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Turner's Syndrome: A Review

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Abstract

Turner's syndrome is the most common cause of primary amenorrhea seen in clinical practice. The syndrome is characterized by absence of one X chromosome [45X0]. About 50% of the Turner syndrome have mosaic forms such as 45X0/46XX or 45X0/46XY. In a female presenting with primary amenorrhea or short stature, possibility of Turner's syndrome must be ruled out. Turner's syndrome is the only monosomy compatible with life. Patients face manifold difficulties which increase over the lifespan. It is also the most common aneuploidy in first trimester losses. Incidence of Turner's syndrome is estimated to be 1 in 2500. Estrogen therapy is indicated lifelong in a patient with Turner's syndrome.

Keywords: Turner's syndrome; Amenorrhea; Karyotype; Short Stature; Estrogen.

Introduction

45X0 Turner's Syndrome was first described by Turner (1938). This syndrome later was found to be caused by monosomy X (Ford, 1959). The prevalence of Turner's syndrome is approximately 1 in 2500 liveborn girls (Cragan, 2009; Dolk, 2010). The missing X chromosome is paternally derived in 80 percent of cases (Cockwell, 1991; Hassold, 1990).[1] Turner's syndrome is an X chromosomal disorder with variable karyotypic abnormalities and clinical manifestations. The chromosomal basis of Turner's syndrome was first recognized by Ford et al. It is now known that Turner's sydrome is characterized by the presence of a single normal functioning X chromosome. The other X chromosome may be missing or abnormal, or mosaicism may be present, so that the X chromosome anomaly is present in at least one cell line.[2] Deletions involving short or long arm of X chromosome also occur.[3]

In Turner's syndrome ovarian development is normal until 20 weeks of intrauterine life and oocytes are found in the ovaries until this stage. Thereafter there is failure of the oocytes to undergo further maturation which requires the influence of both X chromosomes. In Turner, the karyotype is 45X0 and there is only one X chromosome and the oocytes begins to undergo a process of atresia. This probably continues beyond birth and in some cases till late puberty. The ovary in most individuals at this stage consists mainly of stroma and is therefore unable to produce estrogen. There is normal female type organ development with presence of uterus, tubes and vagina. The loss of one X chromosome is associated with short stature since the determining genes for height are lost. Even with Turner's stigmata, all women are not amenorrheic. This will depend on the degree of deletion of genetic material in X chromosome. The loss of two short or long arm of a chromosome maybe complete or partial and the genetic material lost determines the impact of Turner's features on the patient. For example the

incidence of amenorrhea will be 35% with long arm deletion while it will be only 15% with deletion of short arm of the X chromosome.[4]

Table 1: Characteristic physical findings of turner's syndrome[5]

S. No.	Characteristics
1.	Short stature
2.	Webbing of the neck
3.	Hearing impairments
4.	Presence of epicanthus
5.	Low set of ear and hairline
6.	High arch palate
7.	No breast development
8.	Shield chest with widely spaced nipples
9.	Coarctation of aorta
10.	Streak of ovaries
11.	Horseshoe kidney
12.	Wide carrying angle
13.	Short 4th metatarsal
14.	Scoliosis
15.	Lymphoedema

In Turner's syndrome intelligence scores are generally in the normal range, but affected individuals are at risk for difficulties with visual-spatial organization, nonverbal problem solving, and interpretation of social cues (Jones, 2006).[1]

Diagnostic Features of Turner's Syndrome

- Sexual infantilism and short stature
- Associated abnormalities
- High FSH and LH levels
- Bilateral streak gonads
- Karyotype:

  80% - 45XO

  20% - mosaic form 46XX/45X0.[6]

Evaluation of A Girl With Turner Syndrome

- CVS evaluation
- Thyroid function tests
- Blood sugar – F/PP
- Renal function Tests
- USG-abdomen and pelvis
- Intravenous pyelography
- Bone mineral density at first adult visit
- Continued ECHO and MRI of Aorta to access the surgical correlation of severe aortic root dilatation.[7]

Treatment

With recombinant Human GH use, the average height gain varied from 4 to 16 cm. It appears that early initiation of therapy (between 2 and 8 years of age), gradually increasing the dose, and continuing treatment for a mean of 7 years can lead to achievement of a final height greater than 150 cm in most patients. Therapy may be continued until a satisfactory height is attained or until little growth potential remains.

Table 2: Management of children with turner's syndrome[7]

S. No.	Managements
1.	CVS monitoring and treatment of Congenital heart diseases
2.	GH therapy to augment linear growth
3.	Supplementary therapy
4.	Pediatric audiometry
5.	Annual thyroid function, Liver function test, Glucose monitoring
6.	Orthodontic evaluation for tooth anomalies

Management of Adult Turner's Syndrome

Fertility and sexual development are often major concerns for patients with Turner syndrome.

Transition to Adult Treatment of Turner's Syndrome

- Management of atherogenic cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia)
- Calcium and vit D supplement to prevent osteoporosis
- Sex hormone therapy[7]

Even in the presence of typical Turner's stigmata, a karyotype is indicated to eliminate the possibility of any portion of a Y chromosome. Previous reports have shown that the presence of Y chromosome material is associated with a 12% risk of a gonadoblastoma. If a Y chromosome is identified, laparoscopic prophylactic gonadectomy is recommended at the time of diagnosis to eliminate the risk of malignancy. Although gonadoblastomas are benign tumors with, no metastatic potential that can arise spontaneously in gonads containing a portion of a Y chromosome, they can be precursors to germ cell malignancies, such as dysgerminomas (most commonly), teratomas, embryonal carcinomas, or endodermal sinus tumors. In individuals in whom there is no evidence of neoplastic dissemination, the uterus may be left in situ for donor *in vivo* fertilization and embryo transfer. Individuals with Turner's syndrome are at

increased risk of sudden death from aortic rupture or dissection resulting from cystic medial necrosis during pregnancy, and the risk may be as great as 2% or more. If pregnancy is being considered, preconception assessment must include cardiologic evaluation with MRI of the aorta.[9]

Reproductive Potential in Turner's

Age related counselling about infertility treatments canmarkedly reduce the adverse psychological impact of the diagnosis. *In vitro* fertilization (using oocytes harvested and cryopreserved before ovarian regression is complete) is being studied in young women with Turner's syndrome. Spontaneous or assisted pregnancy carries substantial risks; therefore, preconception counseling and cardiac echocardiography or magnetic resonance imaging (MRI) are essential. Primary care providers should monitor the pregnancy as part of a multidisciplinary team in addition to reproductive counseling.[7]

Discussion

Individuals with various forms of gonadal dysgenesis typically present with hypergonadotropic amenorrhea regardless of extent of pubertal development and the presence or absence of associated anomalies or stigmata. Cytogenetic abnormalities of X chromosome can impair ovarian development.

Patients usually have normal intelligence but may have problems with nonverbal, social, and psychomotor skills. Patients are treated for short stature in early childhood with growth hormone therapy, and supplemental estrogen is initiated at adolescence for pubertal development and prevention of osteoporosis. Unlike with Down syndrome, maternal age does not increase the risk of Turner's syndrome, and there are no clearly established risk factors. Recurrence in subsequent pregnancies is rare. Turner's syndrome is caused by a reduced complement of genes that are typically expressed from both X chromosomes in females.[8]

Most of the other phenotypic features may be due to the presence of lymphedema at criticalpoints in development, leading to failure of normal development. Failure to open the embryonic lymphatic channels may be responsible for the lymphedema.[2]

Pubertal Development and Reproductive Options

Spontaneous pregnancy is most common among Turner women with mosaicism for 46XX (or 47XXX) cell lines. Historical case series suggested a high frequency of fetal mortality or malformation in spontaneous pregnancies among women with Turner's syndrome. Since 1990, increasing numbers of women with TS have sought to become pregnant through assisted reproduction, using donor oocytes and *in vitro* fertilization. Extensively screen prospective mothers for cardiovascular system and exclude women with congenital defects such as BAV, coarctation, or aortic dilation.[2]

Recent Advances

Highly sensitive DNA sequencing strategies are developed to detect genetic abnormalities in small quantities of cell-free fetal DNA found in the maternal blood stream as early as 10 weeks gestation. Widespread development of these new early screening tests are motivated by the desire to facilitate "early reproductive decision making." It is completely unknown at present whether the very early pregnancy genetic screening of "cell-free" fetal DNA shed from dead placental cells will have any correlation with more established diagnostic results available later in pregnancy or with postnatal outcomes. Thus, the current enthusiasm for this unproven technology to "facilitate early reproductive decision-making" is very concerning.[10]

Conclusion

Turner's syndrome is a chromosomal disorder that is frequently misdiagnosed or missed completely. In a female presenting with primary amenorrhea and short stature possibility of Turner's syndrome must be ruled out. It is the most common cause of primary amenorrhea seen in clinical practice. Physical findings of Turner's syndrome are specific. Diagnosis of Turner syndrome should be confirmed by chromosomal analysis. The syndrome is characterized by absence of one X chromosome [45X0]. About 50% of Turner's syndrome have mosaic forms such as 45X/46XX or 45X/46XY. Once Turner's syndrome is diagnosed evaluation of female for CVS abnormality, thyroid disorders, Renal function test derangement should be done. Estrogen therapy is recommended lifelong for a female with Turner's syndrome.

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