Case Report

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Prenatal Detection of Trisomy 18q - Edwards Syndrome

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SUMMARY

Introduction: Most fetuses with trisomy 18 have an abnormal ultrasound results. Trisomy of the long arm of chromosome 18 is an important factor in the development of the phenotype of Edwards syndrome.

Case report: A 28 year old woman, in 24th gestational week of her first pregnancy, was referred to our clinic for genetic counseling, after combined screening for aneuploidies in the first trimester of her pregnancy showed increased risk for trisomy 13 and 18, and fluorescent in situ hybridization (FISH) from amniotic fluid results were obtained only for chromosomes 13, 21 and sex chromosomes, showing euploid constitution, but for the chromosome 18 there were no findings. After careful analysis of the obtained results, geneticist suggested a thorough ultrasonography examination of the fetus that showed polyhydramnion, asymmetrical ventriculomegaly and agenesis of corpus callosum. Consequent cytogenetic analysis showed karyotype 46,XX,-13,+der(13),t(13;18)(p11;q11). Parents had normal karyotypes, so finding of trisomy 18q in fetus, is due to de novo translocation. After genetic counseling, on parents demand and after ethic committee approval, this pregnancy was terminated and autopsy revealed dysmorphic facial features (including triangular face, low-set ears, short palpebral fissures), clenched hands, ventriculomegaly, choroid plexus cysts, partial agenesis of corpus callosum, subaortic ventricular septum defect, bilateral, trilobate lungs and saccular stage of lung development.

Conclusion: Karyotyping of fetuses with high risk for chromosomal disorders is necessary not only for the confirmation of clinical diagnosis, but also for a proper genetic counseling.

Keywords: Chromosome 18, Trisomy 18q, Fetal Anomalies

INTRODUCTION

Trisomy 18 is the second most common autosomal aneuploidy, that occurs in about 1 in 6000 live births and causes multiple birth defects in affected infants [1]. In 80% of cases it is present as complete trisomy, with additional chromosome 18. Other 20%, comprising different forms of partial trisomy 18, are result of inherited or de novo translocations involving chromosome 18, duplications or isochromosomes [2].

Trisomy 18 is clinically associated with various anomalies including craniofacial abnormalities such as prominent occiput, narrow bifrontal diameter, low-set and malformed auricles and micrognathia; hand and feet anomalies including clenched hand, overlapping of index finger and hypoplasia of nails; thorax deformities; inguinal hernia; small pelvis; male with cryptorchidism; cardiac and circulatory system anomalies, in particular

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ventricular septal defect (VSD), patent ductus arteriosus (PDA) and auricular septal defect. In addition, 10–50% of cases showed other craniofacial, hand, feet and thorax anomalies, cardiac with pulmonic stenosis, coarctation of aorta, renal anomaly with horseshoe defect, double ureter, hydronephrosis and polycystic kidney, while ≥50% of cases exhibited central nervous system anomaly with cerebellar hypoplasia, agenesis of corpus callosum, hydrocephalus, meningomyelocele and Dandy-walker malformation. Newborns with Trisomy 18 experience severe psychomotor and growth retardation [3].

Almost half of trisomy 18 infants die within the first week of life, and the majority of the remaining die in the next 12 months; only 5% to 10% of these infants survive the first year. The death usually is due to central apnea, upper airway obstruction, respiratory insufficiency, aspiration, cardiac failure, or a combination of these and other factors (including decisions for palliative care) [4].

We present a case of antenatally detected trisomy of a long arm of chromosome 18 (trisomy 18q), due to *de novo* translocation. This is the first case of trisomy 18q reported from Serbia.

CASE REPORT

A 28 year old woman, in 24th gestational week of her first pregnancy, was referred to our clinic for genetic counseling. She presented previous findings of combined screening in first trimester and amniotic fluid analysis. Combined screening for aneuploidies in the first trimester of her pregnancy, showed increased risk for trisomy 13 and 18. After genetic counseling, amniocentesis was performed and the sample of amniotic fluid was analyzed for the most common aneuploidies, 13, 18, 21 and sex chromosomes, using fluorescent in situ hybridization (FISH) technique. Results were obtained only for chromosomes 13, 21 and sex chromosomes, showing euploid constitution. For chromosome 18 there were no findings.

After careful analysis of the obtained results, geneticist suggested a thorough ultrasonography examination of the fetus. Sonographic scan showed polyhydramnios, asymmetrical ventriculomegaly and agenesis of corpus callosum, so fetal karyotype analysis was suggested. Analysis of fetal chromosomes was done from fetal blood sample, obtained after cordocentesis.

Cytogenetic analysis showed karyotype 46,XX,-13,+der(13),t(13;18)(p11;q11). Parents had normal karyotypes, so finding of trisomy 18q in fetus, is due to *de novo* translocation.

After genetic counseling, on parents demand and after ethic committee approval, this pregnancy was terminated in 26th week of gestation.

Autopsy revealed dysmorphic facial features (including triangular face, low-set ears, short palpebral fissures), clenched hands (with the index finger overriding the middle finger and the fifth finger overriding the fourth finger), ventriculomegaly, choroid plexus cysts, partial agenesis of corpus callosum, subaortic ventricular septum defect, bilateral, trilobate lungs and saccular stage of lung development.

Trisomy 18 pregnancies have a high risk of fetal loss and stillbirth. Prenatal diagnosis is based on maternal biochemical serum screening, ultrasonography screening for markers of chromosomal aberrations, and fetal karyotype analysis for confirmation of clinical diagnosis, and it is followed by pregnancy termination in significant percentage of cases [5].

In our case all diagnostic methods were combined. Combined screening the first trimester showed increased risk for trisomy 13 and 18. Fetal ultrasonography scan reveled anomaly of central nervous system and karyotyping gave definitive diagnosis of a partial trisomy 18.

Most fetuses with trisomy 18 have an abnormal ultrasound results. The prenatal sonographic pattern of trisomy 18 is characterized by growth retardation, polyhydramnios, „strawberry-shaped" cranium (brachycephaly and narrow frontal cranium), choroid plexus cyst, skeletal malformations, overlapping of hands fingers (second and fifth on third and fourth respectively), congenital heart defects, omphalocele, and single umbilical artery [6].
Since the deletion of the short arms of the acrocentric chromosomes does not cause any phenotypic effect main clinical findings of trisomy 18 syndrome of our case results from unbalanced translocation of the large segment of the 18q.

Trisomy of a long arm chromosome 18 is an important factor in the development of the phenotype of Edward syndrome, as the pathognomic segments responsible for Edwards phenotype is thought to be located in

the q arm, proximal critical (18q11-18q12), (18q12.1-18q21.1) and distal critical region (18q22.3-18qter) [7,8,9].

Triplication of the q arm will display a range of severity from relatively mild phenotype with no internal organ malformations to the classic characteristics of Edwards syndrome [10].

Peron et al. hypothesized that a single critical regions/candidate genes are likely to be responsible for specific clinical features of the syndrome in an additive manner, while a unique critical region for the whole Edwards syndrome phenotype is unlikely to exist. The most valuable conclusion was that the trisomy 18 phenotype results from interaction of several chromosome 18 regions which may produce a quite different phenotype when duplicated in isolation [7].

Several different technologies are used for prenatal genetic screening procedures, including ultrasonography, the double-marker test, the triple marker test, non-invasive prenatal testing (NIPT). Invasive prenatal diagnostic techniques are feasible tools for confirming fetal chromosomal abnormalities [11]. More than 95% of trisomy 18 fetuses can be identified by a first-trimester combined screening test (a combination of maternal age, fetal nuchal translucency, fetal heart rate and serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A)) [12].

Detection rates for abnormal sonographic findings in trisomy 18 fetuses range from 70% to 100% [13]. In the second and third trimester one or more sonographic anomalies are detected in over 90% of fetuses, and two or more abnormalities are present in 55% of cases [6].

Noninvasive prenatal testing is now widely used in the medical field. The basic principle of NIPT is the need to extract cell-free DNA from the plasma of pregnant women to perform high-throughput sequencing. Combined with economic and health data, NIPT can be used as a sequential screening program for traditional detection techniques. At present, the clinical application of NIPT can generally make a clear analysis of the three most common autosomal aneuploidies, trisomy 21, trisomy 13 and trisomy 18 [14]. The positive predictive value (PPVs) of NIPT for trisomy 18 is 76% [15].

Increased risk on prenatal screening for trisomy 18 requires invasive prenatal tests to confirm the diagnosis. The most widespread diagnostic tests for chromosomal abnormalities are conventional karyotyping and fluorescent in situ hybridization (FISH) or quantitative fluorescent PCR (QF-PCR) for chromosomes 13, 18, 21, X, and Y. FISH is a rapid test since it does not necessarily require metaphases but cells in interphase; however, it is a cumbersome and expensive technique. On the other hand, QF-PCR is also a rapid molecular test; it is very accurate, detects maternal cells contamination and the cost is very low. Conventional fetal cytogenetics (karyotyping) is still the gold standard in prenatal diagnosis of chromosomal aberrations, especially structural chromosomal defects [16,17].

In cases like the one presented, genetic counseling is crucial for parents. They should be aware of probability of fetal loss and stillbirth and the possibility of living, as well as the recurrence risk.

In case of *de novo* structural rearrangement the recurrence risk is considered to be negligible [18].

CONCLUSION

Since trisomy 18 is not curable, proper prenatal diagnosis, including karyotyping, is necessary not only for the confirmation of clinical diagnosis, but for a proper genetic counseling and pregnancy management.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Prenatalno otkrivena trizomija 18q - Edvardsov sindrom

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KRATAK SADRŽAJ

Uvod: Većina fetusa sa trisomijom 18 ima ultrazvučno uočljive anomalije. Trizomija dugog kraka hromozoma 18 (18q) važan je faktor u razvoju fenotipa Edvardsovog sindroma.
Prikaz slučaja: Trudnica stara 28 godina, upućena je na našu kliniku radi genetičkog savetovanja, u 24. gestacijskoj nedelji prve trudnoće. Kombinovani skrining na aneuploidije u prvom tromesečju trudnoće pokazao je povećani rizik za trisomije 13 i 18, nakon čega je urađena fluorescentna in situ hibridizaciju (FISH) iz uzorka plodove vode i dobijeni su rezultati samo za hromozome 13, 21 i polne hromozome, koji pokazuju euploidnu konstituciju, dok za hromozom 18 nije bilo nalaza. Nakon pažljive analize dobijenih rezultata, genetičar je predložio temeljan ultrasonografski pregled fetusa kojim je otkiriveno da fetus ima polihidramnion, asimetričnu ventrikulomegaliju i agenezu korpusa kalozuma. Urađena je analiza hromozoma iz uzorka fetalne krvi i detektovan je kariotip 46, XX,-13,+der(13),t(13;18)(p11; q11). Oba roditelja su imala normalan kariotip, tako da je nalaz trisomije 18q kod fetusa, rezultat de novo translokacije. Nakon genetičkog savetovanja, na zahtev roditelja i nakon odobrenja etičkog odbora, ova trudnoća je prekinuta i obdukcijom su ustanovljene dismorfične crte lica (uključujući trouglasto lice, nisko postavljene uši, kratke palpebralne fisure), stisnute šake, ventrikulomegalija, ciste horoidnog pleksusa, delimična ageneza korpusa kalozuma, subaortni ventrikularni septalni defekt, bilateralna trilobarna pluća u sakularnom stadijumu razvoja.
Zaključak: Kariotipizacija fetusa kod kojih postoji visok rizik za hromozomopatije, neophodna je, ne samo za potvrđivanje kliničke dijagnoze, već i za ispravno genetičko savetovanje.

Ključne reči: hromozom 18, trizomija 18q, fetalne anomalije

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