



MOSAIC TURNER –A CASE REPORT

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ABSTRACT

Turner syndrome is a chromosomal disorder, which mostly results from a 45XO karyotype and is characterized with short stature, gonadal dysgenesis, renal and cardiac abnormalities. The probability of spontaneous menarche in TS is 10%, while the probability of fertility is too low. The frequency of 45, X/47, XXX mosaicism in TS has been reported as 1%-4%.^[1] Cases with this karyotype were reported to have higher rates of spontaneous menarche and fertility with a lower incidence of short stature and renal abnormalities. We are reporting here an eleven year-old girl with short stature (SD score -3.41) having karyotype 45, X/47, XXX.

KEYWORDS: Mosaic Turner, short stature.

INTRODUCTION

Turner syndrome (TS) occurs in 1 in 2000 female live births,^[2] characterized by short stature, gonadal dysgenesis, a webbed neck and cubitus valgus, as a consequence of various abnormalities of one X chromosome in a phenotypic female. Further features may include lymphedema of the hands and feet, characteristic facies, high palate and short fourth metacarpals. Additionally, renal abnormalities, such as horseshoe kidney and cardiac abnormalities, such as dilated aortic root, bicuspid aortic valve, coarctation of aorta which occur in half of the patients can cause serious health problems.

Triple X syndrome (47XXX) is the most common female chromosomal abnormality, occurring in approximately 1 in 1,000 female births. Common characteristics are tall stature (>75th percentile), epicanthal folds, clinodactyly and hypotonia. Possible additional problems can be seizures, renal and genitourinary abnormalities and premature ovarian failure. However, onset of puberty, sexual development and fertility are usually normal. Motor and speech delays, learning disabilities, attention deficits and mood disorders are more common than general population. There is considerable variation in the phenotype with this disorder. This is reflected by the fact that only 10% of cases are diagnosed clinically.

Mosaic forms of TS tend to have improved prognosis and milder phenotypes. The improved growth and ovarian function of 45, X/46, XX patients over 45, X patients have been well established and the rarer

karyotype 45, X/47, XXX (about 2% of those with TS) also results in more mild phenotype.^[3] The study from Glasgow, Scotland, evaluated the seven 45, X/47, XXX girls registered in the Scottish Turner Syndrome database. Three of the seven subjects did not require growth hormone to achieve a satisfactory height, in comparison to the 45, X and 45, X/46, Xi(X)(q10) matched subjects, all 21 of whom required growth hormone. Additionally, all the 45, X/47, XXX subjects underwent spontaneous puberty and all five of those older than twelve had spontaneous menarche with regular menstrual cycles. Only 2 of the 14 girls in the 45, X comparison group had spontaneous puberty and none achieved menarche without the use of estrogen.^[4] Also, none of the 45, X/47, XXX girls had cardiac or renal abnormalities, though two had middle ear issues. This is in contrast to the 13 of 21 matched subjects with abnormalities to the heart, renal system, or both and is in contrast to the 15 of 21 girls with middle ear issues. The subjects were also evaluated for dysmorphic features. 45, X/47, XXX subjects had the most mild expression. Lastly, none of the 45, X/47, XXX subjects had special education needs, in contrast to four in the comparison group. It appears that the haploinsufficiency from the single X chromosome in 45, X is mitigated by the overtranscription of the X chromosome that results from having a 47, XXX cell line.^[3]

CASE REPORT

A 11-year-three-month-old girl presented to the Endocrinology Clinic for assessment of short stature. On physical examination, her height was 116 cm (Ht SDS -

3.41) and weight was 20 kg with both breast and pubic hair development consistent with tanner stage 1. She had frontal bossing, multiple naevus, low set ear, wide spaced nipples and increased carrying angle of the elbow. Remaining systemic examination was normal. She is a sixth grader, who is performing well in school. Her mother height was 145.1cm (and had menarche at age 13yr) and her father height was 169cm. So her Target height was 150.6cm (SDS -1.6).

Laboratory data showed a normal complete blood count, blood sugar, liver, renal function test and routine urine. Skeletal maturation, evaluated by a left wrist x-ray was below 11 years. TSH was 7.72 $\mu\text{U/mL}$ (0.35–4.9 $\mu\text{U/mL}$) and free T4 was 6.1 ug/dL (5.2–14.2 ug/dL). Thyroid anti-TPO autoantibodies was negative. FSH was 5.65 mIU/mL, LH 1.06 mIU/mL. Transglutaminase antibody (tTG) was normal. Abdominal ultrasound, 2-D

Echocardiography was normal. ENT examination including Pure tone audiometry revealed no abnormality.

As she had clinical stigmata of turner syndrome, a chromosome analysis was performed from peripheral blood lymphocytes. Total 25 cells were examined by process of 72 hrs stimulated culture-GTG banding. 17 cells analyzed revealed a total of 44 autosomes and only 1 sex chromosome 'X' (45,X). 8 cells analyzed revealed a total of 44 autosomes and 3 sex chromosomes 'X' (47,XXX). No karyotypically normal cells were identified in the specimen. These two cell lines were presumed to have arisen by a nondisjunctional event at a very early stage of fetal development.

Thus clinical and laboratory findings were consistent with diagnosis of Mosaic Turner Syndrome and Subclinical Hypothyroid. She was started on recombinant human growth hormone therapy to increase her height and Levothyroxine on follow up.

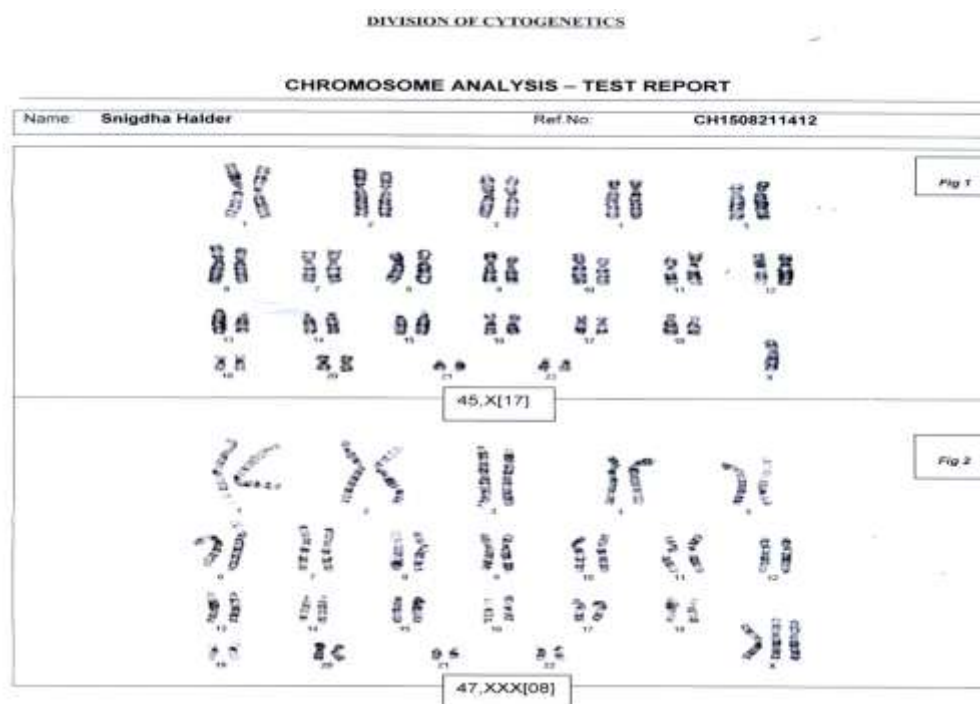


Figure 1: Karyotype of the patient.

DISCUSSION

While 45, X/47, XXX girls have milder phenotypes, as discussed previously, the outcome for any individual is unpredictable. In our patient, we saw severe short stature, but no cardiac, middle ear, pubertal, or learning issues. She was presenting with early stages of spontaneous puberty (B1) and we expect she will probably experience spontaneous menarche shortly, as her FSH was not elevated. Abnormalities in the hypothalamic feedback system, with increased levels of gonadotropins to compensate for blunted ovarian function, or FSH surge commonly seen in TS before the ovarian failure have been hypothesized.

Genes located on the proximal region of the short arm of the X chromosome are important for normal ovarian function and development and the haploinsufficiency of these genes is thought to be implicated in the pathogenesis of gonadal dysgenesis associated with TS.^[5] On the contrary, spontaneous puberty has been reported with a significantly higher frequency among mosaic TS with cell lines having more than one X, which implies increased number of X chromosomes has been shown to reduce the extent of ovarian failure and create a period of potential fertility. These observations suggest a cardinal influence of the X chromosome on the appearance of spontaneous puberty.^[6]

Our patient with Ht SDS of -3.41 has a 17: 8 ratio of 45, X: 47, XXX karyotype in the cells examined from her peripheral blood smear. However, this does not necessarily reflect the uniform distribution of cells throughout every organ systems of her body. Moreover, most patients assessed for Turner syndrome have only been karyotyped from one tissue, so we do not know which lines dominate in which organs. Workers at USC Medical Center reported one patient with short stature whose buccal smear showed 45, X/46, XX/47, XXX in a 67/123/10 ratio, whose peripheral leukocyte culture showed 45, X/47, XXX in a 1/1 ratio and whose skin fibroblast culture showed 45, X/47, XXX in a 5/19 ratio. They confirmed a previous assertion that the proportions of chromosomally different cell lines have little value for phenotype prediction, because the chromosome makeup is so varied depending on the sample tissue.^[7] However, they presumed that 47, XXX line was dominant because of the minor Turner syndrome stigmata. Yet, the 45, X line determined her height.

In contrast to the notion that the ratios do not have predictive value, Akbas et al. present the theory that patients with the 45, X/47, XXX karyotype demonstrate the phenotypes in proportion to their degree of mosaicism.^[8] They present the case of a patient with a 35%/65% 45, X/47, XXX ratio. She has short stature and a horseshoe kidney, but what they otherwise describe as a mild phenotype. They compared their patient to a case of a woman with a 90%/10% 45, X/47, XXX ratio and a severe phenotype. She had streak gonads, amenorrhea, thyroiditis, short stature, and learning difficulties.^[9] Therefore, the cell ratio may be predictive when it comes to the overall assessment of mild phenotype versus severe phenotype. Overall, making predictions regarding what the future has in store for these mosaic girls is nebulous. For prenatal diagnosis, parents of 45, X/47, XXX girls should be counseled for the possibility of Turner symptoms but with optimism for a better outcome. Intellectual impairment is reduced compared to 45, X Turner syndrome, which is an important concern for parents who may be considering selective termination. Future fertility also cannot be guaranteed but can be successful in most 45, X/47, XXX women.

CONCLUSION

Phenotypes of 45, X/47, XXX mosaic girls are unpredictable. Cell counts that provide a ratio of 45, X cells to 47, XXX cells should not be considered to have predictive value, because they vary by tissue. Fortunately phenotypes tend to be milder overall with good adult height, but the height may be quite short in a way that is out of proportion to the relative mildness of the remainder of the phenotype. More research will need to be done in this area to assess impact of growth hormone on 45, X/47, XXX mosaic female with short stature as this has not been well studied.

Here we are reporting an interesting case of a 11-year-old short girl with a 45, X/47, XXX mosaic karyotype with subclinical hypothyroid and normal FSH who had been put on GH therapy along with Levo thyroxine replacement.

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