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Case Report

Mosaic trisomy 12 – A case of a rare phenotypic association and literature review

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ABSTRACT

Introduction: Mosaicism is a phenomenon when a single fertilized egg develops into an embryo comprising two or more cell clones, each with a unique genotype. Mosaic trisomy 12 is a rare condition with a very variable phenotype. Confirmation of the diagnosis is difficult due to the different ratios and distribution of mosaic cells, various affected tissues, false-negative results and presence of extraembryonic mosaicism.
Case presentation: In this study, we report a patient with developmental delay, brain anomalies (mega cisterna magna, hypoplastic corpus callosum and hypophyseal fossa), chorioretinal pigmentary dysplasia, congenital heart disease, bilateral cryptorchidism, hydronephrosis, and dysmorphic features associated to a trisomy 12 mosaicism.
Discussion: The manifestation of trisomy 12 mosaicism is multisystemic, and the most frequent finding is dysmorphic features. Other common findings are developmental delay, congenital heart disease, gastrointestinal system malformations, skeletal anomalies, and hypotonia. Fluorescence in situ hybridization analysis, array comparative genomic hybridisation or single nucleotide polymorphism array are being proposed as first-tier methods for diagnosing mosaic trisomy 12.
Conclusion: This study expands the phenotypic spectrum associated with this rare condition. Detailed investigation allows individualized care of patients with trisomy 12 mosaicism.

1. Introduction

Mosaicism is a phenomenon in which a single fertilized egg develops into an embryo comprising two or more cells clones, each with a unique genotype [1]. Trisomy 12 mosaicism is a rare finding. In 1977, *Richer* et al. reported the first patient with trisomy 12 mosaicism with situs inversus, chronic bronchitis, sinusitis, and infertility [2]. The phenotype of mosaic trisomy 12 varies widely, ranging from nearly healthy individuals [3–5] to neonatal death due to cardiac or respiratory failure [6–8]. Individuals have facial features and frequently affected organ systems include cardiovascular, gastrointestinal, skeletal, and muscular systems. The phenotypic variation depends on the level of mosaicism, affected tissues, distribution of trisomic cell clone, and size of trisomic chromosome fragments [3,9,10]. Mosaicism can be confined to extraembryonic tissues or undetectable in samples taken for diagnostics [11–13]. Therefore, diagnostics, prediction of an outcome, and genetic counselling are challenging [11–15].

We report a patient with trisomy 12 mosaicism who presented with dysmorphic facial features, congenital anomalies, and developmental delay. The mosaicism was confirmed only after extensive postnatal workup using different genetic testing methodologies.

2. Materials and methods

2.1. Single nucleotide polymorphism genotyping array

Genomic DNA was obtained from venous blood using the phenol-chloroform extraction method. Genotyping array was performed using HumanCytoSNP-12 BeadChip (Illumina Inc., San Diego, CA, USA) according to standard protocol provided by the manufacturer. Genotyping results were analysed using GenomeStudio Genotyping Module v2.0 (Illumina Inc.).

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2.2. Karyotype and fluorescence in situ hybridization

Conventional cytogenetic and fluorescence in situ hybridization (FISH[1]) analysis was performed on cultivated peripheral blood lymphocytes and cultivated fibroblasts according to standard laboratory protocols. Subtelomere probes for chromosome 12 short (8M16/SP6) and long (VIJyRM2196) arms (Vysis ToTelVysion, Abbott Molecular, Inc.; USA) were used for FISH analysis. A total 100 metaphases/nucleus were analysed. Analysis results were submitted according to the guidelines of the International System for Human Cytogenomic Nomenclature.

3. Case report

The patient is the 2nd child of a 40-year-old mother. The Prenatal Risk Calculation (PRISCA[2]) showed elevated risk for 21 chromosome trisomy, and the noninvasive prenatal testing (NIPT[3]) results were normal. The parents refused further testing. Ultrasound detected polyhydramnios, hydronephrosis, and enlarged bladder at 20 weeks of gestation.

The male baby was delivered spontaneously at 40 weeks of gestation and weighed 3970 g (<+1.0 SD), length of 52 cm (<+1.0 SD), and head circumference (OFC) of 37 cm (>+3.0 SD). At birth, there were signs of mild hypoxia. The newborn was ventilated for 1 min, and Apgar scores were 6 and 8 after 1 and 5 min, respectively. He showed dysmorphic facial features (short palpebral fissures, broad nasal bridge, and short nose), mild hypotonia and bilateral cryptorchidism. At 5 days of age, increased respiratory work with acrocyanosis manifested. Echocardiography revealed a large atrial septal defect (ASD[4]), two small ventricular septal defects (VSD[5]) and patent ductus arteriosus. Congenital heart anomalies were followed by enlargement of right heart chambers and congestive heart failure (NYHA II) without pulmonary hypertension. Pharmacotherapy with spironolactone (5 mg daily), furosemide (3 mg twice a day), digoxin (0.02 mg twice a day), and captopril (0.5 mg three times a day) was initiated pending surgical treatment. In addition, neonatal transient hypoglycemia with transient hyperinsulinism manifested. Ophthalmological examination revealed chorioretinal pigmentary dysplasia (Fig. 1A). At 2 months, brain MRI showed mega cisterna magna, hypoplasia of the corpus callosum, hypoplasia of the hypophyseal fossa, and smaller cerebellum which could indicate cerebellar atrophy or hypoplasia (Fig. 1B). Also, at 4 months, a hypopigmented spot on the left inner thigh was noticed.

The patient underwent a surgical correction of ASD, VSD, and patent ductus arteriosus at 4 months. Pharmacological management of congestive heart failure was modified and consisted of spironolactone (6 mg daily), and furosemide (4 mg daily). Additionally, the patient underwent bilateral orchiopexy at 11 months.

The patient's last follow-up evaluation was at 2 years old. His weight was 10.5 kg (−2.6 SD), length was 86 cm (−0.5 SD), and head circumference was 47 cm (−1.1 SD). Grade 1 systolic murmur remained in auscultation, and low voltage in an echocardiogram (ECG) was detected. The echocardiography revealed mild tricuspid regurgitation. Also, the echocardiography and CT angiography showed no negative dynamics of the right heart chambers enlargement. As the patient's cardiovascular examination remained stable, pharmacotherapeutic management of heart failure was discontinued. Physical examination revealed a recurrence of cryptorchidism on the right side and a second orchiopexy was scheduled. Additionally, at 19 months, the patient achieved milestones appropriate for 8–14-month-old child on the Diagnostic Inventory for Screening Children (DISC[6]). Expressive language and gross motor skills were the most underdeveloped. He babbled only a few syllables. The patient was able to sit, roll on the sides, and could stand independently for a few seconds. He was able to take a few steps independently but required assistance for sitting up, standing up or walking. He interacted with toys by throwing, sharing, putting them in place but was unable to build a tower from 2 cubes. The patient ate soft foods but had difficulty chewing solid foods and required assistance with clothing and hygiene.

Single nucleotide polymorphism (SNP[7]) genotyping analysis at 3 weeks of age has revealed mosaic trisomy of chromosome 12 (Fig. 2A). The level of mosaicism was predicted to be about 20 %. At 3 months, cytogenetic analysis on cultivated peripheral blood lymphocytes showed normal male karyotype of 46,XY (30 metaphases analysed). The results of genotyping were confirmed by FISH analysis (Fig. 2B, C). At 6 months, FISH analysis of cultured skin fibroblasts has revealed a consistent mosaic distribution of about 22.5 % (7/31 metaphases). The parents' karyotypes were normal.

4. Discussion

Mosaic trisomy chromosome 12 is infrequent finding. To compare our case with other cases in the literature, we reviewed the case reports published on PubMed using the following keyword 'mosaic trisomy 12'. All identified case reports, a total of 23, on prenatally or postnatally diagnosed 12p, 12q, and chromosome 12 mosaic trisomy with clinical manifestations and confirmation in patients' tissues have been evaluated, comprising 30 patients [2–24] (Supplementary Table). The female preponderance of unknown aetiology is evident among reported patients with trisomy 12 mosaicism [11,14,16,17]. Including the present report, female: male ratio is 22:9, and supports this statement from previous case reports. The clinical outcome is variable, ranging from mild phenotypes with normal development to neonatal deaths due to cardiac or respiratory failure [3–8]. In the majority of the reported patients, manifestation of trisomy 12 mosaicism is multisystemic: over 20 patients have symptoms in at least 4 organ systems.

Overall, most patients have dysmorphic features (28/31), developmental delay (16/31), congenital heart disease (16/31), and alterations of their gastrointestinal (16/31), skeletal (17/31), muscular (15/31) systems. Clinical manifestations of respiratory, neurologic, genitourinary, and endocrine systems were described less frequently.

The spectrum of dysmorphism varies widely, and the most common shared features in patients are pigmentary mosaicism of the skin (13/31), low-set ears (14/31), epicanthus (10/31), prominent forehead (8/31), hypertelorism (7/31), broad nasal bridge (7/31), high-arched palate (7/31), and short neck (7/31). ASD (10/31) is the most common congenital heart disease, followed by VSD (4/31), and patent ductus arteriosus (4/31). All patients with muscular system findings have hypotonia (14/15), except one. Various limb deformities, such as clinodactyly (5/31), overlapping toes/fingers (4/31), camptodactyly (4/31), and syndactyly (3/31) are also shared among some patients with trisomy 12 mosaicism. The most prevalent gastrointestinal system malformations are umbilical hernia (3/31), anteriorly placed anus (3/31), and imperforate anus (3/31). Other noteworthy clinical manifestations are respiratory distress at birth (5/31) and abnormal glucose metabolism, ranging from hypoglycemia at birth to transient hypoglycemia in all patients with endocrine manifestations (5/31).

Although reported patients share many common features, patient in this study has a unique presentation in neurologic and genitourinary systems. Congenital brain malformations were reported by several authors, but none of the reported patients had mega cisterna magna or hypoplasia of the corpus callosum and the hypophyseal fossa

[1] Fluorescence in situ hybridization.
[2] Prenatal Risk Calculation.
[3] Noninvasive prenatal testing.
[4] Atrial septal defect.
[5] Ventricular septal defect.
[6] Diagnostic Inventory for Screening Children.
[7] Single nucleotide polymorphism.

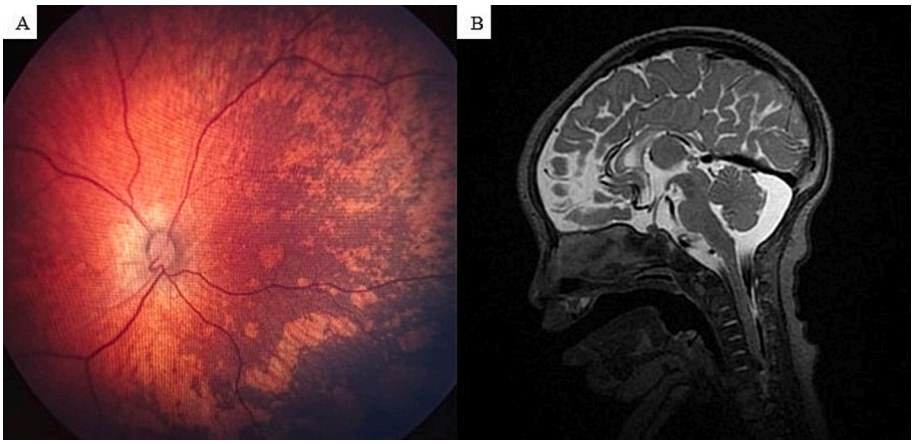

Fig. 1. Phenotypic features and timeline of the patient. (A) Chorioretinal pigmentary dysplasia in the fundus of patients' eye. (B) T1-weighted sagittal brain magnetic resonance images of the patient show mega cisterna magna, hypoplasia of the corpus callosum and the hypophyseal fossa, and smaller cerebellum.

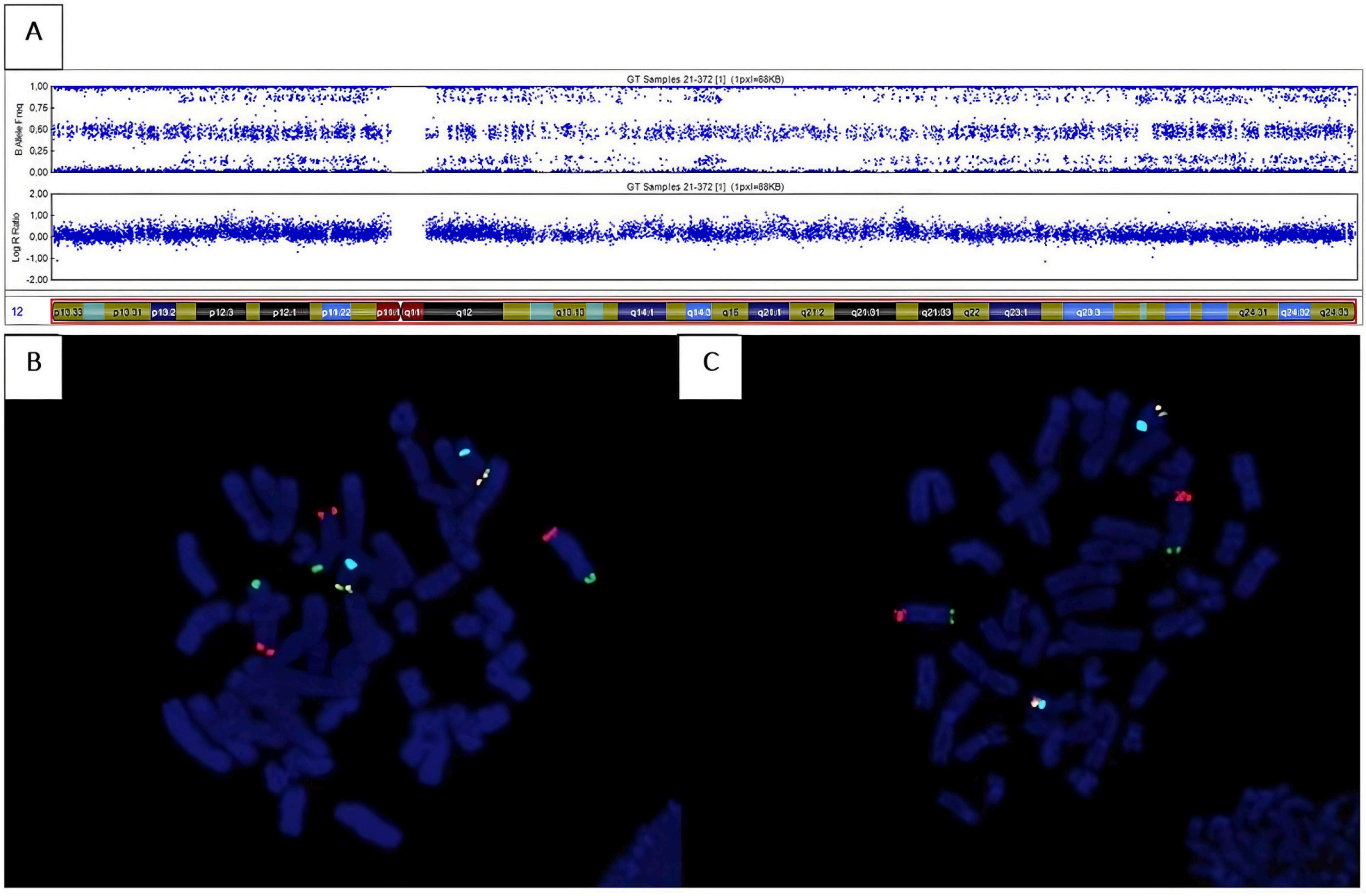

Fig. 2. Genetic analysis results of the patient. (A) SNP-array analysis from blood DNA. SNP-array results showing chromosome 12 mosaic trisomy. Upper and lower panels indicate B allele frequency and log R ratio respectively. The additional B allele frequencies represent genotype present in the trisomic cell line that is not present in the other two chromosomes. A genotype pattern is consistent with non-disjunction in meiosis I. Meiotic crossovers can be identified at the boundaries of these regions with three haplotypes. There is evidence of three recombination sites at the points where genotype complexity changes. (B, C) FISH analysis from fibroblast culture. FISH images of the cell clone with trisomy 12 (B) and normal cell clone (C). Green-labeled probe indicates subtelomeric region of short arm of 12 chromosome, red-labeled probe indicates subtelomeric region of long arm of 12 chromosome. Light blue-labeled and yellow-labeled probes indicate centromere and long arm subtelomeric region of 18 chromosome and are used as control signals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[11,16,18]. Also, only two separate cases mentioned hydronephrosis or chorioretinal pigmentary dysplasia previously [16,17].

Diagnostics of the mosaic trisomy 12 poses several challenges. The clinical phenotype overlaps with mosaic trisomy 12, mosaic trisomy 12p, and mosaic tetrasomy 12p (Pallister-Killian syndrome); therefore, the necessity for differentiation rises [3,5,7,9,10,16,19]. The overlap is especially evident in congenital heart disease because several genes, associated with heart formation during embryogenesis, are in

chromosome 12 [3,7,10]. The distribution and proportion of trisomic cells in tissues is unpredictable and this phenomenon is associated with phenotypic variation [10,13,15,16,20]. The absence of trisomic cells may result in false negative results in some tissues routinely used in genetic diagnostics, such as peripheral blood [10,11,16,20,21]. Prenatal counselling is difficult because normal ultrasound is insufficient to exclude chromosome 12 mosaicism and repeated amniocentesis results are inconsistent [6,11,15]. In our case, prenatal counselling was complicated because parents refused amniocentesis despite the abnormalities determined in the ultrasound. However, elevated risk for trisomy chromosome 21 in PRISCA results may allow to speculate that abnormal results in prenatal screening could suggest genetic conditions other than most prevalent trisomies/aneuploidies. This hypothesis requires further investigation by future studies. Conventional cytogenetic analysis may be an efficient method to reveal mosaicism, however, only if an appropriate number of cells is analysed [6,11]. The accuracy of conventional cytogenetic analysis could also be lowered by the tissue cultivation process as it shows selection against trisomic 12 cell clones in peripheral blood [6,12,16]. Therefore, interphase FISH, array comparative genomic hybridisation or SNP-array are being proposed as first-tier methods due to higher number of cells being analysed, no culture-selection bias, and higher accuracy [6,9,11,12,16].

5. Conclusion

Dysmorphic features are the most prevalent findings in trisomy 12 mosaicism followed by development delay, congenital heart disease, gastrointestinal system malformation, skeletal anomalies, and hypotonia. Our case adds further information about the phenotype being the first with hypoplastic brain anomalies and the second with hydronephrosis and chorioretinal pigmentary dysplasia in literature. To overview the proportion of trisomic cells, several tissues should be analysed and molecular cytogenetic methods are first-tier strategy in trisomy 12 mosaicism diagnostics. Thorough investigation may allow to better understand genotype-phenotype association in patients and plan individualized management and follow-up.

Author contribution

GS, BB: conceptualisation. GS: literature search, analysis, data interpretation, original draft preparation. BB, SP: collection of the clinical data. ED, VS: genetic analyses, data interpretation. All authors read and approved the final manuscript.

Consent

Written informed consent for publication was obtained from parents.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bdcasr.2024.100058.

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