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Case Report

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

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ABSTRACT

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 pelviectasis. 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 mosiacism 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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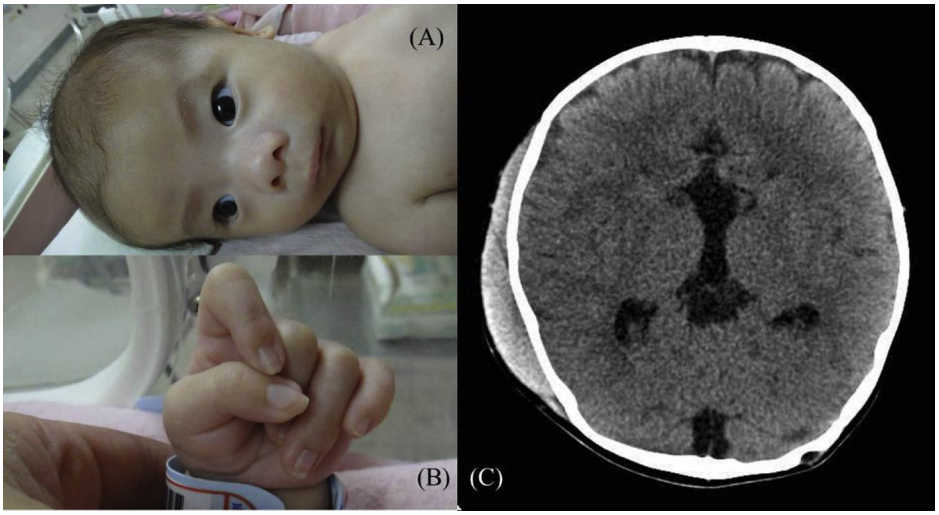

Fig. 1. The patient presented with: (A) facial dysmorphism; and (B) clenched hands. (C) The imaging study of the brain showed a marked ventriculomegaly and agenesis of the corpus callosum.

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, anteverted 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

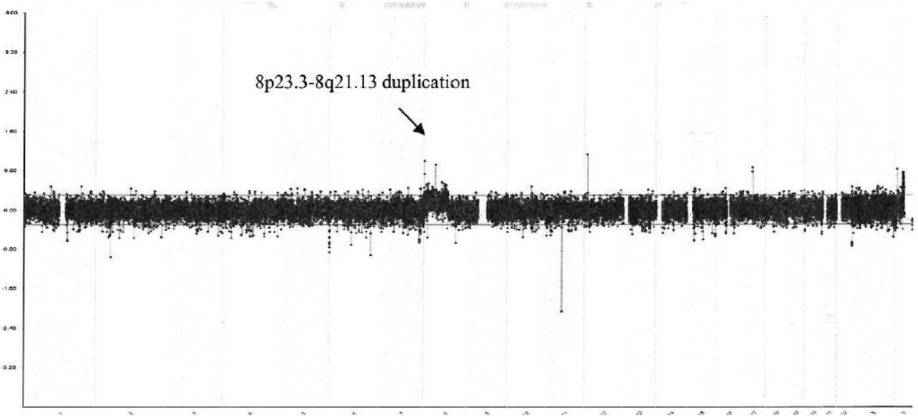

Fig. 2. Array comparative genomic hybridization showed varied gain of gene dosages at the segment of 8p23.3-q21.13 spanning 82.69 Mb.