

Prenatal Diagnosis of 18p Deletion and Isochromosome 18q Mosaicism in a Fetus with a Cystic Hygroma

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ABSTRACT

Although, deletion of short arm of chromosome 18 is one of the most frequent autosomal terminal deletions, mosaic form of 18p deletion is infrequently observed. Furthermore, prenatally detected cases of 18p deletion and isochromosome 18q mosaicism are extremely rare. Herein, we present a case of *del(18p)/i(18q)* mosaicism, prenatally detected after chorionic villus sampling. A 37-year-old woman was referred for prenatal diagnosis because of fetal septated cystic hygroma measuring 4.3 mm. Cytogenetic analysis showed a mosaic *46,XX,del(18)(p11.2)/46,XX,i(18)(q10)* karyotype in both, short- and long-term culture. Parents elected to terminate the pregnancy. Fetal mosaic karyotype was confirmed by chromosomal analysis of cultured skin fibroblasts. Molecular characterization of chromosome 18 structural aberrations was performed by fluorescence in situ hybridization (FISH). Considering variable ultrasound findings among cases with *del(18p)/i(18q)* mosaicism, we emphasized that first and second trimester ultrasound screening examinations for fetal malformations, followed by cytogenetic and molecular evaluations, are very important in the management of prenatally detected cases.

Key words: 18p deletion, cystic hygroma, *del(18p)/i(18q)* mosaicism, isochromosome 18q, prenatal diagnosis, termination of pregnancy

Introduction

Complete or partial deletion of chromosome 18 short arm is chromosomal disorder known as monosomy 18p, deletion 18p syndrome, 18p- syndrome or de Grouchy syndrome. With more than 150 reported cases and incidence of 1 in 50,000 liveborn infants, it is one of the most frequent autosomal terminal deletions. In most cases deletions arise *de novo*, and less commonly result from an unbalanced whole arm translocation, formation of ring chromosome, or appear after recombination in pericentric inversion carriers. Mosaic form of 18p deletion is infrequently observed¹. Furthermore, the presence of an additional cell line containing isochromosome 18q is extremely rare. To our knowledge, only three prenatally detected cases^{2–4} and five cases diagnosed among liveborns have been reported^{5–9}. Patients with *del(18p)/i(18q)* mosaicism show differing phenotypic features consistent

with both, 18p- and trisomy 18q syndromes. Herein, we present a case of *del(18p)/i(18q)* mosaicism with a septated cystic hygroma, prenatally ascertained after chorionic villus sampling.

Case Report

A 37-year-old woman was referred in her third pregnancy for the evaluation of increased nuchal translucency, discovered during a routine first-trimester ultrasound scan. Her previous two pregnancies ended with delivery of healthy infants. At examination, crown-rump length (CRL) was 67 mm. Nuchal translucency (NT) measured at mid-sagittal plane resulted 4.3 mm, and detailed analysis showed septated bilateral cystic hygroma.

TABLE 1
LITERATURE REVIEW OF PRENATALLY DETECTED CASES WITH DEL(18P)/I(18Q) MOSAICISM

References	Maternal age	Gestational age (weeks)	Ultrasound markers	Sample	Karyotype
Sutton and Ridler (2)	36	16	None	AF, FB at TOP	46,XX,18p-[13]/46,XX,i(18q)[10]dn46,XX,18p-[5]/46,XX,i(18q)[15]dn
Qumsiyeh <i>et al.</i> (3)	42	25	Polyhydramnios	AF	46,XX,del(18)(p11.1)[16]/46,XX,-18,+i(18q)[4]dn
Wong <i>et al.</i> (4) (Case 3)	36	13	NT=4 mm, semilobar HPE with proboscis, single orbit and exomphalos	CVS	46,XX,18p-[28]/46,XX,18p+[23]/46,XX,i(18q)[5]/46,XX[5]
Present case	37	12	Septated cystic hygroma of 4.3 mm, negative A-wave of ductus venosus blood flow	Short-term CVS Long-term CVS Skin fibroblasts	46,XX,del(18)(p11.2)[14]/46,XX,i(18)(q10)[1]dn; 46,XX,del(18)(p11.2)[7]/46,XX,i(18)(q10)[1]dn; 46,XX,del(18)(p11.2)[64]/46,XX,i(18)(q10)[3]dn

AF – amniotic fluid, FB – fetal blood, TOP – termination of pregnancy, NT – nuchal translucency, HPE – holoprosencephaly, CVS – chorionic villus sampling

The doppler of ductus venosus showed negative A-wave. Chorionic villi sampling (CVS) was performed transabdominally at 12 weeks of gestation. Cytogenetic analysis by GTG-banding showed a mosaic 46,XX,del(18)(p11.2)/46,XX,i(18)(q10) karyotype (Figure 1a, 1b) in both, short- and long-term culture (Table 1). Parental karyotypes were normal, indicating *de novo* origin of chromo-

somal aberrations in the fetus. After genetic counseling, parents elected to terminate the pregnancy.

Fetal mosaic karyotype was confirmed by chromosomal analysis of cultured skin fibroblasts (Table 1). Molecular characterization of chromosome 18 structural aberrations was performed by fluorescence *in situ* hybridization (FISH), using telomere probes for chromosome 18 (Abbott Molecular). FISH analysis confirmed the presence of two cell lines, one with terminal deletion of chromosome 18p (Figure 2a), and other with the presence of isochromosome 18q (Figure 2b).

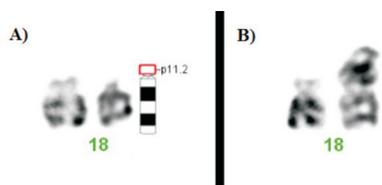


Fig. 1. Partial karyotypes of chromosome 18. a) Normal chromosome 18 (left), deletion of short arm of chromosome 18 and accompanying ideogram (right) are showed. b) Partial karyotype showing normal chromosome 18 (left) and isochromosome 18q (right).

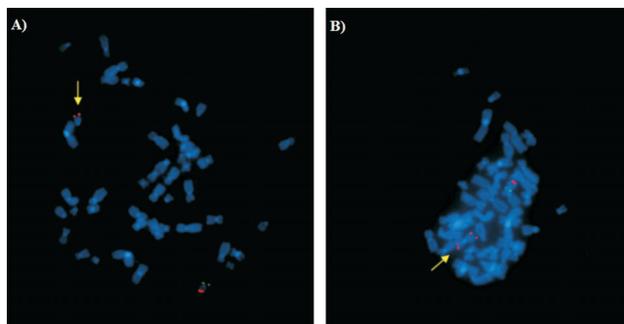


Fig. 2. Fluorescence *in situ* hybridization analysis on a metaphase spreads of cultured skin fibroblasts using telomeric probe 18p (TelVysion 18p Spectrum Green) and 18q (TelVysion 18q Spectrum Orange). a) Absence of the 18p telomere signal (green) indicating the deletion of short arm of one chromosome 18. b) Presence of isochromosome 18q confirmed by 18q telomere probe (orange).

Discussion

Mosaic form consisting of two cell lines, one with 18p deletion and other with isochromosome 18q is rarely seen. About two thirds of monosomy 18p cases arise *de novo*¹. Normal parental karyotypes in our case also indicate *de novo* appearance of 18p deletion, with the formation of isochromosome 18q as a subsequent event.

Since del(18p)/i(18q) mosaicism results in partial monosomy 18p in all cells, and partial 18q trisomy in the percentage of cells, the expected phenotypic characteristics should be consistent with both, monosomy 18p and trisomy 18q syndromes. Still, according to previously reported cases among liveborns^{5–9} patients with del(18p)/i(18q) mosaicism show variable features, mainly associated with 18p deletion, which can be expected if we take into account the number of cells containing 18p-. Thus, certain genotype-phenotype correlations cannot be strictly made, making difficulties in genetic counseling and prenatal diagnosis.

Most prenatally detected cases of del(18p) syndrome are disclosed due to advanced maternal age, or the presence of fetal ultrasound markers such as an increased nuchal translucency or holoprosencephaly¹. However, prenatally diagnosed cases with isochromosome 18q show a

wide range of sonographic findings including those characteristic for trisomy 18 and monosomy 18p: intrauterine growth retardation, holoprosencephaly, omphalocele, facial dysmorphism, radial deviation of limbs, single umbilical artery¹⁰. Interestingly, among cases of del(18p)/i(18q) mosaicism (Table 1), Sutton and Ridler² and Qumsiyeh et al.³ have not found any fetal abnormalities. Furthermore, Wong et al.⁴ reported an increased nuchal translucency and semilobar holoprosencephaly, which are both consistent also with ultrasound markers for del(18p) syndrome. In our case, ultrasound examination showed a septated bilateral cystic hygroma and negative A-wave of ductus venosus. The absence of growth retardation and other severe morphological abnormalities related to trisomy 18q, present in all reported cases, could be explained by a small proportion of the cells with isochromosome 18q and early gestational age at the time when diagnosis was made.

Although, the most common chromosomal abnormalities associated with a fetal cystic hygroma are monosomy X (Turner syndrome) and trisomies 21, 18, and 13, also some structural chromosomal aberrations are seen¹¹. Still, our study represents the first report of the septated cystic hygroma within cases of del(18p)/i(18q) mosaicism.

De novo chromosomal aberrations could be caused by different agents such as X-ray irradiation, chemotherapy, environmental chemicals or drug intake¹². However, appearance of structural chromosomal aberration in our case was probably due to advanced maternal age. Furthermore, in mosaic cases with isochromosome formation for chromosomes other than acrocentrics, there is no notably increased risk of recurrence in the next pregnancy. This assumption is based on the mechanism of postzygotic generation of the isochromosomes. Still, prenatal diagnostics, i.e. ultrasound examinations, and chorionic villi sampling or amniocentesis are suggested in subsequent pregnancies. Also, folic acid supplementation in the pre-conception period should be recommended.

In conclusion, finding of a *de novo* structural chromosomal aberration associated with cystic hygroma, emphasizes the diagnostic value of nuchal translucency measurement, not only as a screening test for common aneuploidies, but also for a less frequently detected structural chromosomal rearrangements. Thus, first and second trimester ultrasound examination, followed by cytogenetic and molecular methods, are all important in the management of prenatal cases with fetal anomalies.

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PRENATALNA DIJAGNOSTIKA DELECIJE 18p I MOZAICIZMA ZA IZOKROMOSOM 18q KOD FETUSA S CISTIČNIM HIGROMOM

SAŽETAK

Iako je delecija kratkog kraka kromosoma 18 jedna od najčešćih terminalnih delecija autosoma, mozaični oblik delecije 18p je rijetka pojava. Nadalje, prenatalno otkriveni slučajevi delecije 18p uz prisutnost mozaicizma za izokromosom 18q su iznimno rijetki. U ovom radu opisujemo slučaj mozaicizma del(18p)/i(18q), prenatalno otkrivenog nakon biopsije korionskih resica. Trudnica, stara 37 godina, upućena je na prenatalnu dijagnostiku zbog septiranog cističnog higroma ploda, veličine 4,3 mm. Citogenetskom analizom kratkotrajne i dugotrajne kulture korionskih resica dobiven je kariotip 46,XX,del(18)(p11.2)/46,XX,i(18)(q10). Na zahtjev roditelja, trudnoća je prekinuta u 14. tjednu trudnoće. Kromosom-

skom analizom kulture stanica fibroblasta kože potvrdi se mozaični kariotip. Molekularna karakterizacija strukturne promjene kromosoma 18 provedena je fluorescencijskom *in situ* hibridizacijom (FISH). S obzirom na prisutnost različitih ultrazvučnih biljega među slučajevima mozaicizma za del(18p)/i(18q), htjeli bismo istaknuti da su ultrazvučni pregledi u prvom i drugom tromjesečju za probir fetalnih malformacija, kao i klasična i molekularna citogenetska analiza, veoma važni u obradi prenatalno otkrivenih slučajeva.