CEOG Clinical and Experimental Obstetrics & Gynecology

18q deletion is difficult to detect by prenatal diagnosis: a report of two cases and a discussion of the literature

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Summary

Fetuses with 18q deletion have few structural abnormalities, therefore ultrasound is unlikely to detect this anomaly. Prenatal chromosome microarray is a powerful tool in detecting subtle cytogenetic abnormalities such as 18q deletion.

Key words: 18q deletion; Prenatal diagnosis; Chromosome microarray; Ultrasound.

Introduction

The incidence of 18q deletion is reported as one in 40,000 live births [1]. The characteristic features of the syndrome are short stature, hearing loss, hypotonia, mental retardation, and endocrine disorders, accompanied by autoimmunity. Previous reports have mainly concentrated on cases after birth [2-5]. There only appears to be two cases of prenatally detected 18q deletion reported in the literature [6-7]. Recently the present authors found two cases at prenatal diagnosis. The aim of this report was to underline that prenatal ultrasound is unlikely to detect this anomaly.

Case Report

Case 1

A 27-year-old-woman was referred for genetic counseling because of a high risk after second trimester prenatal screening for Down syndrome. Fetal gestation was 21 weeks and amniocentesis was done. The chromosome karyotype analysis was 46, XY, r(18). Chromosome analyses of the parents yielded normal results. Systematic fetal screening by ultrasound revealed only low-set ears. Chromosome microarray revealed deletions of 18p11.22-p11.32(10.1Mb) and 18q21.33-q23(18.8Mb) (Figure 1).

Case 2

A 26-year-old-woman was referred for amniocentesis because a 3.6-mm nuchal translucency (NT) was detected at 12 weeks gestation. Apart from the increased NT, no other sonographic abnormalities were present for the first-trimester ultrasound scan. The second-trimester fetal anatomy scan also appeared normal. For fear of the higher abortion risk associated with chorionic villi collection, the woman chose to have an amniocentesis at 19 weeks. The chromosome karyotype analysis was 46, XY, del 18(q21). Chromosome microarray revealed duplication of 10p14-15.3(7.3Mb) and deletion of 18q21.32-q23(21.1Mb). Parental chromosome karyotyping showed the father to have an apparently normal karyotype, but the mother's karyotype was 46, XX, t(10;18)(p15;q21) (Figure 2).

Discussion

The phenotype of 18q deletion syndrome (OMIM601808) is highly variable. Array comparative genomic hybridization analysis (aCGH) of now over 290 people has shown that no two unrelated individuals with terminal or interstitial deletions of 18q have the same breakpoints [8]. With no common genotype, it is impossible to provide a description of the "typical" phenotypic effects of 18q deletions. Common functional findings included developmental delay, hypotonia, growth hormone deficiency, and hearing loss. Structural anomalies included foot anomalies, ear canal atresia/stenosis, and hypospadias. The majority of individuals performed within the low normal range of cognitive ability but had more serious deficits in adaptive abilities [9]. The clinical manifestations are normally seen only after birth. In the prenatal diagnosis process, the syndrome has few common characteristics which are detectable by ultrasound.

From previous reports, the present authors retrieved two cases with prenatal diagnosis of 18q deletion. Kim *et al.* described a female newborn with a de novo 18q22.1q23 deletion [6]. Array analysis on the patient's genomic DNA revealed a 15-Mb (63,244,135-78,013,728) deletion in 18q22.1q23. The authors do not mention any prenatal ultrasound results. Echocardiography revealed atrial septal defect (ASD) after birth. Chen *et al.* reported a case of mosaic ring chromosome 18. A 36-year-old woman, underwent amniocentesis because of her advanced maternal age. Amniocentesis revealed a karyotype of 46,XY, r(18) [27]/45,XY,-18[5]/46,XY [5]. Level II ultrasound revealed only ventriculomegaly. aCGH demonstrated a 14.9-Mb deletion at

Revised manuscript accepted for publication July 15, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIV, n. 1, 2017
doi: 10.12891/ceog3224.2017

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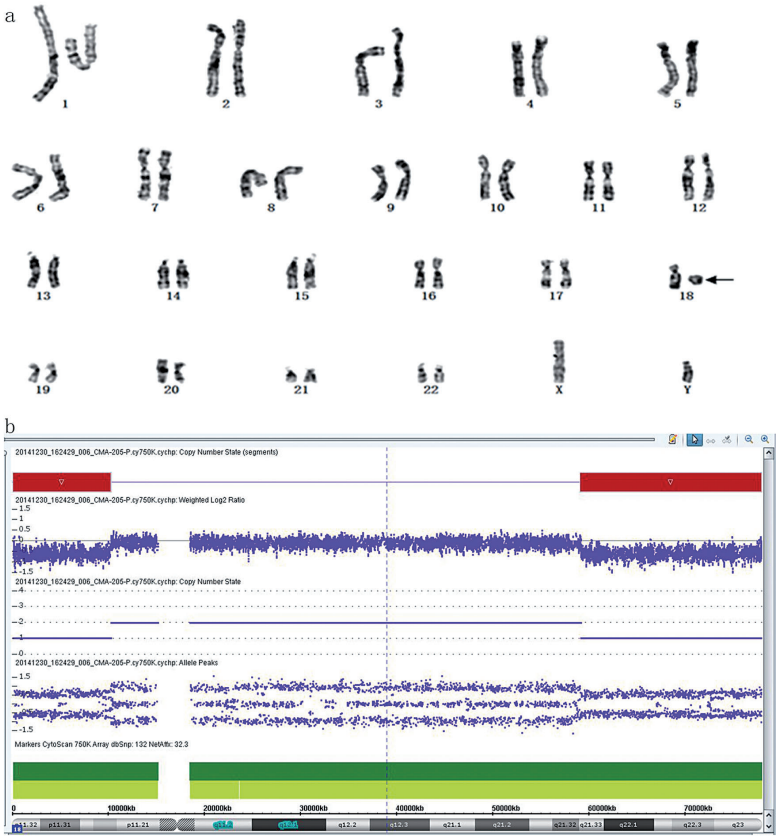

Figure 1. — a) Fetal karyotype of 46,XY,r(18); b) Chromosome microarray shows a 10.1-Mb deletion (136,227-10,285,090) of the short arm of chromosome 18 and a 18.8-Mb deletion (59,194,080-78,013,728) of the long arm of chromosome 18.

chromosome 18p [arr cgh 18p11.32p11.21 (0–14,941,330)× 1] and a 29.6-Mb deletion at chromosome 18q [arr cgh 18q21.2q23 (46,533,430–76,117,153) × 1] after birth [7].

Feenstra *et al.* suggest the critical region for the typical phenotype of 18q deletion is 4.3 Mb region located within 18q22.3-q23, including short stature (18q22.3-q23), delayed myelination (18q22.3-q23), growth hormone insufficiency (18q22.3-q23), and congenital aural atresia (18q22.3) [10]. No specific phenotype can be found by ultrasound. The incidence of congenital heart disease, the most common fetal anomaly, is not high in the population proportion. Cody *et al*. reported 42 individuals with deletions of 18q after birth. Cardiac anomalies were observed in 24%, including atrial and ventricular septal defects, pulmonary stenosis [11].

All of these cases reinforce the usefulness of chromosome microarray for prenatal detection and characterization of microdeletions and unbalanced translocations.

A ring chromosome 18 exhibits breakage and reunion at the breakpoints on the long and short arms of chromosome 18, with deletions of the chromosomal segments distal to the breakpoints. There is no consistent phenotype in patients with r(18), and the phenotype reflects the preponderant localization of the deletion (18p or 18q) and does not depend simply on the size of the genomic rearrangement [12].

The two reported prenatally detected cases of 18q deletion give little information on associated ultrasound findings. The two present cases the reported only showed nonspecific ultrasound anomalies. The literature on postnatally detected cases suggests that heart anomalies are the most likely ultrasound finding and are only present in about a quarter of cases. These findings suggest the ultrasound is unlikely to reliably detect 18q deletions.

Acknowledgments

The authors thank Dr. Ashleigh Murch for reading the manuscript and helpful suggestions. This study was supported by a Research Grant (W9) from the Department of Health, Jiangsu Province, China.

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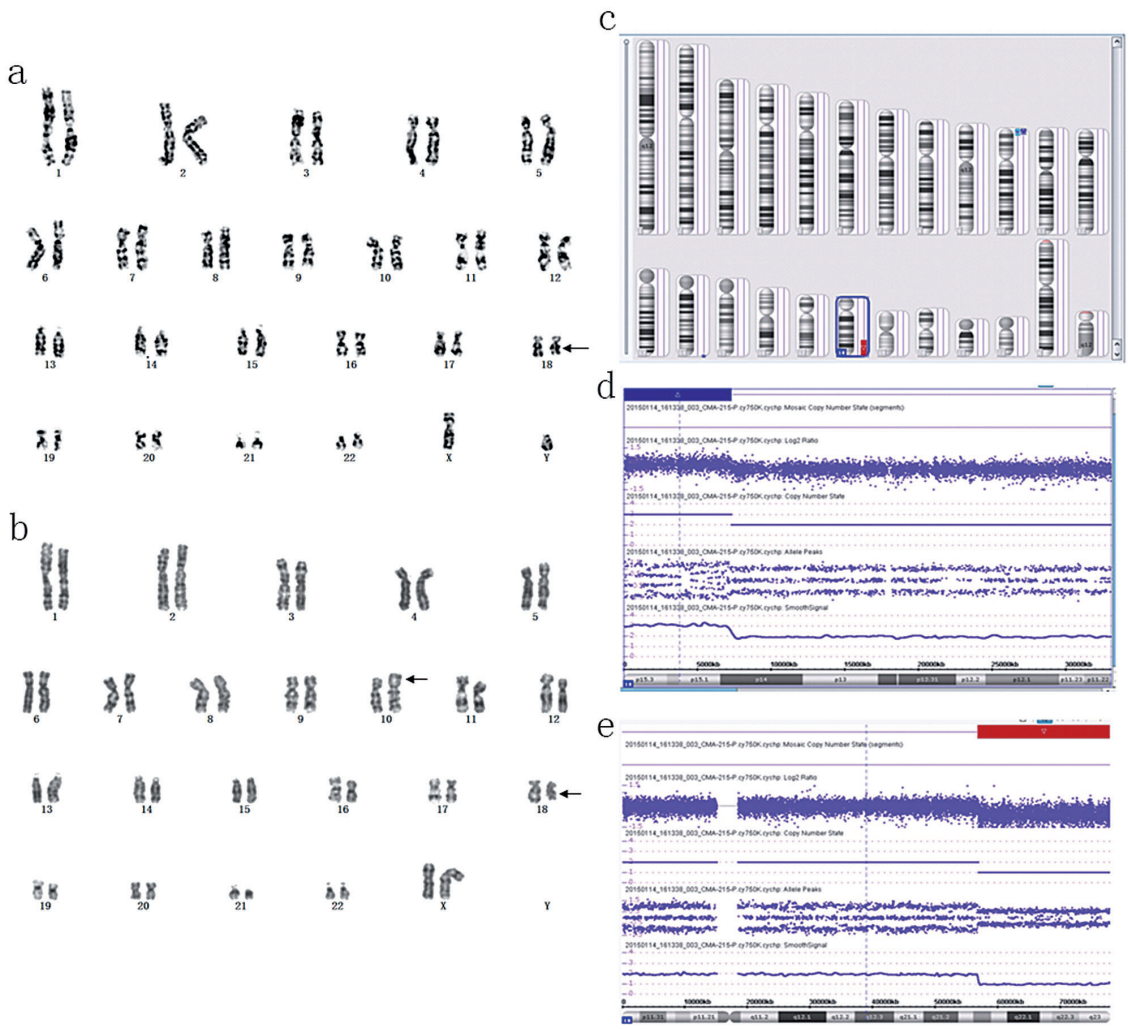

Figure 2. — a) Fetal karyotype of 46,XY,del(q21); b) Maternal karyotype of 46,XX, t(10;18)(p15;q21); c-e) Chromosome microarray shows a 7.3-Mb duplication (100,047-7,330,666) of the short arm of chromosome 10 and a deletion 21.1-Mb deletion (56,909,424-78,013,728) of the long arm of chromosome 18.

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