A rare chromosomal abnormality inherited from the mother in a boy conceived after intracytoplasmic sperm injection: a case report

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Introduction

Couples rarely undergo a karyotype evaluation prior to either natural conception or receiving assisted reproductive technology (ART) if there is no history of abnormal pregnancy or other indicative signs. However, many chromosomal anomalies are not clinically obvious and do not preclude fertility nor do they cause miscarriage. Carriers may then conceive and produce a genetically abnormal child, and the defect is not detected until after birth.

Case report

Patient history

A 29-year-old woman was in a first marriage to a 35-year-old healthy man. Her left fallopian tube had been resected because of an ectopic pregnancy two years before the case described

Capsule A chromosomal defect der (7) t (7;12)(7q36;12q24) in a boy with birth defect who conceived after ICSI, inherited from his mother—a carrier with balanced reciprocal translocation, t (7;12) (7q36;12q24). We should emphasize the importance of chromosome testing before ART.

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here. After one year of attempting to conceive but without success, this couple underwent routine physical and genital examinations including determination of serum sex hormones, diagnostic curettage, and a semen analysis. No clinically significant abnormalities were found in either individual.

Subsequently, the woman underwent ovulation monitoring but still failed to conceive after three months. She was then treated with a gonadotropin-releasing hormone (GnRH) agonist long downregulation protocol to harvest 8 oocytes for in vitro fertilization. These oocytes could not be fertilized using conventional in vitro fertilization. Intracytoplasmic sperm injection (ICSI) was then performed 6 h later, and 4 oocytes were fertilized and underwent cleavage division. Two embryos were transferred on the third day, and the other 2 embryos were discarded for an appearance of poor quality.

The woman had a normal pregnancy, and delivered a baby boy by cesarean section at 38 weeks of gestation. The baby's birth weight and length were 2.3 kg and 49 cm, respectively. He was fed with difficulty and had severe vomiting from birth to now. At 18 months old, the boy was just 66 cm tall, weighed 4.5 kg, and could not speak any words. He suffered from severe growth and mental retardation. He had frontal bossing, macrocrania, hypertelorism, and a broad depressed nasal bridge. He experienced hypotonia and could not sit.

During the same year the woman had another ectopic pregnancy and underwent resection of her right fallopian tube. She has been waiting for donor eggs.

Materials and methods

Metaphase chromosome preparation

The GTG-banded (G-bands produced with trypsin and Giemsa) karyotypes of the mother, father, child and the

mother's sister were developed at a 450-band resolution. Thirty GTG-banded metaphases were analyzed for each sample.

Metaphase chromosomes of the mother and the baby were obtained from peripheral blood lymphocyte cultures and harvested using standard cytogenetic protocols [5] according to the manufacturer's instructions. The slides with good metaphase spreads were used for fluorescent in situ hybridization (FISH) analysis.

FISH procedure

FISH was carried out using the Vysis FISH Probe Kit (Abbott, USA) in accordance with the manufacturer's instructions. Whole chromosome paint (WCP) probes for chromosome 7 (WCP7, orange) and chromosome 12 (WCP12, green), CEP12 probe (green), and ToTelVysion subtle#7 mix probes (7qter orange, 7pter green) were used.

The slides were treated in $2\times$ standard saline citrate (SSC) at 37°C , dehydrated in a graded ethanol series (70 %, 85 %, and 100 %), denatured for 2 min in 70 % formamide, and air-dried. The denatured probe mix was then applied to the slides (10 mL; sealed under a glass coverslip) and allowed to hybridize for 8 h at 37°C in a moist chamber. After hybridization, the slides were washed in $2\times$ SSC/nonyl phenoxypolyethoxyethanol (NP-40) at 72°C for 2 min, washed in $2\times$ SSC at room temperature for 2 min, and then air-dried. The slides were counterstained with 4',6-diamidino-2-phenylindole (DAPI; Sigma). Ten metaphase

cells of each sample were analyzed using an Olympus BX51 fluorescence microscope.

Results

The baby boy's karyotype was 46,XY,-7+der(7)t(7;12)(7q36;12q24) (Fig. 1), while the mother had a balanced reciprocal translocation, 46,XX,1qh+,t(7;12)(7q36;12q24) (Fig. 2).

FISH analyses using orange WCP7 and green WCP12 probes revealed a translocation between chromosomes 7 and 12 in both the baby boy and his mother, but the orange chromosome segment 7q36→qter was too small to be observed on the green chromosome 12. Further analyses using the green CEP12 probe and ToTelVysion subtle#7 mix probes (7qter orange, 7pter green) confirmed the reciprocal translocation in the mother (Fig. 3).

The karyotypes of the husband and the woman's sister were normal.

Discussion

Many children with a chromosomal abnormality have birth defects. In the present case, a boy who was conceived after ICSI was born with severe mental and physical handicaps, and was found to have an unusual chromosomal defect (46,XY,-7+der [7]t[7;12][7q36; 12q24]), interpreted as a

Fig. 1 A GTG-banded karyotype of the child

Fig. 2 A GTG-banded karyotype of the mother

partial monosomy 7q(7q36→qter) and partial trisomy 12q (12q24→qter).

Deficiencies in several genes on 12q24 are associated with growth and mental retardation. These genes include insulin-like growth factor 1 (*IGF1*) and short-chain acyl-CoA dehydrogenase (*SCAD*) [3]. Tein et al. [11] reported that children with a mutation of the *SCAD* gene shared common clinical features, namely, hypotonia, developmental delay, speech delay, myopathy, lethargy, and feeding difficulties. Other studies [1, 12] also reported cases of

partial trisomy 12q24→qter with these clinical features. The baby boy in our study was afflicted with all the above clinical features. His mother had been checked regularly during gestation, but no abnormalities were found in the pregnancy. Genetic testing in utero was not performed, and therefore the abnormality of this baby was not detected prenatally.

Unlike the reported facial features of monosomy 7q (7q36→qter) [2, 4], the special facial appearance of this boy more closely resembled babies with partial trisomy 7q syndrome [9, 13]. These babies present with delays in development, feeding difficulty after birth, mental retardation, serious hypotonia, and unusual faces with frontal bossing, macrocrania, widely-set eyes, low nasal features, and low set ears. We suspect that our case presented unusual clinical features due to the combined partial monosomy 7q36-qter and partial trisomy 12q24-qter. Given that this chromosomal defect was transmitted by his mother, and was not due to the ART procedure, the importance of chromosome testing before pregnancy should be emphasized.

The mother in this case had had two ectopic pregnancies after natural conception. It is not known whether her chromosomal abnormality 1qh⁺,t(7; 12)(q36; q24) is associated with an increased risk of ectopic pregnancy. This infertile couple underwent in vitro fertilization and embryo transfer. Theoretically, a preimplantation genetic diagnosis could have been made if the mother was known to be a translocation carrier. In such cases, a polar body biopsy can reveal genetic anomalies as an alternative to blastomere biopsy [8].

Fig. 3 In the mother karyotype, green CEP12 probe and TotalVision subtle#7 mix probes (7qter orange, 7pter green) identified this reciprocal translocation

However, with only 2 viable embryos produced in this case after ICSI, the pregnancy rate would not have been high and the couple would have had to abandon the procedure to avoid conceiving an abnormal child.

One of the more frequently encountered structural chromosomal abnormalities in people is the balanced reciprocal translocation. These chromosomal anomalies can be inherited from a parent (maternal or paternal) or may occur *de novo* during the formation of gametes or the cleavage of zygotes [6, 7]. Since they involve an even exchange of genetic material with nothing extra or missing, such chromosomal rearrangements do not cause serious problems (including phenotype and intelligence) for the carriers, until they attempt to have children. In the present case 18 types of gametes were possible from this mother, only one of which would have normal chromosomes, and in another the karyotype would be identical to the mother's. All the others would carry the unbalanced form of the translocation that is associated with spontaneous abortion [10, 14], stillbirth, or an abnormal child. Carriers of a balanced reciprocal translocation have high rates of adverse pregnancy outcomes or decreased fertility. It is therefore not surprising that the boy in our case had birth defects. To prevent such cases as these would require that every infertile couple undergo chromosomal analysis. Screening karyotypes, however, would certainly increase the expense and time of ART treatment, and it should be noted that in many cases, false negatives and false positives are possible due to the limitations of the available technologies. Determining whether prospective parents are carriers is very important. It is worth pondering whether every infertile couple seeking ART treatment should be tested to determine whether they are carriers of abnormalities. At the very least, the importance of chromosomal tests and the limitations of technologies should be explained to every infertile couple, so that they can weigh the cost-effectiveness of chromosomal analysis.

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References

1. Bao L, Schorry EK. A girl with partial trisomy 12q24.31 inherited from her father and a possible novel syndrome transmitted from her mother. *Am J Med Genet*. 2005;A138:361–4.
2. Chen CP, Devriendt K, Lee CC, et al. Prenatal diagnosis of partial trisomy 3p (3p23→pter) and monosomy 7q(7q36→qter) in a fetus with microcephaly alobar holoprosencephaly and cyclopia. *Prenat Diagn*. 1999;19:986–9.
3. Corydon MJ, Andresen BS, Bross P, et al. Structural organization of the human short-chain acyl-CoA dehydrogenase gene. *Mamm Genome*. 1997;8:922–6.
4. Frints SG, Schrander-Stumpel CT, Schoenmakers EF, et al. Strong variable clinical presentation in 3 patients with 7q terminal deletion. *Genet Couns*. 1998;9:5–14.
5. Henegariu O, Heerema NA, Lowe WL, Bray-Ward P, Ward DC, Vance GH. Improvements in cytogenetic slide preparation: controlled chromosome spreading, chemical aging and gradual denaturing. *Cytometry*. 2001;43:101–9.
6. Kumar A, Becker LA, Depinet TW, et al. Molecular characterization and delineation of subtle deletions in denovo “balanced” chromosomal rearrangements. *Hum Genet*. 1998;103:173–8.
7. McFadden DE, Friedman JM. Chromosome abnormalities in human beings. *Mutat Res*. 1997;396:129–40.
8. Pierce KE, Fitzgerald LM, Seibel MM, Zilberstein M. Preimplantation genetic diagnosis of chromosome balance in embryos from a patient with a balanced reciprocal translocation. *Mol Hum Reprod*. 1998;4:167–72.
9. Romain DR, Cairney H, Stewart D, Columbano-Green LM, Garry M, Parslow MI, et al. Three cases of partial trisomy 7q owing to rare structural rearrangements of chromosome 7. *J Med Genet*. 1990;27:109–13.
10. Stern C, Pertile M, Norris H, Hale L, Baker HW. Chromosome translocations in couples with in-vitro fertilization implantation failure. *Hum Reprod*. 1999;14:2097–101.
11. Tein I, Elpeleg O, Ben-Zeev B, et al. Short-chain acyl-CoA dehydrogenase gene mutation (c.319 C>T) presents with clinical heterogeneity and is candidate founder mutation in individuals of Ashkenazi Jewish origin. *Mol Genet Metab*. 2008;93:179–89.
12. Vaglio A, Milunsky A, Huang XL. A fourteen years follow-up of a case of partial trisomy 12q and monosomy 12p recombinants of a familial pericentric inversion of chromosome 12: clinical, cytogenetic and molecular observations. *Eur J Med Genet*. 2007;50:224–32.
13. Verma RS, Conte RA, Pitter JH. Tandem duplication of the terminal band of the long arm of chromosome 7 (dir dup (7)(q36→qter)). *J Med Genet*. 1992;29:344–5.
14. Vidal F, Gimenez C, Rubio C, Simon C, Pellicer A, Santalo J, et al. FISH preimplantation diagnosis of chromosome aneuploidy in recurrent pregnancy wastage. *J Assist Reprod Genet*. 1998;15:310–3.