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CASE REPORT OPEN ACCESS

GROWTH HORMONE THERAPY IN A GIRL WITH TURNER SYNDROME – AN EXPERIENCE FROM BANGLADESH

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Abstract

Turner's syndrome(TS) is the most common chromosomal disorder affecting female. Genetics show that most of the patients have monosomy 45 XO and the commonest phenotype is short stature. Growth hormone deficiency is uncommon but consensus statements have endorsed GH treatment for short girls with Turner syndrome as it is found to be effective to increase growth. Here, we describe a nine year and eleven month old girl presented with short stature (Ht-124cm - 2.2 SDS). She had epicanthic fold, cutis valgus and there was no sign of puberty. The diagnosis of TS was confirmed by Karyotype which revealed chrosomomal pattern 45X0/46XX. After evaluation, rGH treatment was initiated and the dose was titrated to 9.5 mg/m2 /wk. After 6 months of therapy the height velocity rose to 10.2 cm/ year. Growth hormone treatment was stopped after 2 years and 4 months as parents were not willing to continue the therapy. The final height of the patient was 144 cm (-1.2SD). She developed spontaneous menarche and other features of puberty at the age of 12 years 4 months. In Bangladesh, we do not have much report of TS who achieved growth with GH therapy. Simple and regular measurement of children's height with chart plotting is necessary to pick up children who have short stature with TS. Girls with TS may be benefited from early diagnosis and initiation of treatment with GH.

Key Words: Chromosomal Disorder, Growth Hormone, Tirner Syndrome .

Introduction: Turner syndrome (TS) is the most common sex chromosome abnormality in females. It was first described by Henry Turner and Laurel Thatcher Ulrich in 1938 and is also known as monosomy X or Bonnevie-Ulrich syndrome.[1] It is a condition characterized by monosomy of the X chromosome and complete or partial absence of the second sex chromosome.[2] Short stature and hypogonadism are principal signs of TS.[3,4] It has an estimated prevalence of 1/2000 to 1/5000 female live births.[5] Typical stigmata include short stature, primary amenorrhoea, estrogen insufficiency and cardiovascular malformations.[6] Girls with TS universally have short stature (>95%), along with

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gonadal failure (>90%) and infertility (99%).[7]The mechanism responsible for short stature in patients with Turner's syndrome is unknown. Growth retardation in the syndrome of gonadal dysgenesis is often present in utero; growth velocity after infancy and early childhood is subnormal, and there is no pubertal growth spurt. Clinical incidence suggests that impaired growth is related to resistance of the growing cartilage to growth factors. [8,9] Untreated these girls continue to be short and rarely achieve 150cm of adult height, barring few mosaics. [10]

The effect of growth hormone (GH) on short-to-medium-term growth in girls with Turner syndrome is well-established. There have been studies that have evaluated the benefits of growth hormone in TS with significant benefit in adult height. There is lack of data on effect of GH therapy on TS in Bangladesh. Here we describe a girl with TS who got growth hormone therapy in our hospital.

Case Report

A 9-year 11 months-old girl who presented to the Paediatric Endocrinologist, with complaint of not growing according to her age. Her growth was noticed to be slow from early age but her parents initially thought it was normal. They however became worried when she was not growing yet to start pubertal development. Her parents eventually took her to this referral hospital for further evaluation and management.

She is 2nd issue of a nonconsanguineous parents, birth history was uneventful. She did not have any perinatal problem. Her medical history was unremarkable and did not show any head trauma, seizure, or infections in the central nervous system. No specific family history was found. There was no history of short stature in the family. Her developmental history was normal. She had a history of small Atrial septal defect (ASD), which was closed spontaneously. She also had hiatus hernia and gall stone but was not symptomatic.

On examination, she had depressed nasal bridge, there was no webbed neck but her carrying angle was high. There was no skin lesions or midline defect. Her respiratory system examination was normal. She had no eye signs and the thyroid gland was not enlarged. She was prepubertal. Examination findings in other systems were normal.

She was stunted, short for her age height was 124.6 cm <3rd centile (- 2SD) on CDC and +1SD on Turner chart. Weight was 23 kg < 3rd centile (- 2SD) percentile on CDC and -1SD on the Turner chart. Her bone age was not delayed. Thyroid function was normal. Karyotype revealed 45XO/ 46 XX(X)(q10) chromosomes, which indicated TS with mosaicism. Echocardiography showed no abnormality. Pelvic Ultrasound scan showed pre pubescent uterus and ovaries. She was started on Growth hormone therapy at 4.5mg/m2/week 6 days per week. After 2 weeks, she developed headache and we stopped GH therapy. Again GH therapy was started after 2 weeks and gradually it was increased to a maximum dose of 9.5 mg/m2/wk.. After 1 year of the rhGH treatment, her growth velocity increased to 8.2 cm/ year. She has gained 19.4 cm in the past 2 years since starting of GH therapy. She developed puberty after 2 years. The growth hormone treatment was stopped because she gained her final height of 144 cm (+2SD) on Turner chart after 2years and 4 months.

Discussion:

TS patients are about 20 cm shorter than the average adult female height of that country and considering the fact that the average height of Bangladeshi women is 150.7 cm.[11]Long-term growth and final height after GH therapy in girls with TS are now available from several studies. Some studies have shown only small gain while others claim significant improvement in height. [12,13] This discrepancy is likely to be due to several factors such as age at starting GH, dose of GH, age of sex steroid replacement, use of anabolic steroids, ethnic and genetic differences, sample size of the study, and use of historical or randomized untreated controls, all of which may account for the variation in final height when treated with GH. Apart from the classic clinical phenotypic features, the diagnosis of TS should be suspected in any girl who presents with unexplained short stature even in the first 3 years of life. [14] The average age at diagnosis in a real-world scenario as in an observational study

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was 12.7 years. Unfortunately, the diagnosis of TS is often delayed, not only because of lack of clinical expertise but also because the girl child is often neglected and brought to the attention of medical help only for evaluation of delayed puberty rather than for short stature. Adding to it is the high cost of GH therapy, and both these factors have significantly affected the use of GH therapy in this country. Short stature and hypogonadism are principal signs of TS. [11,12] Nearly half of the individuals with TS have the typical 45,X karyotype while the rest have various types of chromosomal abnormalities including isochromosome and mosaicism. [3,11,12] Our patient has mosaicism on karyotype. FDA approved recombinant growth hormone for short stature in TS in 1996. [13] The main predictive factor for the best possible response to growth hormone is the age of the patient when she starts treatment. Patients who receive treatment early exhibit better results in terms of final height. [14-17] In this case, the patient began hormonal replacement therapy at around the age of ten years. Although it was started late, this treatment achieved a significant improvement in the patient's skeletal growth. If the therapy had been started earlier, the patient could possibly have exhibited even better results. But the initial estimation had been a final height far below the average population if she did not receive this treatment.

The dose of GH in TS is higher than the dose for GH deficient patients because as mentioned previously, not many TS patients are GH deficient. However higher doses may be required for better height velocity. Growth response could be poor in patients with TS who had been initially diagnosed with GHD. In this case study, growth velocity increased from 5.7 to 8.2 cm/yr after the rhGH therapy.

Puberty is usually delayed in TS because of gonadal dysgenesis and eventual failure. Though spontaneous puberty and assisted reproduction have been reported in about 5% of TS patients, it is usually in those with the mosaic form. [18,19] The objective of starting oestradiol therapy treatment is development of secondary sexual characteristics and increase and maintenance of bone mass. [20] Timing though has been debated and many suggest that oestradiol should be started as soon as possible. Therefore, at the right time, replacement of estrogen to induce puberty is recommended for the majority of patients. [21] Estrogen therapy is usually started when the girl is between 12 and 13 years old. In this patient, without the need for sexual hormone replacement, she started menarche at 12 years of age. Endocrinological follow-up is a constant necessity, since a hormone insufficiency may arise at any point during the course of the patient's life. Cognitive function in some children with TS is grossly reduced when compared with normal girls. Other reasons for reduced brain growth is GH deficiency, which was clearly demonstrated in different case reports. [22-24] But in our patient, there was no cognition deficit and also she did not have GHD.

Conclusion: To our knowledge this is one of the report of TS with GH therapy among few published reports in Bangladesh. TS should be an important differential diagnoses while evaluating any girl with short stature. Early diagnosis should be attempted in these girls, keeping in mind that early initiation with high dose GH, as recommended, could result in much improved adult height, which is very unlikely in untreated TS.

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