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Variant of Turner Syndrome 45, X/46, XY Mosaicism: A Case Report

KEYWORDS: Ambiguous Genitalia, Congenital Adrenal Hyperplasia (CAH), Mosaic.

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ABSTRACT *Turner syndrome (TS) is the consequence of complete or partial absence of one X chromosome in a phenotypic female usually characterized by short stature, gonadal dysgenesis and a variety of other clinical features. About 50% of the patients have a 45,X karyotype, 19-20% show mosaic forms including 45,X/46,XY & 45,X/46,XX while the remaining (30%) have structurally abnormal sex chromosomes . Patients with 45,X/46,XY mosaicism exhibit a wide phenotypic spectrum, ranging from normal females, females with Turner syndrome or normal males with mild hypospadias, to male or female pseudohermaphroditism. Those with Y chromosomal material are at risk for developing gonadoblastoma or dysgerminoma later in life. We had a baby of two days old referred to us before gender assignment as it had presented with ambiguous genitalia & was suspected for CAH.*

INTRODUCTION

Sexual ambiguity commonly known as intersex is a condition of imperfect sexual differentiation between male & female. The incidence is approximately 1 in 2000 live born infants. 45,X/46,XY mosaicism- a varient of Turner Syndrome is one among them . Majority of the people (90%) with 45,X/46,XY are apparently normal men/boys and go unnoticed until puberty or later. 10% are females and have a form of Turner Syndrome- with 45, X genetic constitution. These 10% present with, external reproductive organs that show incomplete male development and may appear as partly masculinised female genitalia. The term "Mixed Gonadal Dysgenesis" (MGD) /"Disorders Of Sex Development"(DSD) is sometimes used for this group .

In 2005, the Chicago Consensus on management of Intersex disorders proposed the substitution of terms such as intersex, hermaphroditism, pseudo- hermaphroditism, for the term disorders of sex development (DSD) as defined by congenital conditions in which development of chromosomal , gonadal , or anatomical sex is typical. A classification was proposed in which DSD associated with sex chromosome abnormalities were separated from those with a normal chromosome complement .Disorders of Gonadal development , including ovotesticular DSD, & Gonadal Dysgenesis , can be found in all group.(Hughes IA et al 2006, & Lee et al 2006)

Dysgenetic testis may be bilateral or associated with contra lateral streak in subjects with 45,X/46,XY karyotype . Histological picture may vary from a gonad with predominance of fibrous tissue & few tubular structures to only a reduced number of germ cells. As a consequence , the external genitalia of Dysgenetic testis ranges from predominantly male to predominantly female, including cases of striking genital ambiguity, & there is usually persistence of mullerian structure.(Scolfaro et al 2003). The MGD was initially used in

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histological context, referring to the finding of dysgenitic testis associated with streak gonads. The same occurred with partial gonadal dysgenesis(PGD), which designated the existance of bilateral dysgenetic testis (Chemes H et al 2003, & Lipay MVN et al 2005) . In subjects with 45,X/46,XY mosaicism , the histological picture of Dysgenetic testis plus MGD is more frequently observed than bilateral Dysgenetic testis (Rohatgi M, et al 1992 & Telvi L et al 1999), while those with a 46,XY karyotype the frequencies are similar(Rohatgi M, et al 1992). Telvi et al (1999) reviewed postnatally ascertained 45, X/46,XY cases ,in which some males who appeared normal at birth can develop late-onset "Turner syndrome like " abnormalities . Gonadal dysgenesis ,infertility, low testosterone levels & azoospermia has also been reported in postnatally ascertained cases. They also found that there was no correlation between severity of phenotype & ratio of 45,X/46,XY cell lines in the blood. In clinical practice ,the new classification proposed by the Chicago Consensus (Hughes IA et al 2006, & Lee et al 2006) the term MGD has been employed in cases of testicular dysgenesis with a 45, X/46, XY karyotype , & PGD in those with a 46,XY chromosome constitution , regardless of the histological picture.

In patients with 45,X/46,XY karyotype management includes not only issues related to sex assignment , gonadectomy and genitoplasty, but also those related to the clinical features of Turner Syndrome derived from 45,X cell line.

METHODS

Clinical, cytogenetic, endocrinological & radiological findings.

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RESULTS:

We had a baby of two days old referred to us before gender assignment, it presented with ambiguous genitalia. Peripheral blood of the baby was brought to our genetic laboratory (Dept of Anatomy, SSIMS&RC DAVANGERE).

Prenatal and postnatal history – the new born was the 2nd child of young healthy unrelated parents delivered vaginally (37 wks). The 1st child is a normal healthy boy of 4 years old.

On examination - weight -2.5kg, length-37cms, head circumference-32cms (all below 3rd percentile) no dysmorphic features.

The external genitalia showed a large phallus (1.3 cm), no separate urethral opening, urogenital sinus with wide

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opening seen, scrotal sac with rugocity seen, but with no contents, no hernia in the inguino perineal region seen.

Pelvic sonography- showed presence of uterus measuring 2.7cms x 9mm x 1.5cms with normal endometrium. No suggestions of testis like structure seen in inguino perineal region.

Both kidneys and adrenal glands appeared normal in size and ecotexture.

Serum electrolytes - serum sodium (130.5m mol/l), serum potassium (5.0m mol/l), serum chloride (100.1m mol/l). All these were within the normal limits for three consecutive days.

Screening for specific conditions - CVS revealed no abnormalities & thyroid profile (thyrotropin & free tetraidothyronin) were normal.

Chromosome analysis- G-banding karyotype showed 45,X/46,XY (75/15 cells). As shown in Appendix -A

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DISCUSSION
45, X cell line occurs as a result of non disjunction at either stage of meiosis (I or 2) during spermatogenesis or oogenesis or from post zygotic error. Nondisjunction involves either of the parents gamete, in 75-85% of 45, X, the X chromosome is said to be maternal in origin

indicating that the paternal chromosome is lost. This is evidenced by the fact that paternal origin of X does not influence survival of the conceptus.

Abnormal X chromosome like the iso chromosome has equal frequency of maternal or paternal origin. While deletion or ring chromosome & also the Y chromosome abnormalities in TS have paternal origin. It is suggested that high proportion of paternal errors in TS are due to absence of pairing along the X & Y chromosomes during meiosis 1 in father, which makes the sex chromosome susceptible to both nondisjunction & structural errors.

Common features seen in TS are short stature, web neck, low posterior hairline, broad chest with widely spaced nipples, high arched palate, micrognathia CVS & renal anomalies. They may present with D.M, thyroid, collagen vascular disorders & obesity. IQ is average/mild retardation.

CONCLUSION
Abnormal maternal serum levels & anomalies of heart, kidneys & uterus during the 2nd trimester should warn for karyotyping. Early recognition of TS & timely investigation will help in improving the quality of life , by improving the adult height in those responding to GH therapy & in initiating sex hormone replacement

In our case ,management of child (45,X/46,XY) was concluded by the team (paediatrician, endocrinologist & cytogenetist) that as there was the presence of uterus & absence of testis like structure, with normal kidneys & adrenals the baby would be reared as a female , with

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genitoplasty & gonadectomy (those with Y chromosomal material are at risk for developing gonadoblastoma or dysgerminoma later in life) . The parents were asked for follow up of the child as it is very essential to monitor her growth & puberty.

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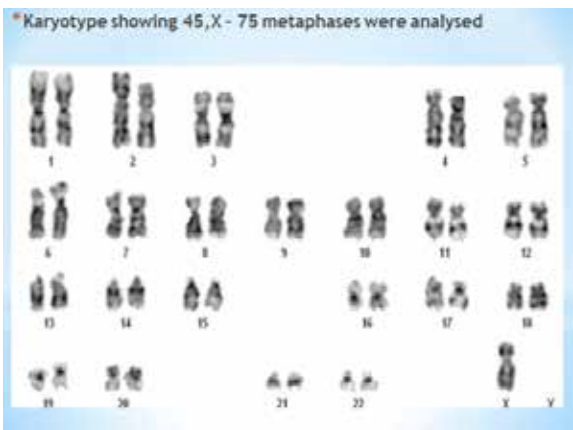
Appendix – A



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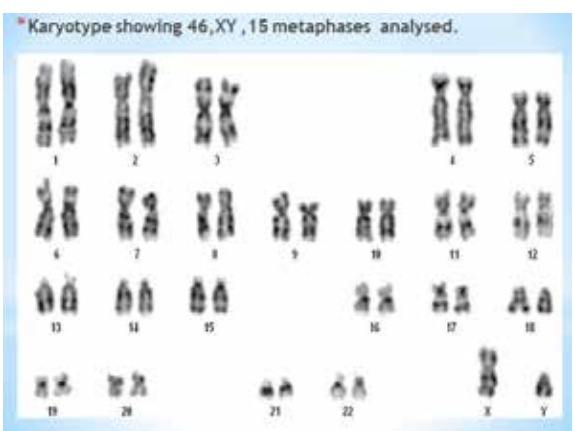

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