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Turner Syndrome – A Report on Three Mosaic and Variant Cases with Subtle Presentation

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Abstract

Turner syndrome is one of the commonest surviving abnormal cytogenetic disorders which is mostly identified at the time of puberty. The cytogenetic abnormality can be in form of classic monosomy X, structural abnormality of X chromosome or mosaicism. The phenotype can be modified in the presence of the chromosomal make-up of an individual. Here we report a series of patients having milder phenotype prompting us to be more vigilant in girls having short height and obtaining cytogenetic studies at the earliest.

Introduction

Turner syndrome, first described in seven females by Dr. Henry Turner in 1938, is one of the most common chromosomal anomalies occurring in humans, with an incidence of about 1 in 2000 live born female infants (1,2). It is characterized by absence of part or whole of the X chromosome in a phenotypic female. The classic form of Turner syndrome is associated with a 45,XO karyotype and occurs in approximately half of the women with this condition. Mosaic forms account for one fourth of the case, and the rest have structural abnormalities of the X chromosome (3).

Turner's syndrome is associated with characteristic clinical features of short stature, gonadal dysgenesis, sexual developmental deficiencies, cardiac and renal defects, webbed neck, low-set ears, skeletal deformities and hearing deficits (4).

Short stature is the most frequently observed clinical feature but varies in severity, others are less consistent. This may be because physical manifestations are influenced by chromosomal constitution [5]. Patients with mosaic 46,XX/45,XO karyotype or isochromosome X characteristically have milder phenotype [5,6,7], while patients with mosaicism for 46,XY cell line or structural rearrangement of the Y chromosome mostly have virilisation of external genitalia and are at increased risk for gonadal tumors [5,8].

Many cases may be diagnosed at birth due to dysmorphic facies, pedal edema and severe anomalies. However, diagnosis is often delayed in less severely affected individuals who present with short stature, delayed puberty, amenorrhea and infertility [9].

In this case series, we discuss three clinical cases who presented with secondary amenorrhea at our institute over a period of eight months. The karyotype of one of the cases was mosaic and two were Turner variants. The presentation was delayed and subtle.

Case report

Case 1

A 24 year old woman presented in the gynecology outpatient department with secondary amenorrhea for past six years. She had only two episodes of menstrual bleeding since her menarche at the age of 18 years. There was no history of weight gain or loss, no family history of delayed puberty. She was 148 cms tall (less than 3rd centile) and her weight was 58 kg. Breasts and axillary and pubic hair were all Tanner's stage III. Galactorrhea from bilateral breasts was observed. No hirsutism or acne was present.

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Apart from her short stature, no other typical features of Turner syndrome were seen in this case.

On hormonal assay, her FSH and prolactin levels were elevated, estradiol was low, TSH was within normal limits (Table 1). Her transabdominal ultrasound showed infantile uterus with bilateral small sized ovaries, rest abdominal organs were normal (Fig 1,2). Karyotype of peripheral blood lymphocytes showed 20 % 45,XO and 80% 46 XX cells, confirming diagnosis of mosaic Turner syndrome. Echocardiogram, glucose tolerance test, hearing and vision test were all normal; her bone densitometry T score was 2.1 SD below the mean.

She was informed of her diagnosis and its implication. Appropriate follow up and management plan was discussed. She was started on oral estradiol therapy, with cyclic oral medroxyprogestrone acetate therapy to prevent signs and symptoms of oestrogen deficiency. Oral calcium and Vitamin D along with exercise were prescribed to correct low bone mass and prevent osteoporosis. Oral cabergoline was started for galactorrhea with hyperprolactinemia.

Case 2

A 16 year old was referred to gynecology outpatient department by paediatrician. Her parents were concerned about her failure to gain height and weight and immature secondary sexual characters when compared to her sisters, and infrequent periods – she had two episodes of menstrual bleeding 4 months apart since her menarche 6 months ago. There was no family history of short stature or delayed puberty. Mother was 155 cm tall, father's height was 166 cm.

Her height was 130 cm, weight was 31.2 kg. Her breasts were Tanner stage IV, axillary hairs were Tanner stage II, and pubic hair were absent. No dysmorphic features were seen, physical examination was otherwise unremarkable. On X rays her bone age corresponded to 16 years, her expected height was 148.65 +/- 8 cms. Her serum FSH and TSH levels were high, estradiol was low (Table 1). Transabdominal USG showed normal size and structure of uterus and ovaries. Karyotype showed 46, X, i(X); Turner syndrome variant with isochromosome X.

Table 1 Hormone assays

Case No	Fsh (Iu/L)	Lh (Iu/L)	Tsh (μiu/L)	Prolactin (Ng/Ml)	Estradiol (Pg/Ml)
Case 1	39.81	12.95	1.39	31.36	10
Case 2	16.7	2.97	12.47	7.98	27.8
Case 3	93.39	40	3.33	4.87	11.8

Fig 1 Small ovaries on transabdominal USG

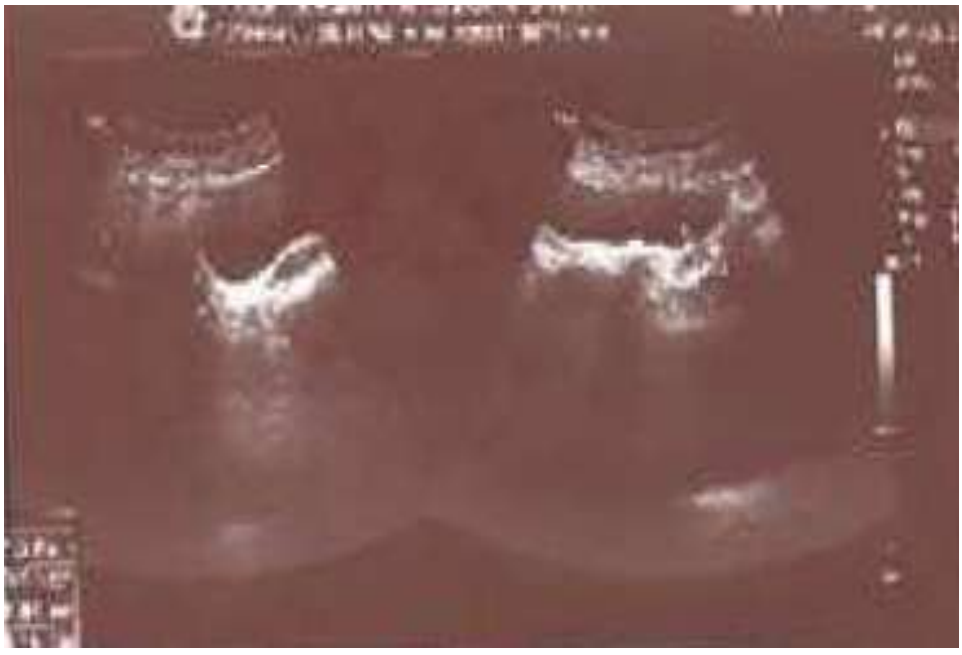
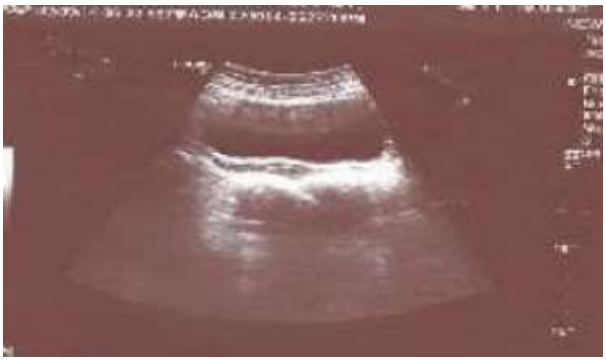


Fig 2. Hypoplastic uterus on transabdominal USG

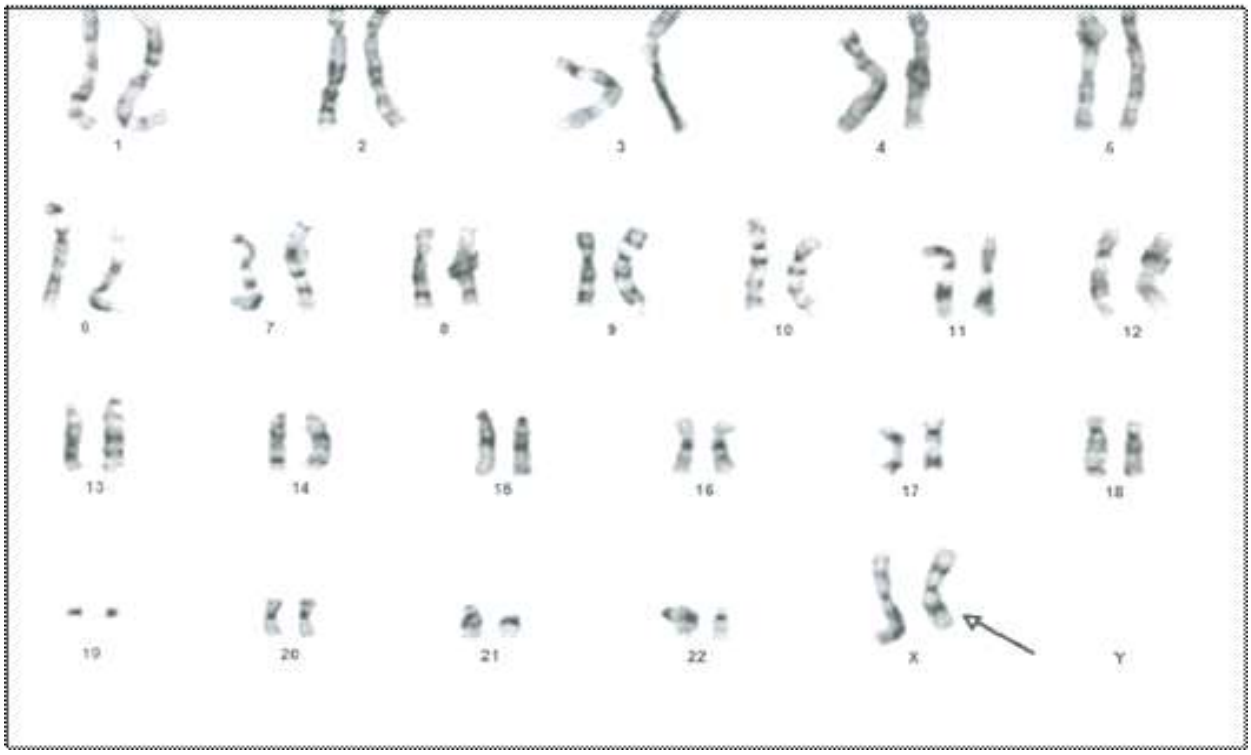


Anticipated systemic involvement was ruled out by appropriate investigations, patient and parents were counselled. She was started on oral levothyroxine and oral estrogen therapy with cyclic progesterone; follow up was explained.

Case 3

A 20 year old woman was referred to gynecology outpatient department by a private practice, with the chief complaint of delayed and scanty menstrual period. She had menarche at 14 years, and her menstrual cycles had been regular in the past. Since the previous one and half years, she had scanty

Fig 3. Karyotype with deletion Xq22.



periods every two to three months. She had been on combined oral contraceptive pills for three cycles, with regular periods. There was no history of weight gain or hirsutism. Her height was 149 cm (less than 3rd centile), weight was 50 kg. Breasts and sexual hair were well developed, Tanner stage 4. No abnormality was seen on physical examination.

Her FSH and LH were raised, estradiol was low (Table 1). Hypoplastic uterus and bilateral small ovaries were seen on transabdominal USG. Karyotype was abnormal and revealed the presence of one normal X chromosome and the deletion of long arm of second X chromosome at band Xq22; Turner syndrome variant was thus, diagnosed (Fig 3).

After relevant examination, investigation and ruling out various complications seen in Turner syndrome; she was started on hormone replacement therapy with estradiol and cyclic progesterone. She was counselled and explained follow up plan.

Discussion

The 45,X cell line arises from meiotic nondisjunction or anaphase lagging during spermatogenesis or oogenesis or from postzygotic error. Mosaicism is the presence of 2 or more cell lines with different chromosomal constitutions in the

affected individuals, mostly due to postzygotic mitotic nondysjunction(10). An isochromosome is a structurally abnormal chromosome consisting of 2 short or 2 long arms; the abnormal transverse mis-division of the centromere yields unbalanced chromosomal constitution - monosomy for the missing arms, and trisomy for the duplicated arms (11).

The frequency of 45XX/45XO mosaic karyotype has been reported by Sybert and McCaulay to be 13% of Turner syndrome cases, while that of isochrome X has been reported at 7% and that of deletion Xq at 2% (6). It has been described that the clinical features of these cases are similar to mild classical Turner syndrome (12,13,14). They are more likely to menstruate. Hypothyroidism due to autoimmune thyroid disease is more common in isochrome X, and those with deletion of long arm of X chromosome often present with gonadal dysfunction alone (12).

The diagnosis of Turner syndrome is often delayed. The mean delay in diagnosis is 7.7+/-5.4 years according to a study by Savendahl *et al*, in 2000. Cases were diagnosed an average of 5.2 years after height had fallen below the fifth percentile for that age (15). Such delayed diagnosis is more likely when the karyotype is mosaic or variant, as the phenotype is milder in most of these cases.

Early diagnosis is imperative to ideal treatment of Turner syndrome. Establishing a diagnosis early in life permits the clinician to counsel the patient and her family of the health and fertility implications and screen for complications before they wreak havoc. If therapy with growth hormone is considered appropriate, treatment can be initiated before the patient falls far below age appropriate growth standards, thereby permitting attainment of normal adult height (16). This will often permit estrogen replacement to start during adolescence, without concerns about estrogen-induced premature epiphyseal fusion (17).

However, in many instances the diagnosis may be delayed until childhood, when evaluated for short stature, or adolescence, when failure to attain expected height or delayed puberty suggest the possibility, or, unfortunately, until adulthood, when a workup for amenorrhea or failure to conceive yield the diagnosis.

Conclusion

All three cases in this report presented at an advanced age, in adulthood or late adolescence, without the characteristic stigmata of Turner syndrome. Short stature and menstrual disturbances were seen in all of them. None of these cases could attain their potential height, and were emotionally distressed to learn that a congenital condition with significant bearing on their lives, was only then being diagnosed.

The authors recommend that there be a high degree of suspicion when evaluating females with short stature, so that such cases with subtle clinical features may be diagnosed in time for further evaluation and treatment. The present scenario where this condition is diagnosed well past childhood, sometimes after years of parental and patient concern regarding short height, is deplorable. This would help many patients to achieve optimum adult height and escape much of the physical and psychosocial trauma associated with Turner syndrome.

With increasing availability of sophisticated cytogenetic studies including the Fluorescent *in-situ* hybridization (FISH), whole chromosome painting and molecular cytogenetic tools we should be able to harness the full potential of technology to help the patient and their family. That was the limitation of our study since these tests are not yet available at our institute and patient could not afford the cost of the testing and hence we had to rely on limited resources for management of patients.

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