Growth hormone deficiency in a Nigerian child with Turner's syndrome: a case report and review of growth assessment in children

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Abstract:

Turner syndrome is the most common chromosomal abnormality affecting women with a prevalence of 1 in 2000 live births. 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.

Case report: A 15 year old Turner syndrome patient who had delayed evaluation for short stature was noticed to be short for age, with a height of 125 cm (-5SDS). Growth hormone stimulation test revealed growth hormone deficiency and she was commenced on growth hormone therapy.

Conclusion: Simple and regular measurement of children's height with chart plotting is necessary to pick up children who have short stature. Growth hormone treatment early in the course of management of a child with Turner syndrome may help achieve normal final height.

Keywords: *Turner's syndrome, short stature, growth hormone deficiency, growth hormone treatment, Nigeria*

Introduction

Turner syndrome (TS) is the most common chromosomal anomalies affecting women with a prevalence of 1 in 2000 live births.[1] It results from partial or complete absence of an X chromosome in a child. Other defects have been reported ranging from partial inactivation of the active X chromosome in a 46 XX to ring X and X q isochromosomes.[2] Short stature is the most prominent and near constant feature of TS with many other phenotypes including webbed neck, delayed puberty streak ovaries and infertility.[1-3] The phenotype of TS is however very variable and those children with 45 X O have more clinical features than those with the other genotypes described. Though Growth hormone is used in high doses for children with Turner syndrome, there are very few Turner syndrome girls with growth hormone deficiency. Another cause of short stature in TS children is haploinsufficiency of the short-stature homeobox-containing gene (SHOX) on the X chromosome.[1-3] We, hereby report our patient with Turner syndrome who is also Growth hormone deficient.

Case report

CD is a 15-year-old female who presented to the consultant paediatric endocrinologist's clinic, having being referred from Canada with complaint of short stature. Her growth was noticed to be slow from school age but her parents initially thought it was normal as their other children were late bloomers. They however became worried when at age 13 years she was yet to start pubertal development. Parents also noticed declining academic performance early in her primary education.

At age 13 years, she presented to a private clinic in Aba, South eastern Nigeria, but her parents were reassured by the physician that she was in good condition even though she did not have proper growth assessment. Her parents eventually took her to the referral hospital in Canada 2 years later because they were not satisfied with her growth pattern. Series of investigations done there, pointed to primary ovarian failure with streak ovaries. The tests also showed hypergonadotropic hypogonadism, reduced bone age of 12 years and Karyotype revealed 45 X i (X)(q10) chromosomes. Her parents are retired civil servants with high socioeconomic status. Review of her systems revealed headaches and apathy. She admitted she was not happy with her stature and would be happier if she were taller.

On examination at presentation, she was obviously short for her age, had a height of 125cm (-5SDS), weight of 27.5kg (-2 SDS) and a BMI of 17.5kg/m^2. Her calculated mid parental height was 165 cm which was in the 75th percentile on the Turner chart. There was no webbed neck but her carrying angle was high. There were no skin lesions noted or midline defect. Her respiratory system examination was normal but the femoral pulse was weak. She had no eye signs and the thyroid gland was not enlarged. She had tanner stage 2 breast and pubic hair. She also had a depressed 4th metacarpophalangeal joint in the hands and feet and an increased carrying angle. Examination findings in other systems were normal.

A diagnosis of short stature secondary to Turner syndrome with Growth Hormone deficiency and possible SHOX gene deficiency was made.

We carried out a Growth hormone stimulation test using 0.01U/kg of regular insulin given at 8.00 am after an overnight fast and the results were as follows;

TIME	FASTING BLOOD SUGAR.	GROWTH HORMONE LEVEL
0 MINS.	3.4MMOL/L.	0.52ug/L
30 MINS.	1.4MMOL/L.	0.34ug/L

We did not bother to go ahead with the 60 and 90 minutes test because we had obtained a critical sample. MRI of the brain showed reduced cerebral cortex but the pituitary gland was intact and there was no other structural anomaly. Echocardiography revealed a normal structural and functional heart

and bone age was 12 years. Pelvic Ultrasound scan showed a rudimentary ovaries and pre pubescent uterus.

Following confirmation of growth hormone deficiency with the insulin Growth hormone stimulation test, patient was started on Growth hormone therapy at 0.05mg/kg/dose 3 times per week, and is on follow-up in the endocrinology and cardiology clinics. Her echocardiograph and serum IGF-1 and GH levels have been normal since her follow-up and she has gained 6 cm in the past 1 year since starting GH therapy.

Discussion and review of literature

Many children with TS are born with normal weight and length but some have IUGR and so they are born small for gestational age. Many have phenotypes that distinguish them from normal babies calling the attention of physicians and allowing for more rigorous evaluation and possibly early diagnosis.[1,2] Suspecting TS in the newborn period is usually predicated on the finding of physical features that are typical e.g. lymphedema, wide spaced nipples, webbed neck, low hairline, and hypoplastic left heart. Our patient did not have any phenotype to suggest any abnormality and thus special attention was not paid to her until her teenage years. There is the possibility that if her parents were aware of any abnormality, they would have been more persistent and insisted that a thorough evaluation was carried out initially when she was not growing well.

Though her siblings were late bloomers suggesting constitutional delay in growth, an endocrinologist would have done a more thorough clinical evaluation before reassuring her parents. About 30-35% of TS children are diagnosed during evaluation for short stature in developed countries.[1-3] There is little emphasis on growth in a society like Nigeria that is still grappling with under nutrition, malaria, HIV and many other diseases but it should be noted that growth assessment is a necessary aspect of child health. It may reveal many other disorders that are masked and some of these are quite sinister. A growth assessment and plotting on suitable growth chart will reveal children that need follow-up, special evaluation or just reassurance. Growth in TS is usually delayed and this is worsened in teenage years when the sex hormonal influence is absent. The good thing about our patient is that her bone age is delayed meaning she has potential for continuous growth and delayed fusion of epiphyses. Starting growth hormone will thus improve her final height even based on the predicted final height.[4]

There are very few reports of GH deficiency in TS girls, but our patient is one of the rare cases noted in literature.[3,4] Many research point to the fact that decreased 24 hour GH concentration in pubertal TS girl was due to lack of oestradiol influence in amplifying the neuroendocrine regulation of pulsatile GH release, but our patient's baseline and critical sample GH levels were extremely low and this was enough

to confirm GH deficiency.[5] Endocrinologists differ in their prescription of GH for TS children with many opting to give the drug and few preferring not to.[5, 6] Several consensus statements allow for the prescription and insurance companies actually pay for the drug in many developed countries as long as the girls meet the criteria.[5,6] In Nigeria, GH is expensive and very scarce even for those who can afford to pay. It is for these reasons endocrinologists ensure strict guideline adherence and follow through before prescribing GH. 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.[5-8] They thus need supra physiologic "acromegalic" dose to overcome the relative GH or IGF-1 resistance in the bones. The proof of this relative resistance is borne from the fact that many TS girls have disturbance in the GH- IGF-1 and IGFBP3 axis.[2,3,4,8] There is increased proteolytic activity of IGFBP-3 with low levels of IGF-1 suggesting a rapid clearance of IGF-1 and GH mediates its action through IGF-1. As a trophic hormone, it is suggested that GH stimulates production of IGF-1, and supra physiologic doses will increase the IGF-1 levels in the system thus promoting growth.[4,7,8] Randomised controlled trials have shown that girls given these supra physiologic doses actually have attained a higher height than those that received therapeutic doses for GH deficiency.[7,8] The risk of malignancy is noted and it is for this reason regular IGF-1 and IGFBP-3 levels must be checked when placing a child on GH therapy.

Puberty is usually delayed in TS because of gonadal dysgenesis and eventual failure. Ovarian follicles are depleted during childhood and adolescent being rapidly replaced by fibrous connective tissues.[1,9,10] It is no wonder the ovaries in our patient were pre pubescent and almost not visualized and the gonadotropins were markedly elevated. Though spontaneous puberty and assisted reproduction have been reported in about 5% of TS patients, it is usually in those with the mosaic form.[9,10] Starting oestradiol therapy shows a synergistic effect with regards to height attainment and also pubertal development.[7] Timing though has been debated and many suggest that oestradiol should be started as soon as possible but others are of the opinion that oestradiol will cause early fusion of the epiphysis and limit the growth potentials of the bone by GH.[5,7] Our patient did not receive oestradiol initially because she has some breast development meaning spontaneous puberty is occurring albeit slow, but we intend to commence oestradiol within a year of receiving GH and after a repeat bone age assessment reveals no fast maturation of the skeleton. Kindly note that though her chronologic age is 15 years, her bone age is still 12 years so she has at least 3 years of physical growth left. Oestradiol has also been noted to improve non-verbal processing speed, motor performance and verbal and non-verbal memory.

SHOX deficiency is well noted in TS girls and though we did not do any genetic test to confirm this deficiency, the phenotype CD presented is strikingly characteristic. SHOX deficiency is also known to

limit physical growth even in normal children, and with CD's GH deficiency and TS, one is not left in doubt as to why her height is so grossly reduced.

This case brings to mind the need for continuous medical education by our general practitioners and even specialists. Growth assessment or growth monitoring is a key component of the child survival strategies and is actually the first in the mnemonic that has stuck with this policy, GOBIFFEEETH. In resource limited settings, where esoteric and sophisticated materials are unavailable, simple and basic tools can be used to achieve optimal health. All health centers have or should have stadiometers to measure height and infant boards to measure lengths. Proper and accurate height and length measurements are more important than plotting these measurements. Plotting on a well recognised and setting-adapted growth chart is key to making important inferences and diagnosis. In assessing a child with growth deficiency, or short stature, a detailed history noting the timing and chronology of this short stature, in relation to peers and siblings. The age of pubertal attainment of both parents, which may not be quite accurate, but can be assessed if they remember that they were in concert with their peers in terms of voice change, pubic hair development, breast development or shaving. Chronic medications and what they are been used for e.g. steroids for nephrotic syndrome or malignancies should also be explored as these drugs cause fibroblast dysplasia and thus short status. Certain diseases have adverse consequences on growth and these must be sought and ruled out as a cause of a child's short stature. Congenital heart defects, chronic kidney diseases, HIV and AIDS, respiratory disorders like tuberculosis, asthma and sickle cell diseases have been known to cause short stature. Nutritional assessment from infancy through to present day must accurately state nature of feeding, frequency and types of food available to the family. The family income and how much of this is spent on feeding should be assessed and the kind of intervention needed should be noted before referral to the nutritionist. The child's psychological and social adjustment or lack thereof must be assessed and notes made on specific arears that may need special evaluation and intervention.

With this, a thorough physical examination should be done, noting the absence or presence of typical facies that point to specific syndromic disorders. Girls with TS have webbed neck, wide spaced nipples, low hairline at the back of their neck, wide carrying angle and at birth, puffy feet. Weight should be measured using balance beam scales or spring balance, or if available, the more sophisticated electronic scales that still use the spring balance principle. The weight should be recorded in the case file of the child and plotted in her chart.

The brain MRI of CD was essentially normal except for reduced brain volume. Some researchers have shown white and grey matter loss in Turner syndrome and they even try to correlate this volume loss with reduced intelligent quotient noted in TS.[1,11,12] This volume loss is seen more in those with

monosomy than in the mosaic TS. Cognitive function in some children with TS is grossly reduced when compared with normal girls and our patient actually demonstrated reduced processing speed and cognitive deficit. Other reasons for reduced brain growth is GH deficiency, which was clearly demonstrated in our patient.[11,12] Early recognition and treatment of GH deficiency in TS may improve brain growth and possibly cognitive function. Self-esteem of some children with TS is decreased especially in the context of social functioning, but major psychological issues are not increased in TS. CD reported being depressed and withdrawn from social activities and evaluation showed this was due to her non-attainment of normal height or start of puberty. Treatment with GH and gonadotropin analogues improves overall psychology in many children with TS as they attain some height and develop secondary sexual characteristics.

Conclusion

This case has highlighted the need for growth measurement, proper plotting and interpretation of a child's height before dismissing this as normal. Though children with TS are routinely given GH, they should be evaluated along the lines of GH deficiency when diagnosis is made, noting the possibility of increased sensitivity of these girls to GH.

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