CASE REPORTS

Prenatal Diagnosis and Genetic Counselling in Turner Syndrome: Case Report and Literature Review

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Abstract

Introduction: Turner Syndrome is the most frequent sexual aneuploidy which affects feminine fetuses, and is represented by a total or partial X monosomy, with or without cellular mosaicism. The wide range of differences between mortality and morbidity corresponding to different Turner karyotypes, sustain the high need for a prenatal diagnosis and an adequate genetic counselling. **Material and method:** We present the case of a IIG IP, 23 years old, with a combined test presenting high risk for Down Syndrome (1:45), Panorama NIPT with a result of high risk for an aneuploidy, with no pathology seen on first trimester fetal ultrasound. The certainty diagnosis came after the analysis of the amniotic liquid, Turner syndrome karyotype (mos 45,X/46,X,i(X)(q10). The article also presents a review of the latest international literature on the subject. **Conclusions:** The main method for diagnosing Turner syndrome antenatally is represented by characteristic fetal ultrasound findings. Nonetheless, modern screening and diagnosis methods should not be neglected. An adequate and informed genetic counselling, based on the karyotype can help lower the abortion rates and raise the life quality for Turner syndrome patients.

Keywords: Syndrome, Turner, Down, prenatal diagnosis, fetuses

Rezumat

Introducere: Sindromul Turner este cea mai frecventă aneuploidie heterozomală ce afectează fetusii de sex feminin, fiind reprezentată de o monosomie X totală sau parțială, cu sau fără mosaicism celular. Diferențele semnificative ale mortalității și morbidității pre și postnatale, în funcție de cariotipul fătului cu sindrom Turner, susțin nevoia ridicată a unui diagnostic și counselling genetic adecvat. **Material și metodă:** Se prezintă cazul unei IIG IP în vârstă de 23 ani, cu un test combinat prezentând risc crescut de Sindrom Down (1:45), testare prenatală noninvazivă, Panorama, cu rezultat risc crescut de aneuploidie cromozomială, fără modificări ecografice ale morfologiei de trimestru I. Diagnosticul de certitudine obținut prin analiza citogenetică din lichid amniotic a identificat un cariotip cu sindrom Turner (mos 45,X/46,X,i(X)(q10). Totodată articolul de față reprezintă un review al literaturii de specialitate de dată recentă pe subiectul propus. **Concluzii:** Principala metodă de descoperire prenatală a sindromului Turner este reprezentată de descoperirea modificărilor ecografice caracteristice cu confirmare prin cariotipare. Totuși, nu trebuie neglijată importanța metodelor de screening și diagnostic prenatal disponibile la momentul actual – dublu și triplu test, testare prenatală noninvazivă, amniocenteză și biopsie de vilozități) ce pot duce la descoperirea întâmplătoare a feților afectați. Un counselling genetic informat și adecvat tipului de cariotip poate duce la scăderea ratei de avorturi medicale și creșterea calității vieții feților cu sindrom Turner.

Cuvinte cheie: Sindrom, Turner, Down, diagnostic prenatal, fetuși

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INTRODUCTION

The first paper describing female patients with Turner syndrome (TS) was published in 1938 by Henry Turner[1]. It was later discovered that in 1930, Otto Ullrich had already reported a case report of a girl with suggestive symptoms of TS[2]. Therefore, the complete name is Ullrich-Turner syndrome.

Turner's syndrome is a pathology found only in females, characterized by the partial or total absence of a second sex chromosome which leads to a wide range of physical findings that often includes congenital lymphedema, short stature, and gonadal dysgenesis[1]. The physical symptoms depend on the karyotype, as only 50% of Turner patients are 45,X the others displaying mosaics or abnormalities in the second sex chromosome.

The most common sex chromosome aneuploidy in female fetuses, TS approximately affects 1 in 1500-2500 female live births but only around 1% of fetuses with TS are born at term, alive[3,4]. It is now believed that almost 15% of spontaneous miscarriages have a TS karyotype[5].

The antenatal identification of TS was demonstrated as possible with multiple biochemical marker screening (combined test or triple test)[6]. The most useful and cost-effective method of screening is the ultrasound, with typical findings as cystic hygroma and hydrops due to the insufficiency of lymphogenic genes, renal and cardiac defects[7]. The only diagnostic method is karyotype confirmation through amniocentesis or chorionic villus sampling.

CASE REPORT

We present the case of a 23 years old IIG IP, with no personal or family history of aneuploidies. The current pregnancy was spontaneous obtained, 6 months after a 5 weeks spontaneous miscarriage. At the first trimester ultrasound, there were no abnormal findings (nuchal translucence = 2,83 mm, visible nasal bone). The only minor discovery was a tachycardic pulse of 179 bpm. The combined test revealed a high risk for trisomy 21 (1:45). PAPP-A was 0.49 MOM and Free bHCG 0.89 MOM. The mother chose to have a non-invasive prenatal test (Panorama) done. The result was high-risk for aneuploidy.

Amniocentesis was the next step for a specific diagnosis. For the 18,X,Y chromosomes, 100 cells were analysed by 2 independent examiners. In 44 of the cells

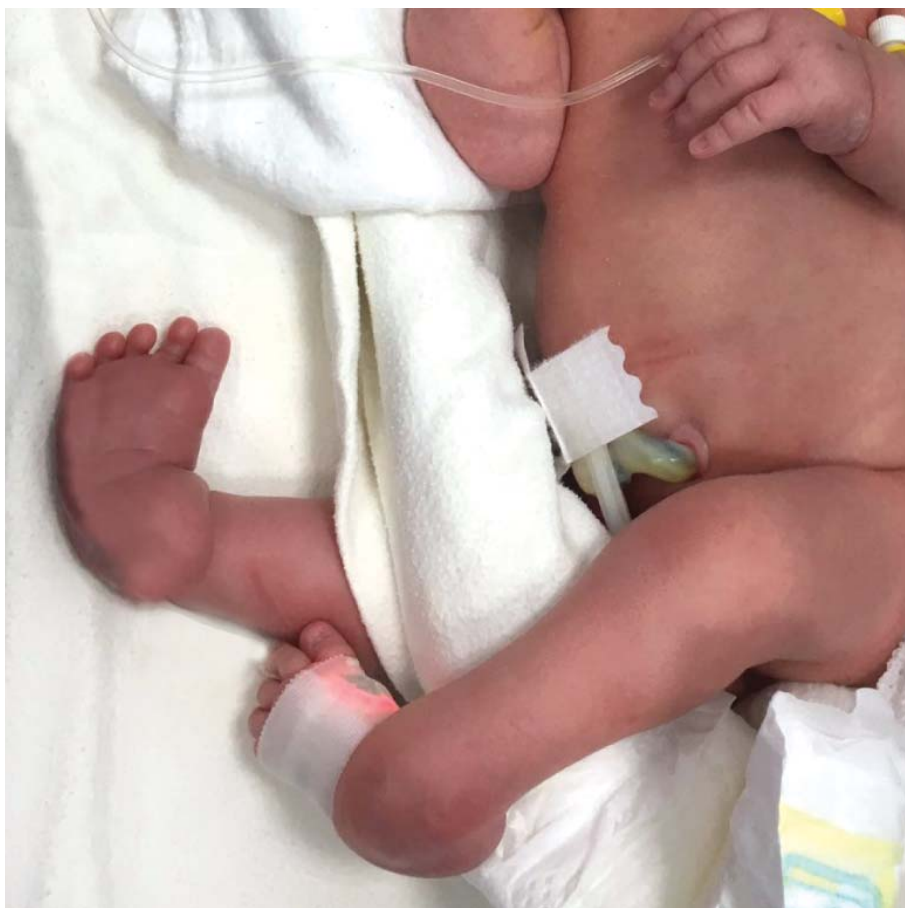

Figure 1. Bilateral var equin feet.

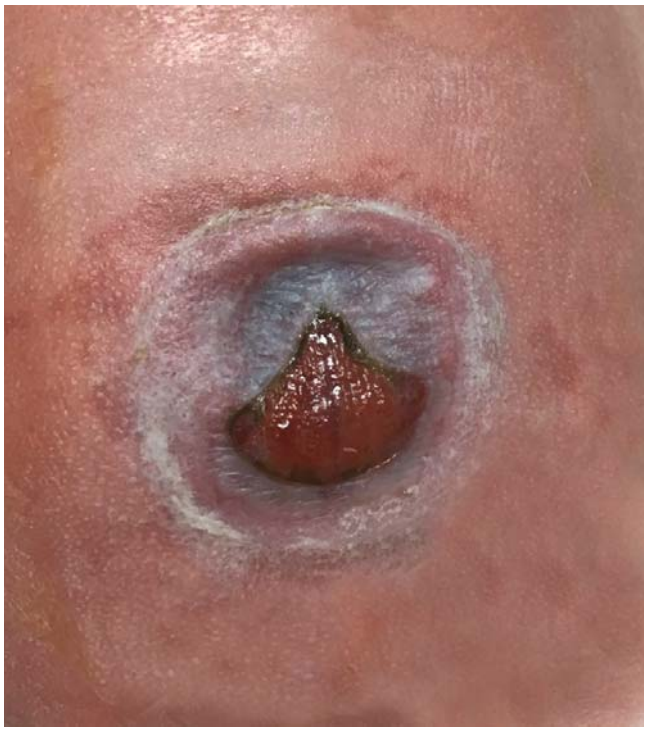

Figure 2. Spina bifida defect.

2 signals were observed for chromosome 18, 1 signal for chromosome X and the probe for chromosome Y presented no hybridization signal. In 56 of the cells 2 signals were seen for chromosomes 18 and X and no signal for Y. The FISH result was X monosomy in a 44% mosaic.

For the karyotype from amniotic liquid, 27 metaphases were analysed and 10 were karyotyped. The cytogenetic analysis from the fetus revealed a feminine karyotype. In 4 of the examined metaphases a single X chromosome was identified, whereas in the rest 23 a normal X chromosome was identified and the other one with a structural modification, the chromosome only having the long arms. The results of the cytogenetic analysis identified a TS karyotype in the form of mos 45,X[4]/46,X,i(X)(q10)[23].

The patient and her spouse also received karyotype analysis with normal (46 X,X and 46 X,Y) results.

Genetic counselling was offered, the pathology – a life compatible aneuploidy- and its complications were all explained to the family, and they decided to continue the pregnancy.

On the second trimester ultrasound, both feet's were seen in var equin position and a spina bifida was also discovered.

Until 36 weeks the pregnancy evolved normally. At a routine ultrasound, intrauterine growth restriction – IUGR-(36,2 weeks chronological, 34.2 weeks biometric), oligohydramnios (AFI = 7.9 cm) and Doppler modification (RI-AO = 0,72 RI-ACM = 0.74) were noted. A caesarean section for IUGR and fetal distress was decided to be done.

A live, female, G=2260g, IA=8, 48 cm long, with bilateral varequin feet (Figure 1) and spina bifida (Figure 2) (2 cm on the exterior side, ulcerated, from with blood and cerebrospinal liquid are evacuated – meningocele 3/3 cm) was born. On the abdominal ultrasound bilateral hydronephrosis was discovered (grade IV on the left side and grade II on the right).

Two days later the newborn was transferred to a pediatric surgery hospital in order to continue the therapeutic conduct for the spina bifida.

DISCUSSION

In the case presented the first analysis that identified the risk for an aneuploidy was the combined test with was done at 12 weeks of pregnancy. Devereaux et al demonstrated in a study from 1992 that in TS pregnancies with hydrops the level of bHCG is elevated and in the ones without it is reduced[8]. In another study of 27,282 triple tests, Wenstrom et al correlated the TS diagnostication with a high risk for Down syndrome, showing in this way that combined and triple tests are screening methods not only for 21, 13 and 18 syndromes but also for TS9. In trisomies low PAPP-A values are seen, which typically is 0.49 for Turner's syndrome (the exact value seen in our patient). Shiefa et al concluded in one of his studies that multiple marker screening can detect TS in more than 90% of cases[10].

On the matter of fetal ultrasound one study on 69 cases presented signs on 68.1% of fetuses. The main congenital anomalies found on ultrasound cystic hygroma; congenital heart and renal anomalies were also noted. Of the 22 cases with no ultrasound signs 20 proved to have mosaic karyotype[11]. Marcin et al concluded that statistically significant differences were found between euploidy and TS fetuses in terms of nuchal translucency (1.7 vs 8.8 mm) and fetal heart rate (150 versus 171 beats per minute)[12].

Spina bifida was not found to be correlated in the international literature with TS. Skeletal dysplasia is also an unspecific finding.

In 2012, Subhashi created a study on 33 TS cases, with the purpose to reveal the phenotypic differences of the karyotypes. The study showed that X isochromosome karyotype does not present the neonatal specific signs – hygroma, webbed neck, oedema). Pertaining the physical findings in adolescent years, short stature was present in 100% of cases, primary amenorrhea

in 66% and secondary in 34%. The prevalence of renal and cardiac complications were also lower that 45,X karyotype[13].

Non-invasive prenatal testing from cell free fetal DNA is the new era method with more and more studies being released. Specificity and sensibility seem to be very high even for sex chromosome aneuploidies.

With the widespread availability of prenatal ultrasound and prenatal diagnosis by amniocentesis or chorionic villous sampling, obstetricians are often involved in the process of genetic counselling. The international literature has very few studies with evaluate prenatal counselling in cases of TS. Robinson et al. suggests that in cases of sex chromosome anomalies, parents who are counselled by a clinical geneticist are less likely to decide to terminate the pregnancy[14]. A more recent study of 61 couples with a prenatal diagnosis of TS concluded that 100% chose to terminate a pregnancy with a 45,X karyotype whereas mosaic karyotype pregnancies were terminated in only 50% of cases[15].

CONCLUSIONS

Turner Syndrome diagnosis is possible prenatal even when the specific ultrasound signs are absent.

Spontaneous miscarriages and fetal intrauterine death is less likely to happen in a mosaic karyotype. Also mosaic phenotype suggests a bigger surviving chance and a better quality of life.

Correct and clear genetic counselling offers the families the chance of a well-informed decision, in agreement with the new trend of the participative medicine.

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