CASE REPORT
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Prenatal ultrasonographic manifestations of partial trisomy 12q(12q24.2→qter) and partial monosomy 2q (2q37.3→qter)

Prenatalne ultrazvučne manifestacije parcijalne trizomije 12q (12q24.2→qter) i parcijalne monozomije 2q (2q37.3→qter)

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Abstract

Introduction. Partial trisomy of chromosome 12 long arm is rare condition with significant clinical impact and is usually diagnosed postnatally. **Case report.** We present prenatal sonographic findings and molecular cytogenetic characterization of partial trisomy 12q and partial monosomy 2q in two consecutive pregnancies of a healthy non-consanguineous couple. A 35-year-old pregnant woman G3P1A1 was referred to genetic counseling due to sonographic anomalies detected in the fetus. First trimester ultrasound examination revealed hyperechogenic focus in the left cardiac ventricle, single umbilical artery, hyperechogenic bowel and unilateral clubfoot with knee joint ankylosis. Previous pregnancy of the couple was terminated at 26th gestation weeks due to multiple fetal anomalies: bilateral ventriculomegaly, corpus callosum hypoplasia, single umbilical artery and clubfoot. In G3P1A1, amniocentesis was performed and cytogenetic analyses revealed a derivative chromosome 2. Subsequent cytogenetic analyses of parental lymphocytes showed that paternal karyotype was normal, while maternal karyotype showed a der(2). Metaphase fluorescence *in situ* hybridization (FISH) studies demonstrated partial trisomy 12q24.2→12qter and partial monosomy 2q37.3→2qter in the fetus, resulting from an unbalanced segregation of a maternal balanced translocation t(2;12)(q37.3;q24.2). To date, this is the first such prenatally detected case. Literature search revealed three more cases of prenatally detected partial trisomy 12q and anomalies described were consistent with ones detected in present case. Our findings contribute to further clinical delineation of partial trisomy 12q. **Conclusion.** Prenatal detection of single umbilical artery, clubfoot, arthogryposis and ventriculomegaly should alert suspicion to chromosome 12q aberrations.

Key words:
pregnancy; ultrasonography prenatal; chromosome 2, monosomy 2q; chromosome 12, trisomy 12q.

Apstrakt

Uvod/Cilj. Parcijalna trizomija dugog kraka hromozoma 12 predstavlja retku hromozomsku aberaciju koja ima značajnu kliničku sliku i najčešće se dijagnostikuje postnatalno. **Prikaz bolesnika.** Prikazali smo prenatalnu ultrazvučnu sliku i molekularnu citogenetičku karakterizaciju parcijalne trizomije 12q i parcijalne monozomije 2q u dve uzastopne trudnoće kod zdravog para koji nije u srodstvu. Trudnica stara 35 godina je tokom svoje treće trudnoće upućena u genetičko savetovalište zbog ultrazvučno viđenih anomalija ploda. Na ultrazvučnom pregledu tokom prvog trimestra trudnoće uočen je hiperehogeni fokus u levoj komori srca, jedna pupčana arterija, hiperehogena creva i iskrivljeno stopalo sa ankilozom kolena. Prethodna trudnoća ovog para prekinuta je u 26. nedelji gestacije zbog multiplih anomalija ploda: obostrane ventrikulomegalije, hipoplazije žuljevitog tela, jedne pupčane arterije i iskrivljenog stopala. Amniocenteza urađena tokom treće trudnoće pokazala je prisustvo derivatnog hromozoma 2. Citogenetička analiza roditeljskog kariotipa iz limfocita periferne krvi pokazala je da je očev kariotip normalan, dok je kod majke bio prisutan derivatni hromozom 2. Metodom metafazne fluorescentne *in* situ hibridizadije (FISH) potvrđena je parcijalna trizomija 12q24.2→12qter i parcijalna monozomija 2q37.3→2qter kod fetusa kao posledica nebalansirane segregacije maternalnih hromozoma. Do danas, ovo je prvi ovakav slučaj dijagnostikovan prenatalno. Prema literaturnim podacima, u tri do sada objavljena slučaja parcijalne trizomije 12q opisane su anomalije koje su u skladu sa anomalijama uočenim kod fetusa iz ovde prikazanog slučaja. Naša studija doprinosi daljoj kliničkoj karakterizaciji parcijalne trizomije 12q.

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Zaključak. Prenatalno uočena jedna pupčana arterija, iskrivljeno stopalo, artrogripoza i ventrikulomegalija treba da ukažu na moguće postojanje aberacije dugog kraka hromozoma 12.

Ključne reči:
trudnoća; ultrasonografija, prenatalna; hromozom 2, monozomija 2q; hromozom 12, trizomija 12q.

Introduction

Unbalanced chromosomal aberrations are rare findings at prenatal diagnosis but they have a significant clinical impact. Partial monosomy 2q and partial trisomy 12q is rarely described in literature. So far, only three cases with partial trisomy 12q24.2 have been seen prenatally [1–3]. We present case on prenatal ultrasound findings in two consecutive pregnancies of a women carrier of balanced translocation t(2;12)(q37.3;q24.2). Since the fetuses were affected with similar pattern of congenital anomalies our findings contribute to further clinical delineation of partial trisomy 12q.

Case report

A 35-year-old pregnant woman was referred for genetic counseling in her third pregnancy due to sonographic anomalies detected in fetus. The women and her partner were healthy and non-consanguineous Caucasians. The first pregnancy of the couple resulted in birth of a healthy boy. In the second pregnancy, first trimester biochemical screening for chromosomal abnormalities showed increased risk for T21 (1:71). Amniocentesis was performed and karyotype was normal (46,XY, banding level not available) when checked by a local community hospital. Level II ultrasound examination at 22nd week of gestation (w.o.g.) revealed several abnormalities in fetus: bilateral ventriculomegaly, single umbilical artery and bilateral clubfoot. Fetal brain magnetic resonance imaging (MRI) scan was performed and it confirmed presence of moderate symmetrical bilateral ventriculomegaly with hypoplasia of corpus callosum rostral part. Pregnancy was terminated at 26 w.o.g. due to multiple fetal anomalies on parents request.

During third pregnancy, fetal ultrasound examination at 14th + 5 w.o.g. showed presence of hyperechogenic focus in the left cardiac ventricle, single umbilical artery, hyperechogenic bowel and unilateral clubfoot with knee joint ankylosis (Figure 1). The fetal biometry was appropriate for gestational age. First trimester biochemical screening was below cut-off for trisomies 13, 18 and 21. At 18th w.o.g., level II ultrasound examination revealed borderline dilatation of lateral ventricles and confirmed previous sonographic findings (Figure 1). Second trimester biochemical screening showed high risk for trisomy 21 (1:86).The pregnancy was terminated at 22nd w.o.g. on parents' request.

Amniocentesis was performed and cytogenetic analyses applying G-banding techniques (550 bands) revealed a derivative chromosome 2 in male fetus. Subsequent cytogenetic analyses of parental lymphocytes showed that paternal karyotype was normal, while maternal karyotype also showed a der(2). Metaphase fluorescence *in situ* hybridization (FISH) studies demonstrated partial trisomy 12q (12q24.2→qter) and partial monosomy 2q (2q37.3→qter) in the fetus, resulting from an unbalanced segregation of a maternal balanced translocation t(2;12)(q37.3;q24.2) (Figure 2). Fluorescence *in situ* hybridization using a subtelomeric probe for chromosome 2qter (Abbott, Vysis) and whole chromosome paints for chromosomes 2 and 12 (home made probes) confirmed the findings (Figure 2).

The study follows the principles of Declaration of Helsinki.

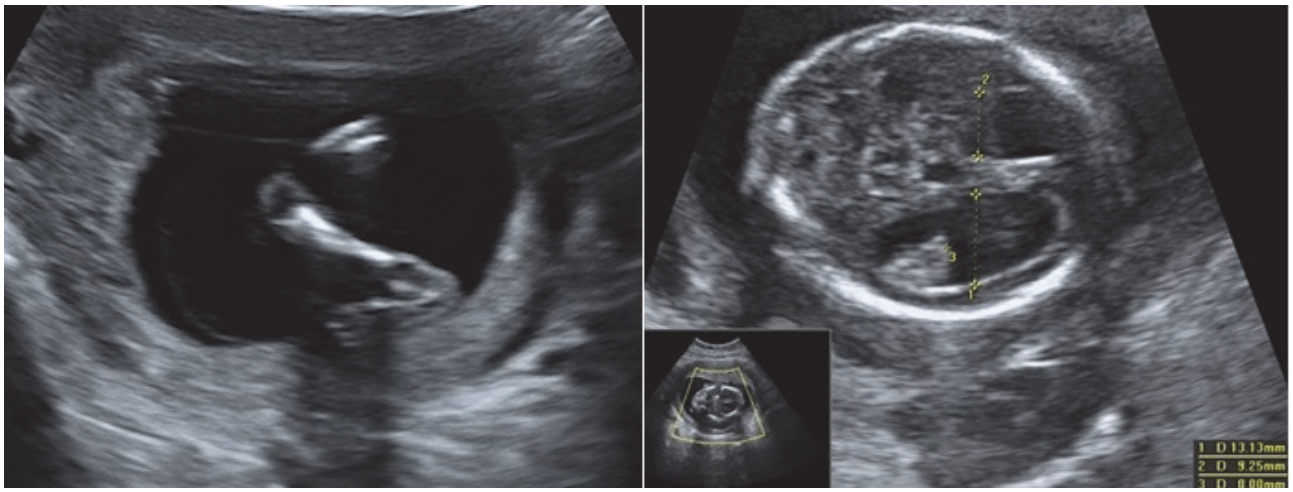

Fig. 1 – Ultrasound image showing: A) clubfoot, and B) ventriculomegaly.

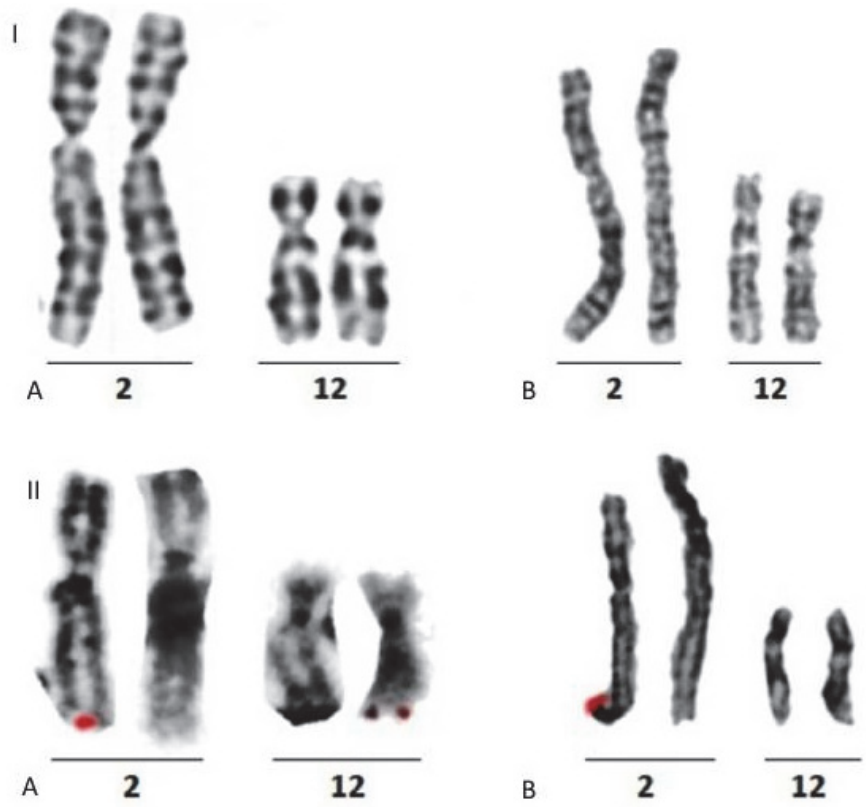

Fig. 2 – Part I: Maternal chromosomes showing balanced 2;12 translocation (A). Fetal chromosomes showing der (2) (B); Part II: fluorescence *in situ* hibridization (FISH) results of balanced and unbalanced situation as present in mother (A), and fetus (B), respectively. Only FISH results for subtelomeric probe 12qter (subtel12qter) are depicted.

Discussion

To date, this is the first case report of early prenatal manifestations of partial trisomy 12q24.2-12qter and partial monosomy 2q37.3-2qter. Although karyotype of the first fetus was reported as normal, based on pattern of detected anomalies in the fetus as well as fact that mother is a balanced translocation carrier, we suggest that it also carried der(2), but that due to relatively small size of translocated segments it escaped detection. Occurrence of almost identical fetal abnormalities in two consecutive pregnancies described here (single umbilical artery, clubfoot and bilateral borderline ventriculomegaly), further contributes to the efforts to establish the partial trisomy 12q as a clinically recognizable syndrome. As the imbalance on chromosome 2 is according to FISH only in the range of 2–3Mb, literature search was concentrated on partial trisomy 12q only. The latter retrieved three more cases with prenatally diagnosed duplication of similar 12q segment. Peng et al. [3] described male fetus who had partial trisomy 12q21.2-12qter with prenatal sonographic findings of thick nuchal fold, pericardial effusion, arthrogryposis, single umbilical artery, micropenis and ventriculomegaly. Chen et al. [1] reported a case of partial duplication 12q24.32-12qter in a male fetus with microcephaly, cerebellar hypoplasia, borderline ventriculomegaly, micrognathia, ventricular septal defect (VSD) and rocker-bottom feet. Third case of partial duplication 12q24.21-12qter presented prenatally was described with single umbilical artery, micrognathia, ventriculomegaly, thick nuchal fold and coarctation of the aorta [2]. Although chromosomes involved in rearrangements, as well breakpoints on chromosome 12 differ among described cases, it is plausible to assume that central nervous system (CNS) malformations (ventriculomegaly, corpus callosum hypoplasia/agenesis, cerebellar hypoplasia), foot deformity and absence of one umbilical artery can comprise a basis of prenatal manifestations for 12q duplication syndrome. Also, in several cases of postnataly diagnosed duplication 12q corpus callosum anomalies (hypoplasia, partial agenesis) and foot malformations have been described [4, 5]. Phenotypic contribution of monosomy 2q37.3 cannot be excluded in our cases, but based on literature review of case reports with pure duplications involving 12q24 region we believe that described anomalies are more consistent with partial trisomy 12q [6–9].

Conclusion

Additional studies are needed in order to make more precise genotype-phenotype correlations, but prenatal detection of single umbilical artery, clubfoot, arthogryposis and ventriculomegaly should alert suspicion to chromosome 12q aberrations.

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