Case Report

Partial trisomy 8 mosaicism not detected by cultured amniotic-fluid cells

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A B S T R A C T

Objective: Prenatal detection of trisomy 8 mosaicism can be misleading and remains challenging in genetic counseling. Identifying cases of partial or complete trisomy 8 mosaicism will highlight the pitfalls of conventional karyotyping in prenatal amniocentesis for partial or complete trisomy 8 mosaicism.

Case report: The patient was born uneventfully at term to a healthy 34-year-old mother. Analysis of the amniotic fluid (AF) cells showed a normal male karyotype. At birth, the newborn presented dysmorphic features, including asymmetric mandibles and ears, anteverted nostrils with a relatively long philtrum, retrognathia, and a clenched hand on the left side. Imaging studies revealed agenesis of the corpus callosum with bilateral colpocephaly, a common arterial trunk bifurcating into the left subclavian and carotid arteries, and bilateral pelves. Cytogenetic analysis of the blood revealed mosaicism of partial trisomy 8: 47,XY,+del(8) (q21.3) [8]/46,XY [12]. Array comparative genomic hybridization (array-CGH) revealed 82.9 Mb duplications at chromosome 8p23.3-8q21.3 with dosage variations. Interphase fluorescence in situ hybridization analysis of urine sediments and buccal smears were compatible with mosaic compositions. A small colony of AF cells was found to have partial trisomy 8 in repeated analysis.

Conclusion: Conventional karyotyping through amniocentesis has limitations particularly in detecting rare trisomy mosaicism if trisomic cells show growth disadvantage. Array-CGH using uncultured cells may be of help in providing more information on genetic dosage variations in such cases.

Introduction

The frequency of constitutional trisomy 8 mosaicism is approximately 1:35,000 in newborn children. The male to female ratio is 5:1. The phenotypes of trisomy 8 mosaicism are highly variable, including anomalies of the central nervous system, dysmorphic faces, joint contractures, skeletal dysplasia, and ocular, cardiac, and renal anomalies [1–4].

Trisomy 8 is also one of the most frequent chromosome changes in cases of acute myeloid leukemia, myelodysplastic syndrome, chronic myeloproliferative disorders, and acute lymphoblastic leukemia. It has been estimated that approximately 15–20% of trisomy 8 mosaicism identified in hematological malignancies represents unrecognized cases of constitutional trisomy 8 mosaicism [3,5–7].

The prenatal detection of trisomy 8 mosaicism can lead to clinical problems in genetic counseling. Prediction of the phenotype is extremely difficult given marked phenotypic variability. In addition, the clinical severity is not related to the level of mosaicism. False-negative cases have been described in chorionic villus sampling as well as in cultured amniotic fluid (AF) cells [8–11]. In this report, we present a case of partial trisomy 8 mosaicism that escaped detection using cultured AF cells.

Case report

A 34-year-old, gravida 3, para 3 woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Cytogenetic analysis of cultured amniocytes revealed a normal male karyotype of 46,XY in a total of 20 colonies analyzed. The

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parents continued the pregnancy, and a 3504-g male baby was delivered at term with weakness, feeding difficulty, and dysmorphic features (Fig. 1). The main presenting features included asymmetric mandibles and ears, antverted nostrils with a relatively long philtrum, retrognathia, and a clenched hand on the left side. Imaging studies further revealed agenesis of the corpus callosum with bilateral colpocephaly, a common arterial trunk bifurcating into the left subclavian and carotid arteries, and bilateral pelviectasis. Initial hearing impairment was noted on the right side, which normalized at the age of 2 months. The neonate was normal in growth, had social smiles, but did not have head control at 4 months of age.

Array comparative genomic hybridization (array-CGH) was applied to the peripheral blood sample. The array-CGH revealed 82.9 Mb duplication at chromosome 8p23.3-8q21.3 with dosage variations suggestive of mosaicism (Fig. 2). Cytogenetic analysis of the blood revealed 47,XY,+del(8)(q21.3)[8]/46,XY[12] (Fig. 3). Interphase fluorescence in situ hybridization (FISH) analysis of urine and a buccal smear using an 8p11.1q11.2-specific probe (Vysis CEP 8, D8Z2, aqua; Abbott Laboratories, Abbott Park, IL, USA) and an 8q24-specific probe (Vysis LSI MYC, red; Abbott Laboratories) showed three green D8Z2 signals in 13% (13 in 100 cells) of the urine and 37% (37 in 100 cells) of the buccal cells, respectively (Fig. 4). Consequently, we reviewed in situ cultured AF cells. Of two slides analyzed, we found a small colony with three metaphase cells with partial trisomy 8 on one slide.

Discussion

Nonmosaic trisomy 8 is not an infrequent finding in first trimester spontaneous abortions, but it has rarely been observed in postnatal cases [12,13]. Nonmosaic trisomy 8 is usually of meiotic origin. It is not compatible with normal fetal growth and almost always leads to spontaneous abortion. However, virtually all trisomy 8 mosaic cases are the result of postzygotic errors (mitotic chromosomal nondisjunction) in a diploid conceptus. As such, it does not affect embryonic development, and the pregnancy may end in a live birth [14,15].

Patients with trisomy 8 mosaicism, or Warkany syndrome, have variable clinical manifestations ranging from early death to being nearly normal [1,2]. Cases without abnormal phenotypes have also been reported [16,17]. The rate of false-negative results is unknown. Recent experience suggests that there may be a particular likelihood for mosaic trisomy 8 to be missed using routine antenatal diagnostic procedures [8–11]. Hulley et al [18] proposed that it is a selective growth advantage of normal cells versus a growth disadvantage of trisomy 8 cells that leads to the false-negative result. In case reports as well as through extensive review, Chen

Fig. 1. The patient presented with: (A) facial dysmorphism; and (B) clenched hands. (C) The imaging study of the brain showed a marked ventriculomegaly and agenesis of the corpus callosum.

Fig. 2. Array comparative genomic hybridization showed varied gain of gene dosages at the segment of 8p23.3-q21.13 spanning 82.69 Mb.
et al [10] reported two cases of trisomy 8 mosaicism detected prenatally with favorable postnatal outcomes. In these two cases, low-level mosaicism was initially detected by conventional cytogenetics of cultured AF cells and was later confirmed by FISH or array-CGH analysis using uncultured AF cells. Chen et al [11] also provided evidence that indicated interphase FISH on uncultured AF cells is practical for the rapid confirmation of low-level trisomy 8 mosaicism in amniocentesis.

The phenotype–karyotype correlation of mosaic partial trisomy 8 is hardly consistent across cases. Gain of gene dosages from the extra copy of chromosome 8 could be masked by mosaic composition. Common clinical phenotypes or conditions associated with mosaic partial trisomy 8 may include, but are not limited to, facial dysmorphism, deep creases and skeletal abnormalities, developmental delay, cardiac anomalies, growth retardation, and genitourinary malformations. Previously, Filges et al [19] reported a 20-month-old case with de novo mosaic ring chromosome 8 presenting with facial dysmorphism, anal displacement, pelvic kidney, ocular anomaly, hearing loss, and mental retardation. Array-CGH confirmed the duplicated region expanded 43.8 Mb from 8p11.21 to 8q21.2 and overlapped part of our patient’s duplication. However, an anogenital anomaly that was supposed to be related to the gene-dosage effect of proximal 8q was not present in our case. Our case also manifested corpus callosum agenesis along with bilateral colpocephaly that has been previously reported in some prenatal and postnatal clinical cases [10,11]. Recent research highlights that duplications of 8p22–p21.3 contribute to corpus callosum agenesis, and the result of the array-CGH in our patient further supports this observation [20].

The occurrence of de novo partial trisomy 8 is extremely rare, and in our case seemed to result from terminal deletion at the 8q21.3 region [21,22]. Although some authors have proposed that

**Fig. 3.** Karyotype of the peripheral blood lymphocyte. Arrows indicate deleted chromosome 8.

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![Karyotype Image](image1)

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**Fig. 4.** Interphase fluorescence in situ hybridization (FISH) analysis revealed partial triplications of the centromere of chromosome 8 in: (A,B) buccal smears; and (C,D) urine sediments. The SpectrumAqua signals denote the alpha-satellite (centromere) of chromosome 8. The SpectrumOrange signals denote the Myc gene located at 8q24, which is not included in the deleted chromosome 8. The SpectrumGreen signals denote immunoglobulin heavy chain (IgH) signals located at 14q32. The IgH locus was used as a dosage control in the FISH experiment.
most physical malformations seen in trisomy 8 mosaicism are associated with trisomy of the long arm of chromosome 8, a genotype–phenotype correlation would be very difficult considering that the percentage of a normal cell line may vary widely in different tissues [23]. From our case, we speculate that genes located between 8pter and q21.3 are associated with growth disadvantage.

In conclusion, our case represents a rare case of partial trisomy 8 with distinctive clinical features. This case also illustrates the difficulty related to prenatal diagnosis of trisomy 8 mosaicism. Diagnosis of trisomy 8 or partial trisomy 8 mosaicism remains a challenging task.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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