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ORIGINAL ARTICLE

CLINICAL MANIFESTATIONS OF PARTIAL TRISOMY 4p

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ABSTRACT

We made the diagnosis prenatally from cytogenetic analysis of amniocytes cultured following amniocentesis performed at 20 weeks' gestation on a woman in whom ultrasound examination of the female fetus showed severe growth retardation, lung and kidney hypoplasia, and a congenital heart defect. Analysis revealed a *de novo* trisomy of the terminal short arm of chromosome 4 (4p16.1-pter). The parents opted to terminate the pregnancy. Fetopathological examination showed dysmorphic features and other abnormalities consistent with clinical manifestations of partial trisomy 4p.

Key words: Partial trisomy 4p, Prenatal diagnosis, Congenital heart defects, Lung and kidney hypoplasia

INTRODUCTION

The imbalance of 4p is a rare chromosomal abnormality, and results in a variety of distinct clinical conditions. Forty cases with duplication of the distal half of 4p are published in the literature [1], and three of these were reviewed by Kleczkowska et al. [2]. Most of them were derived from familial chromosomal rearrangements. Partial 4p trisomy is associated with distinctive multiple congenital anomalies/mental retardation syndrome with clinical manifestations including a characteristic nose with a flat bridge and a bulbous tip, often referred to as boxer nose, abnormal ears, and flexion contractures [3,4]. Such phenotypic variability may depend on the length and location of the duplicated portion of 4p. The characteristic features of partial 4p trisomy are most likely due to duplication of bands 4p15.2 to 4p16.3 [5,6]. We report on a fetus ascertained prenatally because of intrauterine growth retardation, lung and kidney hypoplasia, and congenital heart defects associated with a distal *de novo* trisomy of the terminal short arm of chromosome 4.

MATERIALS AND METHODS

Subjects. A 28-year-old woman with a history of recurrent miscarriages, was referred by the Department of Obstetrics and Gynecology, Çukurova University, Adana, Turkey, to our genetics laboratory for prenatal diagnosis because of fetal intrauterine growth retardation associated with lung and kidney hypoplasia, and congenital heart defects at 20 weeks' gestation. The woman and her 39-year-

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old husband were healthy and phenotypically normal. They were not consanguineous. The family history revealed the occurrence of recurrent miscarriages on both sides but not of congenital anomalies. The mother had been pregnant four times before, which on two occasions had resulted in miscarriages during the first trimester, and on two occasions in healthy children. In the present pregnancy, a level III ultrasound showed hypoplasia of fetal lungs and kidneys, free intra-abdominal fluid, and increased occipitofrontal diameter of the head/biparietal diameter of the head (OFD/BPD) ratio. Fetal echocardiography showed cardiomegaly, right venticular hypertrophy, tricuspid insufficiency and ventricular septal defect.

Cytogenetic Analysis. The mother was referred to our amniocentesis laboratory for karyotyping. Amniotic fluid (20 mL) was obtained transabdominally. The karyotype of the fetus was obtained from an amniotic fluid sample, using flask cell culture and submitted to cell culture lasting 10 days. Karyotyping was routinely performed by G-banding using the trypsin-giemsa staining technique [7]. At least 20 metaphases were analyzed. Both parents were subjected to chromosomal analysis, based on standard blood lymphocyte culture and G-banding techniques. Twenty metaphases were microscopically analyzed for parents.

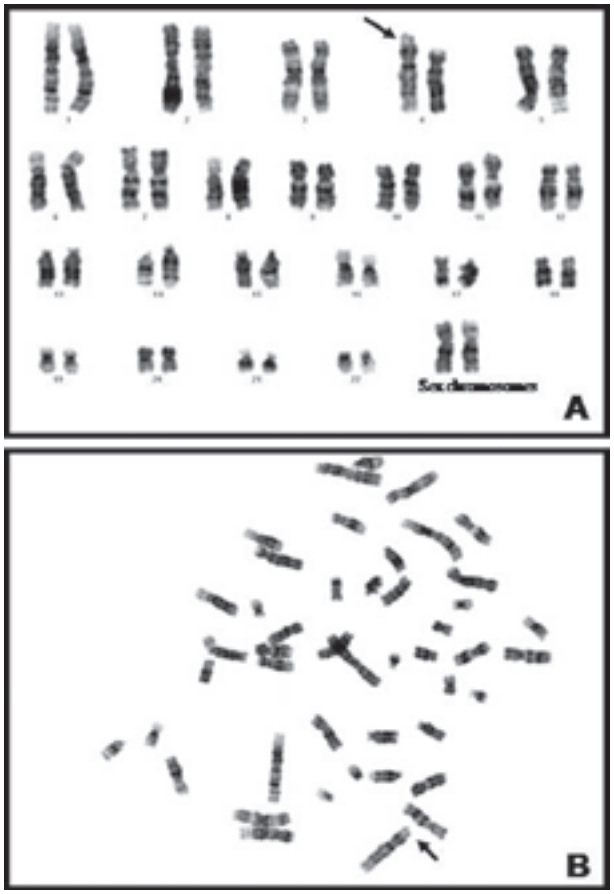

Figure 1. Karyotype and a metaphase spread of the proband showing the partial trisomy 4p.

RESULTS

Chromosome analysis showed that all the fetal cells had partial trisomy of the 4p16.1-pter region of one chromosome 4 (Figure 1). Both parental karyotypes were normal, indicating a *de novo* rearrangement in the fetus.

DISCUSSION

Chromosome imbalance affecting the short arm of chromosome 4 results in a variety of distinct clinical conditions. Most of these share a number of manifestations, such as mental retardation, microcephaly, pre- and post-natal growth retardation, anteverted and low-set ears, which can be considered as non specific signs, generally attributable to gene dosage impairment. On the other hand, more distinctive phenotypic traits correlate with the segmental aneuploidy. Although, duplication of the distal half of 4p leads to trisomy 4p syndrome, a distinct clinical entity with a characteristic facial appearance [8]. The fetus described in our study had a duplication of 4p16.1-pter, and the phenotype of the fetus we described, with an intrauterine growth retardation, lung and kidney hypoplasia and congenital heart defects. Duplications of the distal half of 4p characterized by a boxer nose configuration and deep-set eyes. These signs are usually observed even in cases of small terminal duplications [9]. The smallest duplicated segment leading to the dup(4p) phenotype was described by Wyandt et al. [6] in an 18-month-old infant. Despite the small size of the duplication, the region 4p16.1 to 4p16.3 appears to represent the region responsible for the typical phenotype.

Recurrent infections of the respiratory tract seem to be a typical feature in partial trisomy 4 (4p21) [4,10]. Affected infants may have respiratory difficulties, potentially leading to life-threatening complications. In some cases, additional

abnormalities may include protrusion of portions of the intestine into muscles of the inguinal hernia, structural abnormalities of the congenital heart defects, kidney malformations, or absence of the band of nerve fibers that join the two hemispheres of the brain [8]. Congenital heart defects may be detected with specialized tests that enable physicians to evaluate the structure and function of the heart. Cardiac evaluation may include clinical examination with a stethoscope to evaluate heart and lung sounds, x-ray studies, tests that record the electrical activities of the heart muscle, a technique in which sound waves are directed toward the heart, enabling evaluation of cardiac motion and function, or other measures (*e.g.,* cardiac catheterization). The large variability of the phenotype in trisomy 4p may be explained by the variation in length of the duplicated segments [11,12].

In summary, genetic counseling will be of benefit for individuals with partial duplication 4p and their families. The parents of a child with *de novo* duplication usually have normal chromosomes and a relatively low risk of having another child with the chromosomal abnormality. Early intervention may be important in ensuring that children with partial duplication 4p reach their potential.

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