CASE REPORT

A Case of Prenatal Diagnosis of Turner Syndrome with Ultrasonography

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Abstract

Objective: To report a case of Turner syndrome diagnosed in prenatal care.

Method: A case report.

Case: Case of Mrs. Y 26-year-old woman G2P1A0L1 diagnosed on 19-20 weeks of gestation with Turner syndrome. Ultrasound examination findings were hydrops fetalis on the neck region, multiple septated cystic masses, subcutaneous edema, ascites, and hydrothorax. Subsequently, amniocentesis was performed and the chromosome analysis result showed Turner syndrome (45, X0). The patient was induced vaginal delivery on 22-23 weeks of pregnancy due to intrauterine fetal death indication. The baby was born with ambiguous genitalia, birth weight 500 grams, birth length 22 centimeters, and Apgar’s score was 0/0. The congenital anomalies discovered include subcutaneous edema, ascites, hydromacolony, and hydrops fetalis.

Conclusion: Turner syndrome can be diagnosed at a prenatal period by ultrasound examination.

Keywords: Turner Syndrome, Hydrops Fetalis, Ultrasonography

INTRODUCTION

Turner syndrome, first described by Henry Turner in 1938, is one of the most common monosomies in fetuses. This syndrome is associated with the abnormal karyotype 45, X0 observed in 1959. The incidence of Turner syndrome at conception is about 3%. Turner syndrome has an incidence rate of 1: 2,500 female babies born alive.1

Based on cytogenetic analysis, more than half of Turner syndrome cases have pure X monosomy. 20-30% of cases have structural abnormalities on the X chromosome, such as rings, isochromosomes in long arms, and partial deletions of short arms; and 30-40% have a mosaic pattern (a karyotype that has two or more distinctive cell types). The most common mosaic patterns were 45, X / 46, XX or 45, X / 46, XY.2 Congenital anomalies were detected more frequently in fetuses with 45, X0 pure compared with the mosaic pattern. Patients with a Y chromosome can have ambiguous genitalia and are at risk of developing gonadoblastoma in their dysgenetic gonads. X chromosome structural abnormalities are seen in 10% to 20% of cases and often involve a mosaic pattern. The fact that these patients have more than one cell line may explain the variability in the phenotype of the individual.
diagnosed with Turner syndrome. The nondisjunction that most commonly causes Turner syndrome is unrelated to the age of either parent. There is no increased risk of subsequent pregnancies for other fetuses with chromosomal abnormalities.3,4

Several studies have been conducted to determine the pathophysiology that occurs in Turner's syndrome. A review conducted by Viuff et al in 2018 described the pathophysiology of Turner syndrome. Monosomy X usually occurs spontaneously or de-novo due to non-disjunction in the process of cell division in Meiosis. Starting from an X chromosome imbalance requires a mechanism to equalize the dose of genes between the sexes and relative to the autosome to avoid potentially useless double doses. This mechanism involves inactivation of the X chromosome, and upregulation of the X chromosome leading to increased gene expression on a single active X chromosome in males or females. All genes in PAR1 (escape gene) escape X inactivation and are therefore candidates for the etiology of Turner syndrome. The initial stage of X inactivation is regulated by the XIST gene. Inactive X-specific transcript gene (XIST) was significantly decreased (p <0.0001) in Turner syndrome. Other genes involved such as SHOX, NFATC3, IGFBP5, LDLR receptors support the phenotypic abnormalities in Turner syndrome.5,6,7

Figure 1. Current phenotype and genomic understanding of Turner's syndrome.5

Infants with Turner syndrome tend to have clinical characteristics of short stature, short neck, cubitus valgus, pterygium colli, low hairline, leg edema, hyperconvex nails, characteristic dermatoglyphs, gonadal dysgenesis, cardiovascular disorders, renal malformations, pigmented navi, eyelid ptosis, hearing loss, Hashimoto's thyroiditis and carbohydrate intolerance.8 The clinical features vary widely, depending on the age at diagnosis. In most patients diagnosed prenatally, the diagnosis is made on the basis of an abnormal karyotype and / or the discovery of a cystic hygroma, hydrops fetalis, or cardiac defect on ultrasound examination. A definite diagnosis is confirmed by means of chromosome analysis (karyotype) with or without FISH. Girls diagnosed in infancy almost always have lymphedema, with / or without a webbed neck and other dysmorphic features. In contrast, girls who do not experience the classic features often go undiagnosed until late
childhood or as adolescence with complaints of short stature and/or late puberty, or in adulthood when they experience ovarian failure (late puberty, primary amenorrhoea).9

The diagnosis of Turner syndrome is made based on clinical features and chromosome analysis (karyotype with or without FISH). Based on the chromosome results, there are two types of Turner syndrome: 1) classic Turner syndrome with analysis of chromosomes 45, X0 or 46, XiXq 2) Turner mosaic syndrome with analysis of chromosome 45, X0 with additional cell lines such as 45, X / 46, XX; 45, X / 46, X, i (X) and 45, X / 46, XY. The clinical picture in mosaic Turner syndrome is lighter than classic Turner syndrome.10

Ultrasonography (USG) has been reported in many studies to be a reliable tool in diagnosing Turner syndrome in the prenatal period. Common ultrasound features reported in fetuses with Turner syndrome include cystic hygroma, increased nuchal translucency (NT) thickness, non-immune fetal hydrops, renal and cardiac defects, leg anomalies, and other rare structural anomalies. Although some of the sonographic markers mentioned are transient, which can also be lost in the later stages of pregnancy, detection of these markers in early pregnancy can alert obstetricians to the importance of these markers in Turner's syndrome.1,2,8,9,10 However, confirmatory testing with amniocentesis or chorionic villi sampling is required to aid in the prenatal diagnosis of Turner syndrome. However, it is mandatory to repeat the postnatal karyotype in all individuals previously diagnosed before birth. Noninvasive prenatal testing using maternal free-cell DNA has not been shown to have a good positive predictive value for diagnosing Turner syndrome and so it is not recommended to do so.6,7

Table 1. Prenatal Ultrasound Overview of Turner Syndrome and Differential Diagnosis2

<table>
<thead>
<tr>
<th>Prenatal sonographic features</th>
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<tbody>
<tr>
<td>Increased nuchal translucency</td>
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<tr>
<td>Cystic hygroma</td>
</tr>
<tr>
<td>Non-immune hydrops fetalis</td>
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<tr>
<td>Cardiovascular anomalies</td>
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<tr>
<td>Aortic coarctation, hypoplastic left heart syndrome, atrioventricular septal defect, tricuspid regurgitation, bicuspid aortic valve, partial pulmonary venous return anomaly, tetralogy of Fallot, right ventricular dilatation, etc.</td>
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<tr>
<td>Urinary system anomaly</td>
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<tr>
<td>Horseshoe kidney, bladder malformation, multicystic dysplastic kidney, etc.</td>
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<tr>
<td>Limb anomaly</td>
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<tr>
<td>The femur is short</td>
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<td>Another rare structural anomaly</td>
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<tr>
<td>Central nervous system anomalies: hydrocephalus, enlarged cisterna magna, ventriculomegaly</td>
</tr>
<tr>
<td>Abdominal wall defects: omphalocele, gastroschisis</td>
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<tr>
<td>Lung defect</td>
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Differential Diagnosis
Cystic hygroma not associated with Turner's syndrome
Non-immune related hydrops fetalis non-Turner syndrome
Noonan Syndrome

There is no genetic therapy to correct the genetic disorder in Turner syndrome. However, multidisciplinary therapy including pediatricians, endocrinology, ophthalmology, otolaryngology, cardiology, genetics, psychology, gynecology and reproduction is recommended for patients born with Turner syndrome to have a good lifespan and quality of life. Currently, growth hormone therapy and estrogen hormone replacement therapy are the basic therapies for patients born with Turner syndrome. Most conceptuses with Turner syndrome have spontaneous abortion, and only 1% of these embryos survive term.2,10,11 However, the long-term prognosis for infants born with Turner syndrome is good. Life expectancy is shorter than the average age of the normal population, but can increase with better multidisciplinary management and management of comorbidities such as obesity and hypertension. Regular follow-up can improve the quality and age of children with Turner syndrome.9

CASE REPORT
Mrs. Y, 26 years old with gravid G2P1A0H1 19-20 weeks came to the fetomaternal polyclinic on 21 August 2019 and performed an ultrasound examination (USG), obtained an image of a single live fetus intrauterine, with fetal biometry; BPD (Biparietal Diameter) 44 mm, FL (Femur Length) 29 mm, AC (Abdominal Circumferential) 161 mm, HC (Circumferential Head) 138 mm, EFW (Estimation Fetal Weight) 327 grams, SDP (Single Deepest Pocket) 18 mm, and FHR (Fetal Heart Rate) 168x / minute, gravid 19-20 weeks, live fetus, fetal biometry according to gestational age, and placenta implanted in grade II posterior corpus. On ultrasound examination, fetal hydrops were seen in the neck region, multiple cystic hygromas with septum, subcutic edema, ascites, and hydrothorax and diagnosed fetal hydrops with a suspected Turner syndrome. The findings were described to the patient and the patient opted for ultrasound guided amniocentesis because of the presence of several congenital anomalies that were suspected of suggesting Turner syndrome on ultrasound examination.
Figure 2. a) Fetal biometry. BPD = 44 mm, FL = 29 mm, AC = 161 mm, HC = 138 mm, EFW = 327 grams, and FHR = 168x / minute. Gravid 19-20 weeks, live fetus, fetal biometry according to gestational age, and placenta implanted in grade II posterior corpus. b) Description of phenotypic abnormalities in the fetus with Turner syndrome. There were hydrops fetalis in the neck region, multiple cystic hygromas with septum, subcutic edema, ascites, and hydrothorax. c) Picture of SDP in fetuses with Turner syndrome. SDP = 18 mm.

Amniocentesis was carried out on August 28, 2019. The diagnosis of Turner's syndrome was confirmed through chromosome analysis carried out on samples derived from amniotic fluid. With the G-Banding technique, the chromosomes of 40 cells from 3 different cell culture preparations from the sub-culture were studied, and the number of chromosomes in each studied cell was 45, X0. This means that the number of chromosomes is 45 with one X chromosome (X monosomy) whose clinical symptoms correspond to Turner's syndrome.

Monosomy X usually occurs spontaneously or de-novo due to non-disjuction in the process of cell division in Meiosis. The recurrence rate was very small and was not passed on for the patient's parents. For this reason, chromosome examination of the patient's parents is not necessary.
The patient returned to control on September 18, 2019 at 22-23 weeks of gestation, with complaints of fetal movement that were not felt, and without signs of labor. Another ultrasound examination was performed and an IUFD (Intrauterine Fetal Death) was obtained. Then planned for pregnancy termination after laboratory examination.

On 23 September 2019 the patient was treated at the Gynecology Ward, Dr. M. Djamil Padang for planning pregnancy termination based on IUFD indication. Then performed labor induction, and catheter placement. After that the catheter balloon is released, followed by the progress of labor and birth vaginally. Babies born with ambiguous genitalia, birth weight 500 grams, birth length 22 centimeters, and Apgar Score 0/0. There are congenital disorders of subcutis edema, ascites, hygromacolly and hydrops fetalis.

DISCUSSION

Mrs. Y G2P1A0H1, 26 years old, diagnosed at 19-20 weeks' gestation with Turner syndrome. On ultrasound examination, fetal hydrops in the neck region, multiple cystic
hygromas with septum, subcutaneous edema, ascites, and hydrothorax were performed by amniosynthesis, with the results of chromosomal analysis of Turner syndrome (45, X0). Vaginal induction of labor was performed at 22-23 weeks of gestation as indicated by intrauterine fetal death. Babies born with ambiguous genitalia, birth weight 500 grams, birth length 22 centimeters, Apgar Score 0/0. There are subcutic edema, ascites, hygromacolly and hydrops fetalis.

Turner syndrome is a chromosomal disorder characterized by the absence of part or all of the second sex chromosome in some or all cells. There are two types of Turner syndrome - classic and mosaic. Classic Turner syndrome causes the complete loss of the X chromosome; Mosaic Turner Syndrome indicates that the abnormality occurs only on the X chromosome of a few cells in the body.1,2,4 Turner syndrome is usually not inherited because it occurs during random events during reproductive cell formation in the patient's parents.9 Ultrasound findings in classic Turner syndrome include edema diffuse fetus, cystic hygroma with septation, renal and cardiac abnormalities such as horseshoe kidney and aortic coarctation, non-immune fetal hydrops, short cervical spine, increased nuchal translucency, brachycephaly, hydramnios, and growth restriction. Ultrasonography is the best method to diagnose Turner's syndrome prenatally, genetic amniocentesis or chorionic villus sampling should be performed to confirm the karyotype and establish a definitive diagnosis.1,9,11

Nonimmune Hydrops Fetalis

This case report is presented with several predictors of ultrasound imaging associated with Turner's syndrome including hydrops fetalis in the neck region, multiple cystic hygroma with septum, subcutic edema, abdominal ascites, and hydrothorax. This predictor suggests non-immune hydrops fetalis. Fetal hydrops has been defined as the pathological accumulation of excessive fluid in two or more fetal compartments.1,9,12 These features can be detected ultrasonographically, including scalp and body wall edema (defined as skin thickness greater than 5 mm) ascites, pleural effusions, pericardial effusions, presence of polyhydramnios (amniotic fluid index greater than 25 cm or maximum verticular bag greater than 8 cm), and placental thickening (≥24 cm in the second trimester and ≥6 cm in the third trimester).13

The underlying process in some hydrops fetalis conditions can be explained by dysregulation of fluid movement between the vascular and interstitial spaces, caused by increased interstitial fluid production or decreased lymphatic flow. Hydrops fetalis has a variety of known causes, including haematological disorders, infections, chromosomal abnormalities, congenital abnormalities, and tumors. In Turner syndrome, Hydrops fetalis (25.0%) is the second most common predictor of ultrasound after cystic hygroma.1,9,12,13

Turner syndrome can cause lymphatic vessel dysplasia and obstruction that can lead to the formation of a cystic hygroma. Fetal structural abnormalities in various organ systems, such as the musculoskeletal, neurological, and gastrointestinal systems, have also been
associated with the development of hydrops, although the exact mechanism may not always be known.9

**Cystic Hygroma**

On ultrasound examination of this patient, multiple cystic hygroma with bulkheads were seen. Cystic hygroma is characterized by the accumulation of abnormal fluid behind the neck of the fetus after the second trimester or, occasionally, in the first trimester.1 Cysts often contain thin or rough septa, which appear on the occiput and posterior aspects of the fetal neck with a diameter greater than the biparietal diameter. The etiology of the cystic hygroma is unclear. Although many theories have been described, the most common is that a cystic hygroma occurs due to failure of the jugular lymphatic sac to drain into the internal jugular vein. This causes the internal jugular sac to enlarge, causing obstruction and hydrops fetalis.9,12 The appearance of a cystic hygroma can also vary in size and structure. The characteristic feature is bilateral hypoechoic cystic structures in the posterior nuchal area separated by a thick midline structure corresponding to the nuchal ligament. This fluid cystic compartment may have some fine linear septation.13,14

Research shows that the presence or absence of a barrier is associated with fetal outcomes. The prognosis is much better for the fetus with a decreased nonseptated hygroma at week 16. The theory behind regression is that the increased buildup of lymph substances creates enough pressure to clear the blockage. The resolution of the obstruction is most likely to occur with the smaller cystic hygroma size in the euploid fetus.13,14 With complete obstruction of the lymph duct, an increased volume of lymph fluid accumulates in the subcutaneous neck tissue, leading to visualization of sonographic septation. Since this mass effect extends to the level of the ascending aorta, flow-related cardiac defects are possible. The protein-rich nature of lymph fluid can cause fetal hypoproteinemia, leading to fetal edema and ultimately nonimmune hydrops fetalis. Cystic hygroma, together with hydrops fetalis, will result in a mortality rate of nearly 100%.9,14 Large-insulated hygromas rarely heal spontaneously. In those cases when the cystic septation hygroma heals in utero, the fetus is most likely present at birth with a webbed neck appearance (pterygium colli), a typical finding associated with Turner's syndrome.1,9,14

Evaluation of the second trimester karyotype of cystic fluid in all fetuses with cystic hygroma showed that 86.5% of fetuses were affected by Turner's syndrome, 9.4% had a normal karyotype, 2.7% had trisomy 21, and 1.4% had trisomy 18. The size of the cystic hygroma in a fetus with Turner syndrome is observed to be much larger than that of other chromosomal abnormalities, such as trisomy 18, trisomy 21, or with a normal karyotype. Transvaginal sonographic screening in study by X, of 13 fetuses with Turner syndrome who had a 45, X0 karyotype at 14-16 weeks of gestation revealed that all fetuses had large cystic hygroma, hydrops, and subcutaneous edema.13,14
Chromosome Analysis

The diagnosis of Turner syndrome must be confirmed by collecting amniotic fluid samples (amniocentesis) or chorionic villus sampling for cytogenetic analysis. Amniocentesis in this patient was performed in the second trimester of pregnancy (20-21 weeks). Ultrasonography-guided amniocentesis is essential for the definitive diagnosis and management of chromosomal abnormalities. With the G-Banding technique, the chromosomes of 40 cells from 3 different cell culture preparations from the sub-culture were studied, and the number of chromosomes in each studied cell was 45, pure X0. This means that the number of chromosomes is 45 with one X chromosome (X monosomy) whose clinical symptoms correspond to Turner's syndrome. Monosomy X usually occurs spontaneously or de-novo due to non-disjuction in the process of cell division in Meiosis. The recurrence rate was very small and was not passed on for the patient's parents.

Prognosis

Prenatal diagnosis allows for proper family education and counseling as well as proper care regarding this pregnancy. The prenatal diagnosis of Turner syndrome can vary widely depending on the degree of the abnormality present and how early the syndrome is diagnosed. Turner syndrome is associated with high rates of fetal mortality, with estimates that more than 90% of fetuses do not survive term. Missing or random X chromosome changes. Family history has not been shown to be a risk factor, therefore it is unlikely that parents who have a child with Turner syndrome will have another child with the disorder as well. The overall prognosis for Turner syndrome is variable and largely depends on the anomaly that is present and the severity of the anomaly. Most pregnancies with Turner syndrome result in spontaneous abortion.
syndrome will experience spontaneous abortion in the second trimester of pregnancy. If the anomaly is not diagnosed in utero or is not severe, the fetus can survive the pregnancy and be born alive. Most of these children will have a long life expectancy. If Turner syndrome is diagnosed during childhood, recommendations for an extensive medical examination have been developed to detect the associated anomaly. Children living with Turner syndrome will present with various problems throughout their lives; most of these children will have a short stature which will be seen by the age of 5.5,2,13,8

CONCLUSION
Turner syndrome can be diagnosed in the prenatal period by taking into account the screening of maternal serum markers, and detection of organ abnormalities using ultrasound. Ultrasound is the best method to diagnose Turner syndrome prenatally, genetic amniocentesis or chorionic villus sampling should be performed to confirm the karyotype and establish a definitive diagnosis. There is no genetic therapy for Turner syndrome. Most fetuses with Turner syndrome have spontaneous abortion, and only 1% of these embryos survive term. However, the long-term prognosis for infants born with Turner syndrome is favorable as well as multidisciplinary management.

REFERENCES


