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RESEARCH ARTICLE

Incidence and prevalence of chromosomal abnormality among turner syndrome and turner variant with variable clinical spectrum

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Abstract

Turner syndrome is one of the most common and important sex chromosomal disorders. They have wide spectrum of abnormalities ranging from short stature, primary amenorrhea, and infertility. Cytogenetic findings determine different types of karyotype and variable percentage of mosaicism. In this study, our main motto is to correlate the genotype with the phenotype of the patients with short stature, primary amenorrhea, and infertility and characteristic of Turner Stigmata. Cytogenetic evaluation was done by peripheral leukocyte culture with conventional GTB banding and karyotype analysis by cytovision software. Chromosome profiling was done by cytovision software 3.92 and florescence in situ hybridization was carried out in single indicated cases for further confirmation. In our study we included 20 suspected cases with turner characteristic or turner like characteristic. Among them we found karyotype with 45X , 44,X/46,XX , 46XX/46XY, 45,X/46,XY 46X,del(Xq), 46,del(Xp), 46,X,i(Xq). In the present study the variable degree of mosaicism and variable chromosomal abnormality were clinically correlated with wide spectrum of abnormal phenotype and established the importance of cytogenetic evaluation in such cases before therapy or management.

INTRODUCTION

Turner syndrome is one of the most common and important sex chromosomal disorders. This kind of sex chromosomal aneuploidy affects 1 in every 2000 girls (Donaldson et al, 2006). They have wide spectrum of abnormalities ranging from short stature, webbed neck, peripheral edema, renal and cardiovascular anomalies, sexual infantilism, primary amenorrhea, hypostatic uterus, blind vagina, mullarian dysgenesis and infertility (Turner, 1938). The chromosome constituent of turner syndrome is usually monosomy X, but sometimes other structural variations in single chromosome X can also result this syndrome. It was observed that the presence of different degree of mosaic cell lines is responsible for causing tuner syndrome variant (Jacobs et al, 1997).

In this present study we include 20 suspected cases to find out the correlation between karyotypic abnormality and phenotypes with turner stigmata. The age ranges of the patients are 9 to 33. Among 20 cases, two cases are of married individuals with age 29 yrs and 33 yrs, other patients are mainly 11 to 19 years old. Among all, 11 have primary amenorrhea, 2 patients with amenorrhea, 1 have the history of recurrent pregnancy loss and 1 patient have history of infertility, 2 have sexual infantilism. Other characteristic observed in the patients are blind vagina, transverse vaginal septum, absence of auxiliary and pubic hair, underdeveloped breast, small nipple, nipple placed in abnormal position, low posterior hairline, microcephaly, high arched palate, short neck etc. In case of 5 patients we have the reports of ultrasound. The USG reports of these five patients' shows different internal anatomical abnormalities like streak and apparently smaller sized ovaries, absent uterus, hypostatic and rudimentary uterus,

mullerian dysgenesis and no uterine felt in midline. In some cases puberty is considered delayed as there was no development of secondary sexual characters. In two cases we found normal female karyotype though the patients have primary amenorrhea (Table-1). Cytogenetic evaluation revealed presence of chromosomal abnormality in most of the cases of suspected turner syndrome and the degree of mosaicism affect the phenotype and severity of symptom accordingly. So, the present survey provides additional information to the growing literature in Turner syndrome and Turner Variant Database.

Materials and Method

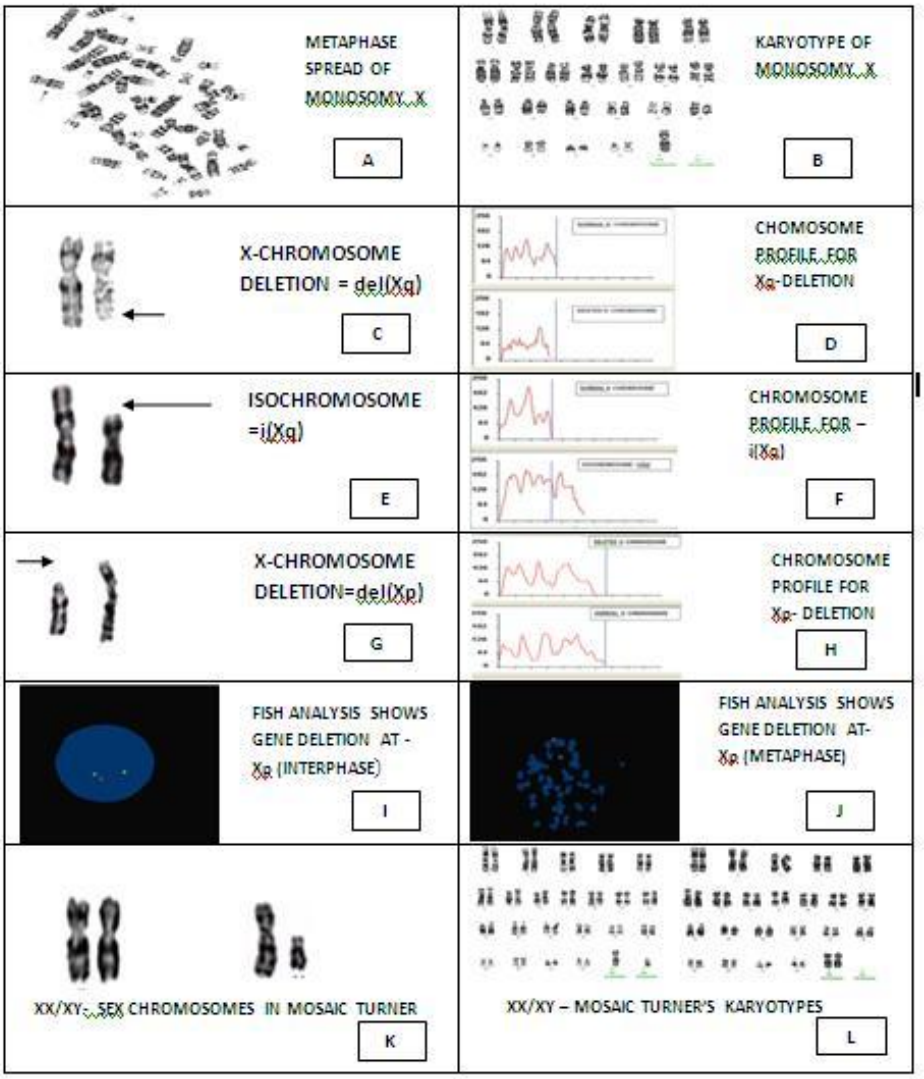
Suspected patients are examined by the clinician and then note down the characteristic of the patients. Biochemical profile and ultrasonography reports are included. Then patients consent was taken and Cytogenetic analysis was carried out based on phytohaemoaglutinin-stimulated peripheral blood lymphocytes culture method (Verna and Babu, 1989) of all the patients. Lymphocyte culturing and GTG banding (Seabrigh, 1971) were performed following standard protocols as described by the AGT Cytogenetic Laboratory Manual. Karyotypes were described according to the International System for Cytogenetic Nomenclature (ISCN-2005).

The FISH was used to determine the presence or absence of gene at Xp21.2. Analysis was performed using DAX1 (NROB1) probe (BAC RP11-112945). (Red Signal) and double signals were visible from the centromeric X chromosome probe DXZ2 (Green Signals)(Saikh et al, 2007).

Result-

Chromosome analysis of clinically diagnosed or suspected cases of turner syndrome or turner variant revealed variant karyotypes like 45;X (5cases), 45;X/46;XX (7cases), 45;X/46;XY (2 single case), 46;X;del(Xq) (2cases), 46;X;del(Xp) (single case), 46XX/46XY (single case) an 46,XX. The percentage of mosaic cell line present in the individual varies from 35% to 65%. The florescence in situ hybridization study confirmed the presence of deletion in the p arm of the X chromosome.

FISH analysis confirmed the gene deletion at Xp21.2. a signal was visible on only one X Chromosome (Red Signal) at Xp21.2 and double signals were visible from the centromeric X chromosome probe (Green Signals).



Legands of Figure:1

1(A); Figure Showing Metaphase Spread of Monosomy X.
1(B); Figure Showing karyotype of monosomy X.
1(C); Figure Showing Normal and Deletion at 'q' arm of X- Chromosome.
1(d); Figure Showing Chromosome Profile (Loss and Gain Analysis With Cytovision Software 3.92) For Xq Deletion.
1(E); Figure Showing Normal and Formation of Isochromosome at 'q' arm of X- Chromosome.
1(F); Figure Showing Chromosome Profile (Loss and Gain Analysis With Cytovision Software 3.92) For Isochromosome Xq.
1(G); Figure Showing Normal and Deletion at 'p' arm of X- Chromosome.
1(H); Figure Showing Chromosome Profile (Loss and Gain Analysis With Cytovision Software 3.92) For Xp Deletion.
1(I); Figure Showing FISH analysis For a gene deletion at Xp. a signal was visible on only one X Chromosome (Red Signal) at Xp21.2 and double signals were visible from the centromeric X chromosome probe (Green Signals)(Interphasic View).
1(J); Figure Showing FISH analysis For a gene deletion at Xp. a signal was visible on only one X Chromosome (Red Signal) at Xp21.2 and double signals were visible from the centromeric X chromosome probe (Green Signals)(Metaphasic View).
1(K); Figure Showing XX/XY Sex Chromosomes in Mosaic Turner Individuals.
1(L); Figure Showing Karyotypes of Mosaic Turner Individual.

Table: 1- Table Showing Age, Characteristic, Ultrasound Findings and Chromosomal Constituents of Twenty Suspected Turner or Turner Variant Cases.

Patients No	Age	Characteristic	USG Findings	Karyotype
1	16 Years	Primary amenorhaea, Auxillary and pubic hair absent	Apparently normal	45;X/46;XX
2	16 Years	Transverse vaginal septum, primary amenorhaea	Uterus absent, streak overies	45;X/46;XX
3	17 Years	Primary amenorhaea	-	45;X
4	19 Years	Primary amenorhaea	-	45;X
5	14 Years	Primary amenorhaea, absence of auxllary pubic hair	-	45;X/46;XX
6	18 Years	Primary amenorhaea	-	46;XX
7	17 Years	Primary amenorhaea, breast turner stage II, auxallary pubic hair +++, blind vagina.	No uterine felt in midline, hypostatic uterus, mullerian dysgenesis.	45;X/46;XX
8	20 Years	Delay in psychosocial development, learning difficulty, hypothyroidism	-	46;X,i(Xq)
9	33 Years	Recurrent missed abortion	-	46:X,del(Xq)
10	11 Years	Sexual infantilism, short stature	Rudimentary uterus and reduced size of overies.	45;X/46;XX
11	19 Years	Primary amenorhaea	-	46;XX
12	14 Years	Left breast only, small nipple above the usual place, short stature	-	45;X/46;XX
13	19 Years	Amenorhaea, breast turner stage- III	Blind vagina, small and rudimentary uterus, smaller left overy,	45;X/46;XX
14	12 Years	Microcephaly, short neck, low posterior hairline	-	45;X
15	17 Years	Primary amenorhaea, secondary sex development (-)	-	45;X/46;XY
16	11 Years	Short stature, high arched palate, short neck, secondary sex development (-)	-	46;XX/46;XY)
17	16 Years	Primary amenorhaea	-	45;X
18	13 Years	Short stature, Sexual Infantalism	-	46;X,del(Xp)
19	14 Years	Primary amenorhaea	-	45;X
20	29 Years	Amenorrhea, infertility	Apparently normal	46:X,del(Xq)

Discussion-

Humans have two types of chromosomes, autosomes and allosomes or sex chromosomes. In case of female individual there are 22 pairs of autosomes and 1 pair of sex chromosomes while in male along with 22 pair's autosomes, single X and Single Y chromosome are present. Sex chromosomal abnormality like turner syndrome is very common but less attentive syndrome because sex chromosomal abnormality may not be as severe or fetal as those from autosomal abnormality (Ford, 1959). But, This kind of sex chromosomal abnormality have various kind of phenotypic expression because genes present on X chromosomes are partially responsible for the development of body stature, puberty, primary and secondary sexual characters. So, mutation and complete or partial deletion of these genes may cause developmental failure of body stature and puberty. Generally turners are phenotypically female and suffering with ovarian dysgenesis and many other characteristic collectively called turner stigmata (Rao et al, 1997).

Cytogenetically turners are generally X chromosome aneuploids or 45X, but other chromosomal numerical variation also occurs. This may be presence of cell line like 46XX or 46XY along with 45X, are call mosaic individuals. Presence of structural abnormality like deletion, duplication and isochromosome formation in both arms of X chromosome also occurs in significant manner (Jacobs et al, 1997).

Short stature is one of the most common characteristic among 95% turner syndrome. With other autosomes, the short arm of X chromosome (Xp) also helps in somatic development. The SHOX (short stature homeobox) gene, located on the p arm of the X chromosome (Xp22.33), which encodes a transcription factor for skeletal development (Jacobs et al, 1997 and Chen et al, 2009). Thus, Patients with monosomy X or deletion or duplication in Xp causes skeletal abnormality like short stature (Therman, Susman, 1990 and Kaiser et al, 1977). In our present survey the two cases with del(Xq) have the normal stature. But deletion in the long arm of X chromosome produces several degree of gonadal dysgenesis which causes recurrent spontaneous abortion in one case and infertility in other case. In a single case we have found deletion in short arm of X chromosome which creates short stature and sexual infantilism. In this case, though the short arm of X chromosome was affected, the body stature is also affected along with gonadal dysgenesis.

It is important not to confuse the 46,X,i(Xq) syndrome with the 45,X classical Turner's syndrome. There are profound cytogenetic and clinical differences between the two syndromes, which must be borne in mind in the differential diagnosis of amenorrhea and of infertility (Santana, Gardner, Neu, 1977). In our study a single case of 46,X,i(Xq) was observed and the individual have delayed cognitive and psychosocial development with hypothyroidism. The individual have irregular cycle with amenorrhea. Comparing the patient with isochromosome Xq with individuals who have the 45,X , the probability of mental retardation was higher but the probability of other typical turner characteristic was lower. Delayed cognitive and psychosocial development and several degree of mental retardation may occur due to the deletion or duplication of XIST region (Zinman et al 1984).

Apart from the above mentioned three different types of structural chromosomal abnormality, in our present study, chromosome analysis of clinically diagnosed or suspected cases of turner syndrome or turner variant revealed several types of numerical cellular mosaicism. Along with the classical aneuploids like 45;X we also observed 45;X/46;XX, 45;X/46;XY and 46;XX/46;XY. Clinically we found most of the patients have primary amenorrhea, short statute, under developed breast, no development of axillary pubic hair. Severity of the abnormally depends on the degree of abnormal mosaic cell line present in the individual. As per our study presence of 40% abnormal mosaic cell line, the clinical manifestation is primary amenorrhea and loss of axillary pubic hair with apparently normal USG report. While the percentage reaches 65%, we found blind vagina, underdeveloped breast along with primary amenorrhea and loss of axillary pubic hair. Not only that, The USG of whole abdomen shows smaller ovaries and hypostatic uterus. So, the presence of abnormal cell lines in greater percentage was increase the severity.
Patients with karyotype of 45,X/46,XY and 46,XX/46,XY does not show typical turner characteristic like webbed neck, peripheral edema, low posterior hairline, abnormal finger arrangement or size etc. We cannot find any phenotype- genotype relationship in these two cases. Presence of XY chromosomes along with single X chromosome may be suppressing the expression of typical turner characteristic. So, it will be the future area of interest. In two cases we have found primary amenorrhea with normal stature and normal female karyotype 46;XX. Endocrinological disorder or abnormal hormonal regulation or pituitary dysfunction may cause of primary amenorrhea in these cases (Rosa et al, 2008).

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Conclusion:

the present study reemphasizes the need of genotype and phenotype correlation in turner or turner variant patients. X chromosome which is mainly responsible for determination of individual's sex and development of primary and secondary sexual characteristic is also responsible for the development of somatic cell line. It is established that the spectrum of the variant phenotypic characteristic are consistently associated with structural and numerical sex or 'X' chromosomal abnormality. Our study also proves the essentiality of chromosomal analysis in a syndrome like turner or turner variant to remove the diagnostic dilemma to the clinician.

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Patients Consent Statement: The signed consent from all the patients are taken before test was performed and kept them as official documents. In case of any unusual condition it will be presented in front of the concern person.

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