A RARE VARIANT OF TURNER SYNDROME- CASE REPORT

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PRESENTATION OF CASE

Turner syndrome occurs in one out of every 2500-3000 live female births and the diagnosis is usually based on the clinical presentation. It is a genetic condition in which a female does not have the usual pair of two X chromosomes. Deletions of proportions of the X chromosome result in various Turner variants who have varied spectrum of clinical presentation. We report on a rare variant of deletion on long arm of X chromosome in a 35-year-old female with short stature, lack of secondary sexual characters, primary amenorrhea, average intelligence and diabetes mellitus. Chromosomal analysis using GTG-banding showed 46, X, del (X), (q13) in all cell lines. Hence, suspicion of rare variants of Turner syndrome in females must be done who present at a later age with atypical features.

A 35-year-old female presented to us for evaluation of primary amenorrhea. She was diagnosed with T2DM two years ago with poor compliance to OAD. She also was detected with primary hypothyroidism 3 months before presenting to us and had been on levothyroxine supplementation since then. She is a first order child born of a nonconsanguineous marriage at 40 wks. of gestation, delivered at term in hospital by normal vaginal delivery. Her fathers and mothers age during her delivery was 28yearsand 22years, respectively. Clinical examination revealed height 130.8cm (<3rd centile ht. SDS- -4.6), weight 31kg (<3rd centile, wt. SDS- -1.94).Pubertal status was A1B1P2, arm span 136cmwith US:LS ratio of 0.85.General examination revealed normal placement of posterior hairline, neck length to height ratio of 1:11, right and left carrying angle of 11 degrees and 14 degrees, respectively (Figure 1a, 1b). She was hypertensive with all peripheral pulses being well palpable. Systemic examination were within normal limits. Routine haemogram revealed microcytic anaemia. Biochemical parameters revealed elevated FPG and PPPG and elevated S.urea and creatinine level. Urine ACR was 5000mg/gm. Fundoscopy revealed modNPDR.2D echo (transthoracic) was normal. USG abdomen revealed hypoplastic uterus (3.4x0.8x1.6), endo echo of 1mm and small atrophic ovaries with features of bilateral medical renal disease (Figure2). Her hormonal parameters revealed ft.4-17.48pmol/L (12-22pmol/L), TSH-5.64mIU/Ml (0.27-4.2mIU/mL), S.Prolactin-18ng/mL (6-29ng/mL). Her gonadotropins were elevated FSH-204mIU/mL (1.4-9.9mIU/mL), LH-57mIU/mL (1.7-15mIU/mL) and E2 was 19pg/mL (21-251pg/mL). Her karyotyping revealed 46, X, DEL(X), (q13) (Figure3). Her glycaemic status was controlled with premix insulin therapy. Hormone replacement therapy could not be started due to other associated medical illness. Levothyroxine dose titration was done. She was explained regarding the genetic nature of her disease and fertility aspects.

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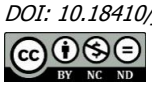

DIFFERENTIAL DIAGNOSIS

Turner Syndrome (TS) or Ulrich-TS is the most common sex chromosome abnormality in phenotypic female. It is caused due to chromosomal abnormality where incomplete or a part of one X chromosome is absent.[1]The most common karyotype of Turner syndrome is 45 XO in 80% of affected females and approximately the remaining 20% may have some variants on the second X chromosome such as an isochromo some of the long arm, ring chromosome or else small short deletions or interstitial long-arm deletions.[2]

The incidence of Turner Syndrome (TS) is estimated to occur in 1:2000 to 1:5000 livebirth.[3] Mortality rates in TS is about 4 to 5 fold higher than in the general population reducing the life expectancy by upto 13 yrs.[4, 5]

The main characteristics of this disorder are short stature, gonadal dysgenesis, primary amenorrhea, decreased fertility, webbed neck, widely-spaced nipples, broad chest and anomalies of cardiac, renal and endocrine origin.[1,6] Though various disorders such as multiple pituitary hormone deficiencies, hypothyroidism, constitutional development in growth and puberty can manifest with short stature and poor development of secondary sexual characters, but the characteristic phenotypic features of Turner syndrome are absent.

CLINICAL DIAGNOSIS

Based on the clinical history, phenotypic and auxological parameters with a high pretest probability suspicion of TS, various hormonal, imaging studies and karyotyping was send for. Though the typical clinical features were lacking, yet strong suspicion of TS was made.

PATHOLOGICAL DISCUSSION

Turner syndrome (TS) variants include female individuals with partial deletion in the p or q arms of one X chromosome.[7]The deletion of certain X chromosome regions/genes can lead to specific phenotypic features leading to spectrum of clinical presentation of in TS variants. The lack of a second X chromosome leads to the development of streak gonads, because a second X chromosome is essential for full development of ovaries.[8]

On chromosomal analysis, the percentage occurrences of various karyotypes observed in TS are 45XO(50%), 46X/46XX(20%), 46Xi (Xq)(15%), 46Xr(X) or 46X del(X) (10%) and others 5%.[9] Sybertand McCarley[10] observed occurrences of 46Xi (Xq)(7%), 45X/46Xi(Xq)(8%), 45X/46Xring(6%), +mar(1%), 45, X/46, XX/47XXX(3%), 45X/46XX(13%), 46, X, Xp(short-arm deletions)(2%), 46, X, Xq(interstitial long-arm deletions)(2%) and others 6%.

It has been reported that most women with Xq deletion are short and can present with either primary or secondary ovarian failure.[11]T2DM is also known to be associated in 40-50% of cases of TS and more with Xq deletion.[12]Some reports[13,14,15] have indicated that patients with the 46X(Xq) deletion karyotype have high risk for hypothyroidism. The probability of a low posterior hairline, neck webbing and hypoplastic nails are lower.[16] In our case, the patient has similar features as present in Xq deletion variants.

The influence of maternal age may not be related to the birth of TS children.[17] Moreover, it is now known that in 80% of the TS, the paternal X chromosome may have been lost from a 46XX or 46XY zygote.[18]Hence, TS cannot be correlated to maternal age.[19]

If the status of ovarian function is unclear, measurement of FSH, LH andestradiol level can help to determine the need for HRT. Hormone replacement therapy should be initiated at the age of 12 to 13 years. Psychosocial issues and patients' wishes also need to be considered.

The prevalence of CHD among patients with TS ranges from 17-45% with no clear phenotypic, genotypic correlation.[10]Congenital cardiac defects and renal malformations are consistently less in TS variants. Our patient also didnot have any congenital cardiac or renal malformations.

Approximately, 70% of patients with TS have learning disabilities affecting nonverbal perceptual motor and visuospatial skills. A meta-analysis of 13 studies identifies deficits in visuospatial organisation, nonverbal problem solving and psychomotor functioning in patients.[10]Our patient also had specific problem with number work, mathematics and spatial orientation tasks.

DISCUSSION OF MANAGEMENT

TS represents a condition with both genetic and hormonal determinants that contribute to various clinical features. Early recognition of TS and timely investigations are helpful in improving the quality of these individuals by potentially improving the adult height in those who respond to GH therapy initially along with sex steroid replacement. It becomes imperative that once there is clinical suspicion of TS, irrespective of the age, it must be confirmed by karyotyping to establish the variable karyotypes associated with the syndrome.[20]Thus, karyotype will help establish the type and the prognosis in various cases.

Also, early detection and management of co-existing illness maybe lifesaving for these patients. Almost, all the patients with TS have short stature and loss of ovarian function, but the severity of these problems varies among individuals. Physicians should discuss, infertility issue and reproductive options with their patients.

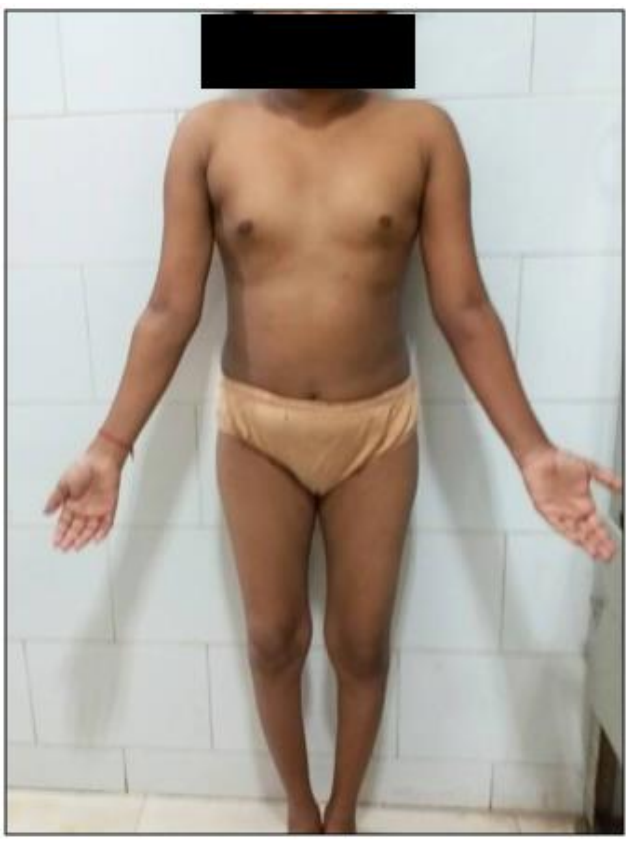

Figure-1. Clinical picture of Patient

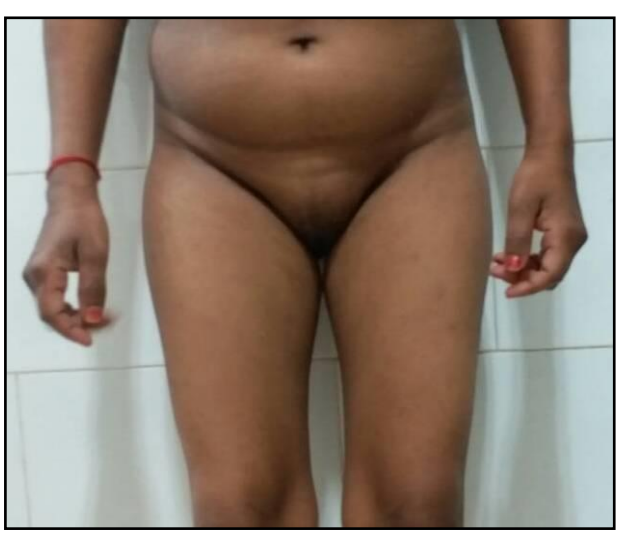

Figure 1b. Showing Poor Development of Pubic hair

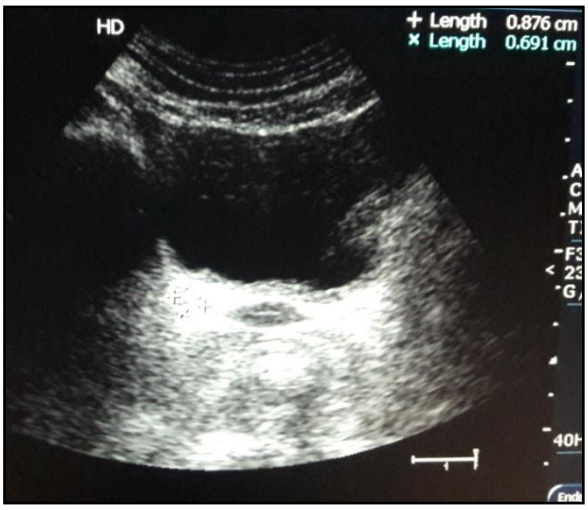

Figure 2. (USG Showing Hypoplastic Uterus with Streak Gonads)

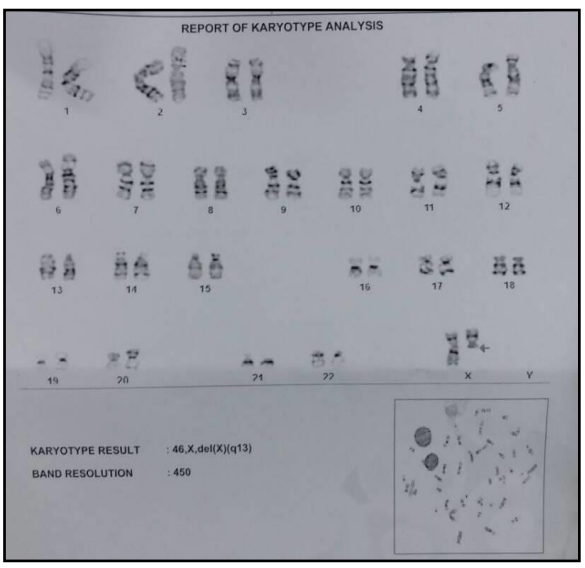

Figure 3. Karyotyping Image

FINAL DIAGNOSIS

Based upon the clinical, hormonal and karyotyping findings, a diagnosis of a rare variant of TS was made. Hence, we suggest that chromosome analysis for TS should be considered even in patients presenting with normal intelligence when height is short and other associated autoimmune thyroid disease and type2 diabetes mellitus is accompanied for appropriate counselling and management.

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