A case report of prenatally diagnosed tetrasomy 18p

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Abstract
Two copies of the p arm of the 18th chromosome form a rare genetic disorder called isochromosome 18p or 18p tetrasomy. This genetic malformation is found in approximately 1:140 000 live births but like other chromosomal malformations is probably more frequent in 1st trimester fetuses. Since no specific 1st trimester sonographic features for this disease have been reported to date, such a rare chromosomal malformation may present a real diagnostic challenge in the routine ultrasound-based screening at 11 weeks + 0 days to 13 weeks + 6 days of gestation. Here, we report a case of fetal tetrasomy 18 detected prenatally in a 40 years old woman G8P6. A routine first trimester scan revealed no apparent fetal abnormalities but due to maternal age and low serum concentrations of placental proteins PAPP-A and free beta hCG amniocentesis was performed at 15th weeks of gestation. Conventional karyotyping and fluorescence in situ hybridization confirmed fetal 18p tetrasomy. The only complication of the procedure was fetal bradycardia of 100 bpm, however 3 minutes after the procedure, but fetal heart rate returned to normal values after 5 minutes and remained stable at 140 bpm 40 minutes following the amniocentesis. Unfortunately, after 2 weeks fetal death occurred and was confirmed during ultrasound 18th week scan. Despite several genetically induced malformations in other children of this family, the parental karyotypes were not determined due to the lack of their agreement to genetic testing and no further reproductive plans.

Key words: isochromosome 18p, prenatal diagnosis, tetrasomy 18p

Introduction
Supernumerary isochromosomes that consist of the several copies of the same chromosome arm are very rare genetic disorders [1]. Tetrasomy is one of the most frequent type of supernumerary chromosomes and may affect both genders at an equal rate [2]. Maternal age is one of the most important contributing factors [3]. The malformation occurs usually de novo as a result of nondisjunction which is one of the forms of the failure of homologous chromosome or sister chromatids to separate properly during cell division. Tetrasomy is the failure of sister centromers of one chromosome to separate during meiosis II [4]. The disorder has an estimated prevalence of 1 to 140 000-180 000 [1, 5, 6, 7]. However, due to high early 1st trimester mortality rate related to fetal trisomies, tetrasomy 18 is likely to be more frequent in the first half of gestation [7, 8]. Since no specific 1st trimester sonographic features for this disease have been reported to date, such a rare chromosomal malformation may present a real diagnostic challenge in the routine ultrasound-based screening at 11 weeks + 0 days to 13 weeks + 6 days of gestation.

In neonates affected by tetrasomy several nonspecific morphological abnormalities include: microcephaly, low birth weight, abnormal muscle tone, weakened deep tendon reflexes, strabismus, low set ears, scoliosis and kyphosis as well as developmental and mental retardation [1, 6, 7, 10]. The relatively low mortality rate is probably related to the absence of concomitant severe cardiac and renal malformations in the majority of neonates [10, 11]. In adolescent children with the confirmed tetrasomy 18 many efforts should be directed towards their behavioral management, improving communication and social skills to improve the quality of life of the affected individuals. Prenatal diagnosis is difficult and since the reports on such cases are relatively rare with only approximately 100 cases reported to date we decided to present our own case of fetal tetrasomy 18 confirmed by amniocentesis and chromosomal analysis [12].

Case report
A 40-year-old G8P6 woman was referred to our Maternal-Fetal Medicine Centre for the routine first trimester ultrasound scan at 12 weeks + 3 days of gestation. Because of the advanced maternal age she was included into the population fetal anomaly national screening program which has been started in Poland in 2005. Ultrasound examination with the GE Voluson E6 scanner
and RAB 4-8 MHz volumetric 3D/4D probe (GE, Zipf, Austria) was difficult because of the patient’s obesity (her BMI was 35), but during 30 minutes of scanning we were unable to detect any apparent fetal anomalies. Fetal growth and gestational age were compatible with the patient’s last menstrual period date [Fig. 1].

![Fig. 1. Fetal biometry at 12 weeks + 3 days](image)

Nuchal translucency thickness was assessed according to the Fetal Medicine Foundation guidelines and NT = 1.61 mm, we were also able to demonstrate that both nasal bones were present [Fig. 2].

![Fig. 2. Fetal nuchal translucency measurement: NT = 1.61 mm at 12 weeks+ 3 days. Nasal tip and nasal bone with the parallel hyperechogenic line of nasal skin are visible](image)

The umbilical cord contained 3 vessels, the placenta appeared normal and ductus venous blood flow examined with the color Doppler revealed normal spectrum for this week of gestation [Fig. 3]. Following ultrasound examination a blood sample with the venipuncture was taken for PAPP-A and free beta hCG assessment. The assay was performed with the use of FMF approved placental protein kits and Cobas 601 analyzer (both Roche, Switzerland). Both placental proteins assessed in the maternal blood serum had low values for the gestational age with free beta hCG = 18.4 IU/l (0.534 MoM) and PAPP-A = 1.454 IU/l (0.289 MoM).

![Fig. 3. Normal fetal heart rate of 140 bpm and normal ductus venosus blood flow spectrum at 12 weeks + 3 days](image)

The risks of trisomy 21, 18 i 13 were calculated with the FMF licensed software v.2.8.0. The calculated risk of trisomy 21 was 1 : 382, for the trisomy 18 the was 1 : 131 and for the trisomy 13 the risk was calculated at 1 : 646.

Because of the high risk of trisomy 18 (Edward’s syndrome) amniocentesis was performed at 14 weeks + 3 days of gestation to identify fetal karyotype. Before the procedure we performed transabdominal ultrasound fetal examination with same scanner and probe and found that the fetal growth was concordant with the menstrual age and that the fetal heart rate was 156 bpm. Amniocentesis was difficult due to patient’s obesity, fetal position in the uterine cavity and relatively low amount of amniotic fluid. A supra-T needle (0.8 × 120 mm, TSK Labs, Japan) was used for amniopunction. Following the visualization of the needle tip in an amniotic fluid pocket free of umbilical cord and fetal parts a sample of 14 ml of clear amniotic fluid was drawn [Fig. 4].

![Fig. 4. Amniopunction at 14 weeks + 3 days. A white tip of the needle in the amniotic fluid pocket and the needle path are well visible (“hand” markers)](image)
After the completion of the procedure fetal bradycardia was shown with the fetal heart rate of app. 100 beats per minute, which increased to 144 bpm after 5 minutes and remained within normal range after 40 minutes [Fig. 5].

No other complications of the amniocentesis were recorded. The patient reported no pain and/or uterine contractions during next 2 hours observation period and was discharged home. However, during the next obstetrical ultrasound at 18th week of gestation no fetal heart rate was detected and fetal death was confirmed at approximately 16 weeks + 3 days.

The karyotyping results obtained by Giemsa trypsin banding (GTG) and fluorescence in situ hybridization (Genos Medical Genetics Laboratory, Łódź, POLAND) confirmed tetrasomy 18p [Fig. 6].

The characterization of the marker chromosome using only conventional cytogenetic methods was difficult. Therefore, molecular cytogenetic techniques were applied to metaphase chromosomes preparations. The marker was identified with the use of Fluorescence In Situ Hybridization (FISH) and it turned out to be a monocentric isochromosome 18p (47,XY,+i(18)(p10)). Guidelines provided by the International System for Human Cytogenetic Nomenclature (ISCN 2009) [13] were used to analyze chromosomal structure.

The mother and father of the proband weren’t tested to determine if the i(18p) was inherited from one of them and to accurately assess the recurrence risk of the tetrasomy 18p in the possible further pregnancies. Both of them refused further genetic testing, they explained their decision by having no future reproductive plans.

**Discussion**

Due to clinical symptoms variety and its rarity the prenatal diagnosis of tetrasomy 18 remains a clinical challenge. To date, only less than 100 cases have been reported in the literature and a vast majority of them were diagnosed postnatally. The clinical features of this disorder vary with the combination of central nervous system defects with accompanying mental retardation, facial and head malformations such as microcephaly with low-set ears, scoliosis and kyphosis were among the most commonly reported. Abnormal muscle tone and spasticity of lower limbs with delayed ability to stand and walk were also described in affected cases. We report here a case of fetal tetrasomy at 18p detected during routine antenatal screening program.

The reproductive history of this family indicates several genetic-related disorders and congenital malformations in previous pregnancies. The sixth child born in this family, a male who is now 4-years-old, was born with severe anatomical malformations including mild facial dysmorphism, myelomeningocele, hydrocephaly, spasticity of the lower limbs, neurogenic bladder, spasticity of the anus sphincter, ribs deformations, developmental delay, mild-to-moderate mental retardation and delayed ability to stand and walk. Most of these anatomical malformations were detected during the last ultrasound examination performed at 40 weeks of gestation. The
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karyotype of this male is unknown. Unfortunately, despite apparent need to extend genetic investigation in this family, the parents and, especially the mother, refused to have a genetic counseling and determination of their karyotypes. In the same family, the oldest son of the patient and his brother are affected with haemophilia, which is another genetically transmitted disorder. However, haemophilia does not seem to have any apparent relationship with the presented case of fetal tetrasomy 18p because hemophilia is the chromosome X-linked disorder which is inherited in a recessive manner.

The disorder is usually developing by the de novo formation as in most reported cases both parents had normal karyotypes. It is also possible to develop from inherited mosaic karyotypes [14]. Unfortunately, in the presented case the parental karyotypes were not determined due to lack of their agreement to genetic testing and no further reproductive plans. With an increased parental age the risk of centromeric nondisjunction and/or chromosome 18 misdivision during meiosis II is substantially elevated and eventually may result in tetrasomy 18p [4].

Sebold et al. [2] presented a review of genotypic and phenotypic variants in 43 cases of tetrasomy 18. Detailed molecular analysis showed that in 43 cases 4 copies of the whole p arm of the chromosome 18 were present whereas in one case was trisomic with the section of proximal arm 18q. In this series the rate of fetal cardiac defect was 12.3% and the most common anomalies included patent foramen ovale, atrioventricular septal defect accompanied by mitral and tricuspid valve regurgitation or stenosis. Moreover, review of the literature indicates that combined fetal heart anomalies are rare in tetrasomy 18 reported cases. For the more detailed information on chromosome 18 related pathology the reader is directed to an excellent and the most recent work of Soileau et al. [15] from the Chromosome 18 Clinical Research Center. The Authors have recently presented data on 483 patients with various chromosome 18 defects. Each of the affected individuals had one of the following conditions:18q-; 18p-, tetrasomy 18p and Ring 18. Interestingly, in this review only 23 patients died of the disease complications. Additionally, a report on the living situation with educational and behavioral phenotype of the 151 patients who are older than 18 years is presented.

Diagnosis of a rare genetic disorder such as tetrasomy can be suspected in late pregnancy if multiple anomalies accompanied by IUGR are found during routine sonographic assessment. A good illustration of such a case has been recently reported by Jung et al. [16], who presented a case of a 28-years old-Korean woman referred at 33/34 weeks of gestation to rule out congenital heart defect with the confirmed intrauterine fetal growth retardation. The fetus had anemia and multiple anomalies which included cardiomegaly and imperforated anus. Fluorescent in situ hybridization along with conventional karyotyping confirmed fetal tetrasomy 18p.

Prenatal genetic counselling should include the information on rare genetic conditions because the final identification of chromosomal abnormality being the reason of neonatal and children maldevelopment is found in many cases. The affected families are often left with more questions than answers when it comes to detailed explanation of the very rare conditions, like the case of fetal tetrasomy 18. Lack of agreement for parental genetic testing such as in the presented case poses another problem, not for the parents who claim that they are not planning any future pregnancies, but for their children’s future. On the other hand, extremely rare chromosomal abnormalities do not allow detailed studying longitudinal data on fetal or children development which makes counselling to these families problematic.

References


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