

CASE REPORT

Double autosomal trisomy with mosaicism 47,XY(+8)/47,XY(+21). Morphological and genetic changes of a rare case

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Abstract

The co-occurrence in the same individual of two numerical chromosomal abnormalities (double aneuploidy) is a very rare condition, especially for autosomes. Clinical presentations are variable depending on the predominating aneuploidy. The authors present a rare case of a male infant with multiple congenital anomalies: craniofacial dysmorphism, short neck, agenesis of the *corpus callosum*, ventricular septal defect, bilateral broad hallux, large first interdigital space of the toes, plantar furrows, prominent calcaneus and right kidney agenesis. The karyotype identified 82% of mitosis with trisomy 8 (47,XY,+8) and 18% with trisomy 21 (47,XY,+21). The evolution was fatal because of eating difficulties, severe growth retardation and recurrent respiratory infections. He died at the age of five months. We report this case as a very rare double autosomal mosaicism, with a complete clinical and morphological description, as the first documented case in Romania.

Keywords: chromosomal mosaicism, aneuploidy, trisomy 8, trisomy 21.

Introduction

Mosaicism occurs in 10% of autosomal trisomies [1]. Double trisomies are rarely found in viable individuals. They may involve two autosomes, two sex chromosomes or one autosome and one sex chromosome (the latter being the most frequent) [2, 3]. Trisomy 8 and 21 in mosaic is very rare in live newborns (just a few cases communicated). The condition is more frequently described in some miscarriages and in acute myelocytic leukemias (6–10% of persons with myeloid leukemia) [4, 5]. Complete trisomy 8 is a very severe condition, which usually causes miscarriage or early death, whereas trisomy 8 mosaicism (Warkany syndrome) is less severe. Trisomy 21 is the most common chromosomal abnormality in humans, although approximately 80% of trisomy 21 pregnancies end in a miscarriage [6]. The mechanism of the double trisomy mosaicism might be a double post-zygotic non-disjunction, occurring in the first stages of the mitotic divisions [7]. The non-disjunction would generate a trisomic 21 cell line (47,XY,+21) with the loss of the monosomic non-viable cell line (45,XY,-21) and sometime a trisomic 8 cell line (47,XY,+8), also with the loss of the monosomic non-viable cell line (45,XY,-8). Finally, the body will have a mosaicism of 47,XY(+8)/47,XY(+21) (Figure 1) [8–10].

The diagnosis is made by cytogenetic examination [karyotype, fluorescence *in situ* hybridization (FISH)], indicated given multiple congenital anomalies. Clinical evolution and prognosis are unfavorable and depend on the predominance of one or the other of the abnormal

cell lines. It is to be expected that in the predominance of cell line 47 (+8), the prognosis will be worse than the predominance of cell line 47 (+21). If the cell line 47 (+21) has a higher predominance, the clinical picture, implicitly the prognosis approaches that of Down syndrome. If the cell line 47 (+8) has a higher predominance, prognosis is worse, being fatal in the full trisomy 8. The most common complications are delayed development, eating difficulties, malnutrition and respiratory infections.

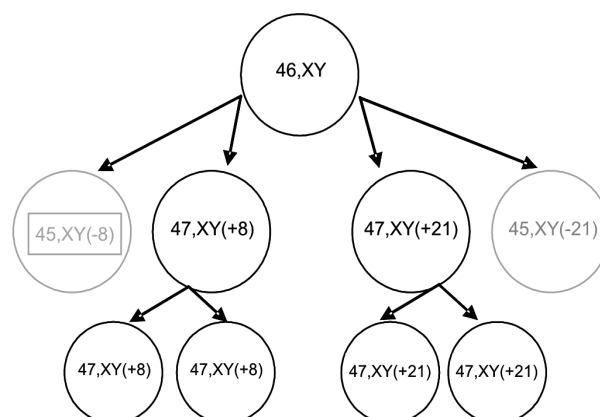


Figure 1 – The mechanism of the double trisomy mosaicism.

The purpose of this case presentation is to contribute to a better knowledge of the genotype–phenotype relationship in the rare cases of a chromosomal mosaicism, especially in the very rare double autosomal aneuploidy.

Case presentation

The patient, a male newborn, was referred by his neonatologist to the Department of Genetics, “Dr. Gavril Curteanu” Municipal Clinical Hospital, Oradea, Romania, on the first day of the life in 2012, for evaluation of craniofacial dysmorphism and eating difficulties. The infant was the first child of healthy and non-consanguineous parents; his father was 27 years old and his mother 37 years old. He was born at 40 weeks gestational age by Cesarean section delivery, after an uneventful pregnancy, without perinatal incidents. At birth, his weight was 3600 g, length was 52 cm and Apgar scores were 8 at one minute and 9 at 5 minutes.

Clinical signs and symptoms

Clinical signs and symptoms revealed multiple congenital anomalies at birth and severe malnutrition by five months of age:

- craniofacial dysmorphism: microcephaly, brachycephaly, prominent frontal and parietal bosses, hypoplasia of the middle third of the face, microphthalmia, upslanted palpebral fissures, depressed nasal bridge, large and bulbous nose with anteverted nostrils, prominent upper lip, frenula of the upper lip adherent to the gum, hyperplastic central superior incisor's gum, micrognathia; multiple anomalies of the ears: dysplastic ears with partial absence of the helix, prominent antihelix, large and plicatuated lobula (Figures 2 and 3);
- short neck with extra folds of skin, lowered shoulders;
- multiple, confluent, various in dimensions, Mongolian blue spots in the lumbo-sacral and posterior thorax area;
- bilateral broad hallux, large first interdigital space of the toes, plantar furrows, prominent calcaneus;
- eating difficulties requiring permanent gavage feeding; severe malnutrition, 3300 g weight (less than 5th percentile) at five months of age.

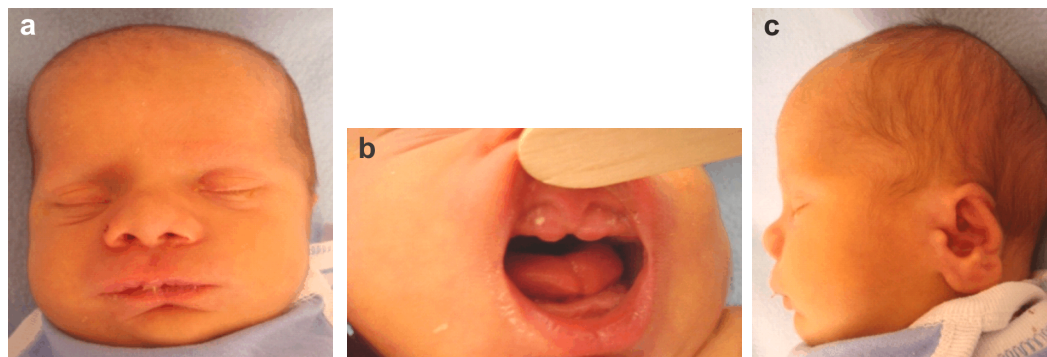


Figure 2 – Cranio-facial dysmorphism: (a) Brachycephaly, prominent frontal and parietal bosses, hypoplasia of the middle third of the face, microphthalmia, depressed nasal bridge, large and bulbous nose with anteverted nostrils, prominent upper lip; (b) Frenula of the upper lip adherent to the gum, hyperplastic central superior incisor's gum, micrognathia; (c) Dysplastic ears, with partial absence of the helix, prominent antihelix, large and plicatuated lobula.

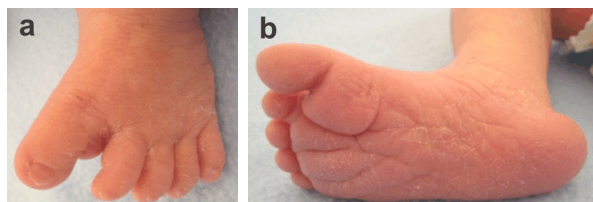


Figure 3 – Limb abnormalities: (a) Broad hallux, large 1st interdigital space of the toe; (b) Plantar furrows.

Imaging investigations

Skull radiography showed: large anterior fontanelle, Wormian bone in the posterior fontanel and occiput, blurred cranial sutures, sclerosis of the orbit and the skull's base, hypoplastic viscerocranium; the cranial line at the parietal level is not visualized (Figure 4). Chest radiography revealed a deformed thorax, with bilateral widening and sclerosis of the III–VII ribs, curvature of the I–VII ribs, slightly hypoplastic first costal arches and long, wide, curved collarbones. Abdominal ultrasound showed: right kidney agenesis, left hydronephrosis. Transfontanellar ultrasound showed agenesis of the corpus callosum. Cardiological examination and echocardiography showed ventricular septal defect and small patent foramen ovale.

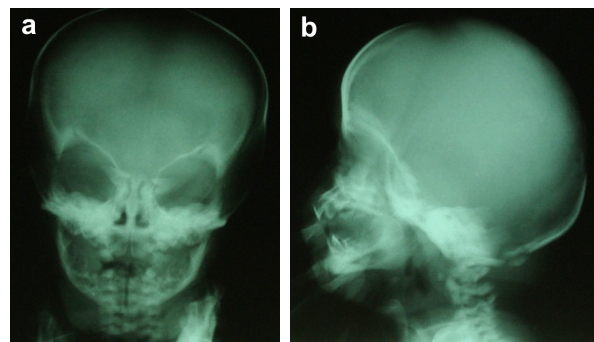


Figure 4 – Skull radiography showed: (a) Large anterior fontanelle, Wormian bone in the posterior fontanelle and occiput, blurred cranial sutures, sclerosis of the orbit and the skull's base, hypoplastic viscerocranium; (b) The cranial table at the parietal level is not visualized.

Laboratory investigations

Hematological, immunological and biochemical analyses were normal.

Genetic analysis

Karyotype was performed by blood sample (lymphocytes) analysis. The cells were stained by Giemsa (G), 500 bands resolution in 53 metaphases analyzed. We used

an Olympus BX51 light microscope with white and black camera and software provided by CytoVision. The

karyotype result was 47,XY,+8 (82%)/47,XY,+21 (18%) (Figure 5).

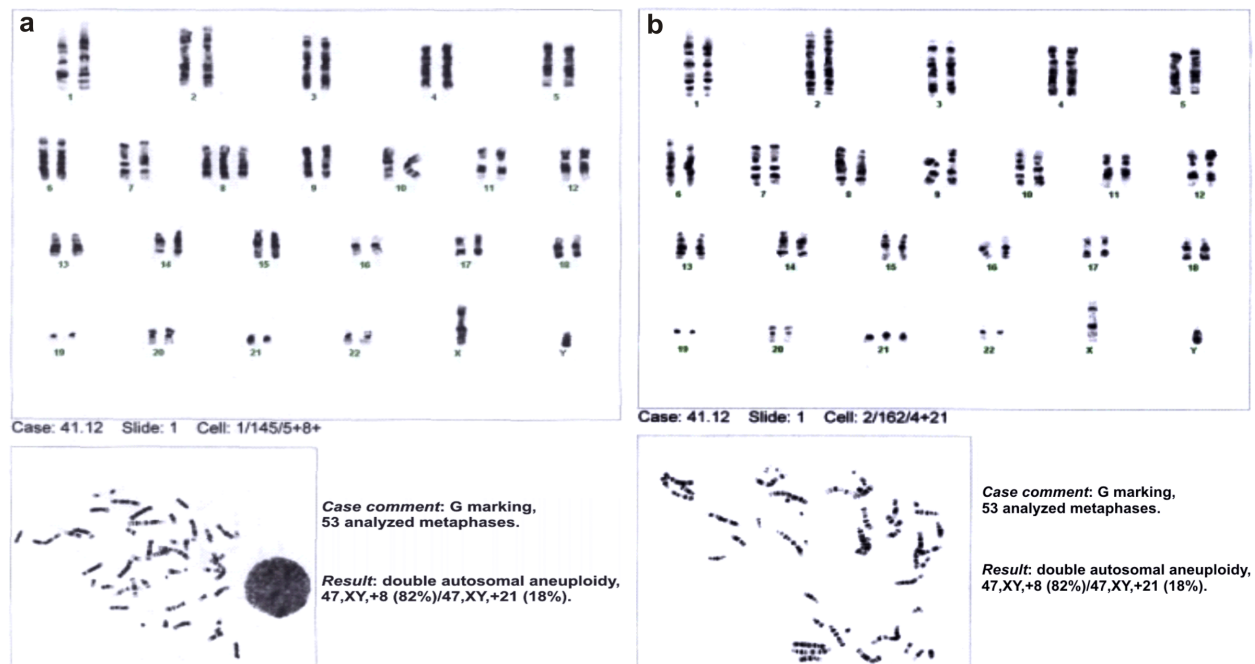


Figure 5 – (a and b) The karyotype: 47,XY,+8 (82%)/47,XY,+21 (18%).

Evolution

The patient had a non-satisfactory evolution, with permanent eating difficulties, descendant weight curve and frequent intercurrent respiratory infections. He died from a severe bronchopneumonia at the age of five months.

Morphopathological diagnosis

Cerebral edema, dilated lateral ventricles, agenesis of *corpus callosum*; ventricular septal defect and patent *foramen ovale*; right kidney agenesis, left kidney hydronephrosis; increased bladder volume; liver stasis; focal condensation of the lung and slightly hemorrhagic appearance.

Discussions

Chromosomal aneuploidy may involve either autosomes or sex chromosomes [11]. Mosaic aneuploidy consists of the presence of two or more different cell lines differing in number of chromosomes, and results from either gain or loss of a chromosome from some cells during development; it is found in 1–2% of prenatal diagnoses performed by chorionic villus sampling (CVS) [12] and in 0.2% of all amniocenteses, with a large proportion involving the sex chromosomes. Double aneuploidy involving autosomal chromosomes is very rare (only occasional reported in epidemiological studies) [13, 14]. Similar with singular aneuploidies, the double aneuploidy might be caused by the advanced maternal age as in our case but we have not explanation for the simultaneous occurrence of two different, independent non-disjunctions [15].

Our patient had some characteristic features mixed for both trisomies 8 and 21. Suggestive signs for the trisomy 8 are facial dysmorphism (prominent forehead, large dysplastic ears with prominent antihelix and large lobules), agenesis of the *corpus callosum*, kidney agenesis,

skeletal anomalies and plantar furrows. Some of the patient features (brachycephaly, upslanted palpebral fissures, anteverted nostrils, short neck, large first interdigital space of the toes) and the cardiac defect might have been caused by the trisomy 21, but the phenotype and delayed development were much more severe than is common in Down syndrome [16].

Trisomy 8 is frequently reported in myeloid leukemia (6–10% of affected individuals). This aneuploidy could also be present in lymphoid neoplasms and in a few solid tumors suggesting its role in neoplastic development [17, 18]. Wang *et al.* showed that approximately 30% of patients with chronic myeloid leukemia have additional cytogenetic abnormalities [19]. Our patient had no clinical, hematological or morphological traits of malignancy but there is the supposition that, in evolution, this severe chromosomal anomaly can contribute to the development of neoplastic disease, especially leukemia.

The most important investigation defining the diagnosis is the karyotype. Karyotype can help exclude other types of mosaicism such as trisomy 8 (47,XY,+8/46,XY) or trisomy 21 (47,XY,+21/46,XY). If the karyotype is normal, the Schinzel–Giedion syndrome [Online Mendelian Inheritance in Man (OMIM) 269150] may be considered because there are a few common traits as facial dysmorphism, skeletal, renal and cardiac malformations, hydronephrosis, ventriculomegaly, recurrent respiratory infections with respiratory failure [20].

Conclusions

The co-occurrence in the same individual of two numerical chromosomal abnormalities (double aneuploidy) is a very rare condition, especially for autosomes. Clinical presentations are variable depending on the predominating aneuploidy.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient's parents for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

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