second toes and deep plantar grooves bilaterally. The perinatal period was complicated with seizures and apneic episodes.

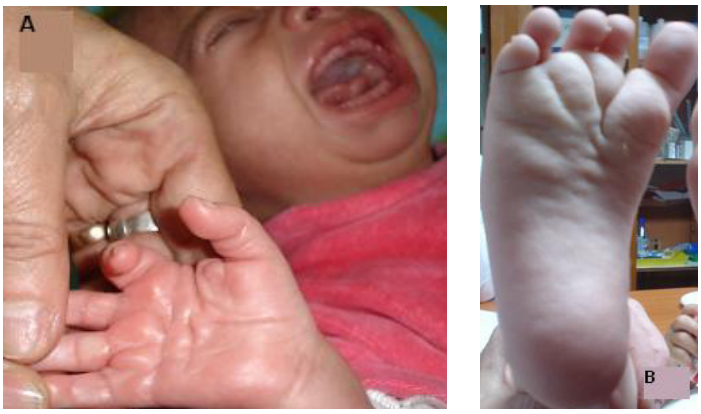

Fig. 2 (A) Bifid tip of tongue and grooved uvula, deep palmar creases, single flexion crease on the fifth finger. (B) Foot image - "hallmark " sign of the syndrome.

Transfontanellar ultrasound revealed absence of corpus callosum and enlargement of the occipital horns of lateral ventricles. MRI imaging confirmed the agenesis of corpus callosum and mild enlargement of lateral ventricles, on the other hand excluded associated cerebral malformations (Fig. 3 A, B). Cardiac ultrasonography showed an atrial septal defect. On oto-rhino-laryngologic examination left choanal atresia was found.

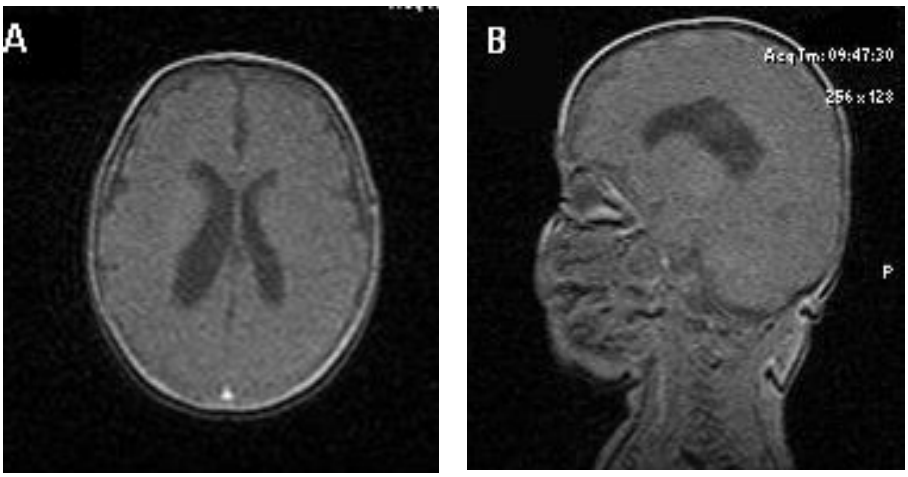

Fig. 3 (A) Mild enlargement of lateral ventricles (B) Agenesis of corpus callosum.

On clinical examination at six weeks of age, she had telecanthus, broad nasal bridge, bulbous nasal tip with a small pit in the midline and micrognathia (Fig. 1B). A small midline cleft of the maxillary alveolar ridge, a bifid tip of tongue and grooved uvula were noted. The ears were low-set, abnormally shaped with thickened cartilage. She had soft dark hair on the forehead extending to the eyebrows. The neck was short with redundant skin folds and the chest was narrow with widely spaced nipples.

The deep palmar and plantar creases in association with corpus callosum agenesis were highly suggestive of trisomy 8. Chromosome analysis on peripheral blood lymphocyte culture revealed trisomy 8 (Fig. 4) in 12 metaphases of a total of 50 examined metaphases. FISH analysis on cultured blood lymphocytes with a centromeric probe of chromosome 8 (CEP8-Spectrum Orange, Abbott-Vysis) showed 3 hybridization signals in 25 % of cells (120/ 492 nuclei) (Fig. 5).

Fig. 4: Metaphase showing three copies of chromosome 8.

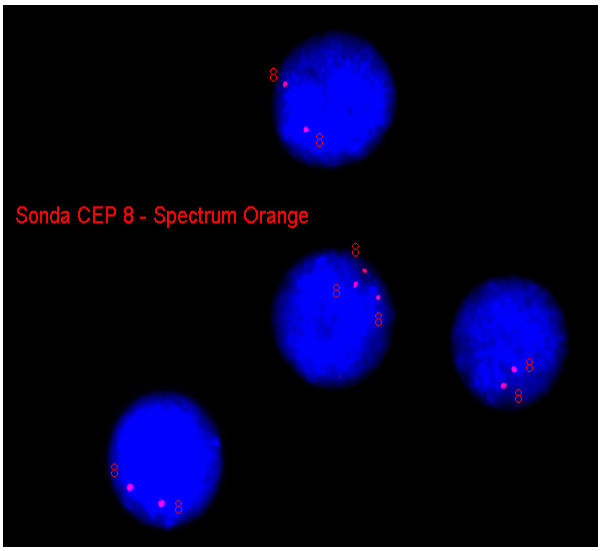

Fig. 5: Interphase FISH with a centromeric probe for chromosome 8 (CEP 8-Spectrum Orange) 1/4 of nuclei with three hybridization signals.

In view of the patient's facial appearance not typical of mosaic trisomy 8 and especially the midline defects previously not reported in trisomy 8 mosaicism, an array-CGH was performed to investigate the possibility of cryptic unbalanced rearrangements. The commercially available array (GenoSensor Array 300, Abbott) contains 287 genomic targets that include telomere, microdeletion, oncogenes, tumor suppressor genes and other selected loci scattered along each chromosome arm. No genomic imbalance could be detected.

We reassessed the patient at the age of 14 months: length was 84 cm (> 95 %), head circumference was 46 cm (50 %); she had a slender body habitus, broad face (Fig. 1C), short webbed neck and funnel-shaped chest. Except for mild limitation of movement in the right ankle, no restriction of movement at any joints could be detected. Developmental milestones were grossly delayed: she can sit alone briefly, cannot stand or crawl, she started to babble recently, using single syllables, does not recognize her name or respond to simple commands.

Discussions

Trisomy 8 mosaicism is characterized by a great variability in clinical expression due to the variation in tissular repartition of normal and trisomic clones [3, 4], therefore reported patients show a highly variable combination of clinical findings. Mental retardation is variable from mild-to-severe, but individuals with normal intellect and even with entirely normal phenotype have been described. However, cases with phenotypic abnormalities tend to present with a distinct clinical picture. Our case has many of the characteristic features of mosaic trisomy 8, including the long and slender body habitus, the deep plantar creases and the agenesis of corpus callosum. However, the facial appearance is not typical of trisomy 8 mosaicism, and the midline clefts and choanal atresia have not been described to date in patients with mosaic trisomy 8.

Corpus callosum agenesis generally prolonged latencies of interhemispheric stimulus-response paradigms, but not with unilateral stimulation paradigms to be processed. Peru et al. [5] found in patients with traumatic lesion of the corpus callosum, both temporary and permanent impairment such as dyspraxia, dyslexia and dysnomie firmly. Lassonde et al. [6] thought that different morphological and functional pathology of the corpus callosum, regularly lead to impairment in tasks that the integration visual and tactile information crosses the midline or the transfer of motor or visual-spatial skills required. Sauerwein et al. [7] discussed that the cognitive functions are not generally impaired in the absence of the corpus callosum, but it may appear a greater variability of these functions. For the clinicians is particularly important that the mosaic trisomy 8, may be associated with language impairment, respectively cognitive deficits. If language impairment is found cytogenetic investigation may be initiated. This is especially true when a combination with congenital malformations (kidney, skin, brain, heart, vertebrae among others) is present.

The diagnosis of mosaic trisomy 8 is not only for the assessment of development, but also has other significant consequences. Trisomy 8 is a frequently acquired cytogenetic abnormality in myeloid disorders. In patients with myeloid disorders the abnormal cells appeared to have developed from the trisomic clones. Patients with mosaic trisomy 8 may be at increased risk for the development of CML and MDS [8, 9, 10].

The additional anomalies might be part of the more severe manifestations within the phenotypic spectrum of

mosaic trisomy 8, due to a high proportion of trisomic cells in the developing facial structures. The array-CGH did not reveal further imbalances, however the array used is not pangenomic, and small gains or losses of genetic material may have escaped detection [11]. Trisomy 8 mosaicism, unlike the other common trisomies, in the majority of cases results from postzygotic mitotic nondisjunction [12, 13, 14], nevertheless, a proportion of cases are due to meiotic nondisjunction. Inasmuch as we could not investigate the parental origin of the three copies of chromosome 8, it cannot be excluded that uniparental disomy of chromosome 8 in the euploid cell lines might be responsible for the atypical phenotypic features, through either homozigosity for a mutation in a gene located on chromosome 8 or abnormal genomic imprinting. However, the latter seems improbable, since individuals reported with both maternal and paternal uniparental disomy of chromosome 8 had an entirely normal phenotype [15].

Conclusions

We described a case with mosaic trisomy 8, which in addition to certain characteristic features of this syndrome presented with craniofacial midline defects, previously not described in this chromosomal disorder. We consider the clinical findings in our patient may contribute to the extension of the phenotypic spectrum of trisomy 8 syndrome.

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