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Original Article

Final Height Outcome in Girls with Turner Syndrome Treated with Growth Hormone and Low Dose Estrogen

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ABSTRACT

We reported final height data of collected 28 cases with Turner Syndrome (TS) were confirmed with chromosomal analysis during height growth hormone therapy and late estrogen therapy. Participants were allocated into one of 3 Groups, Group A: 11 patients aged between 15-18 years-old, group B: 10 patients aged between 10 -15 years-old, group C: 7 patients younger than 10 years-old. In contrast to the duration of growth hormone & presentation, group B showed a significantly higher final height mean (147.5 ±6.5 cm) the best result well be obtained in group B treated with high doses of growth hormone for longer period. Records of female patients with TS confirmed by karyotype analysis were examined; 15 patients had the typical Turner karyotype and 13 patients had a karyotype indicative of one of the TS variations. Four of the sixteen individuals in variations lacked clinical stigmata associated with Turner Syndrome; the other nine had one or more of the usual clinical stigmata associated with TS. Two cases who had a complicated mosaic karyotype also possessed a Y chromosome. Three patients in group of classics had coarctation of the aorta and one patient in had variants of TS. 5 patients had primary hypothyroidism and received levothyroxine. two pts has hyperthyroidism. In Turner syndrome (TS), Growth Hormone (GH) treatment promotes growth and adult height. The benefit-risk ratio of supplementing GH with the weak androgen oxandrolone (Ox) is undefined. Growth hormone were administered (1.33 mg/kg/d) from the age of 8 years-old while estrogens were initiated at the age of 12 years-old. The increase in adult height (adult height minus predicted adult height) and safety factors were evaluated in a systematic manner.

Keywords: *Turner Syndrome, Growth Hormone, Estrogen, Treatment Outcome, Short Stature*

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INTRODUCTION

Turner Syndrome (TS) is induced by a phenotypic female lacking one X chromosome. It is often distinguished by reduced gonadal dysgenesis and height. The typical type of TS is linked with a 45,X karyotype and affects about half of those diagnosed with the disease. Mosaic variants of TS (45,X/46,XX) make up 25% of Turner cases, while the remainder have X chromosome structural abnormalities [1]. External physical characteristics (stigmata) of TS include small height, cubitus valgus, webbed neck, micrognathia and shield thorax [1,2].

Congenital heart malformations, hypothyroidism, hypertension, hearing loss, osteoporosis, poor body balance and fractures are common in women with TS (3). Since 1988, Sweden has utilized Growth Hormone

(GH) therapy to address low stature in TS patients. Besides its impact on height, nothing is known about its impact on Quality of Life (QoL)linked to health. Psychological and social difficulties have been documented in TS females, although they vary significantly, and not all females with TS experience these difficulties [4].

While adult height is increased by 5–12 cm with GH treatment, it could be raised even more adding the weak androgen oxandrolone (Ox). Nevertheless, in earlier trials, Ox doses of 0.1 mg/kg/day or higher were reduced to 0.05 and 0.06 mg/kg/day based on numerous observations of virilizing adverse effects and enhanced bone maturation. Even though the current standard Ox dose is 0.05 mg/kg/day or less, its effectiveness and toxicity are undetermined [5-6].

This analysis was aimed to assess the optimal dose of Ox required to achieve ultimate height growth possible as we predicted that, as a result of Ox's impact on bone development, the optimum dose could be reduced to less than 0.06 mg/kg/day.

METHODS

We examined retrospectively the medical history of female patients who had their peripheral blood lymphocytes karyotyped in our outpatients Department of Endocrinology from 2006 to 2020. All of these patients were evaluated for short stature (height less than 2SD for the chronological age) coupled with either any two of the gonadal dysgenesis stigmata or primary or secondary amenorrhea. Routine laboratory investigations such as thyroid functions (TSH and Free T4), 2-Dimensional echocardiography, audiogram and ultrasound examination of genitourinary system were carried out on all patients. We also measured serum FSH and LH levels in females aged 12 years and older. Patients with TS according to classic karyotype and variant karyotype were compared in terms of clinical and laboratory parameters.

Three to four times observers performed measurements per year during the total Study period. Adult height gain (cm) was the main outcome measure, defined as adult height (the final measured height before stopping GH) subtracting expected adult height as determined by the modified projected adult height approach (mPAH). By modifying the predicted adult height of untreated TS females (which implies that adult height SDS is equal to height SDS at a younger age), adult height in TS can be predicted through a regression equation (7-8).

The equation was mPAH = 146.95 + 6.37 × (−0.2 + 0.836 × height SDS at baseline).

The target height (cm) was specified as 0.5 × (height (maternal) + height (paternal) − 13) + 4.5 and was corrected for sex and secular trend. At each visit, the height was recorded using a Harpenden stadiometer as well as Blood pressure (BP).

Secondary outcomes have covered how estrogen might be affected by age group, and the impact of estrogen on adjusted adult height gain for bone age at beginning, short-term height gain, pubertal development, bone maturation and length, safety parameters and GH therapy expense. To determine the bone maturation (Δbone age/Δcalendar age), the bone ages of annual hand x-rays were evaluated retrospectively and chronologically using the Tanner and Whitehouse radius, ulna, and short-bones scores [9]. According to Tanner, pubertal phases were evaluated biannually and expressed as SDS adjusted for age and sex [10].

Each adverse event disclosed by the patient, parent, or physician was recorded. Virilizing adverse effects included a depth of the voice, expansion of the clitoral region, or a rise in body hair. If a case has reported virilization at least 2 times, these occurrences were included in the study (i.e. whether it was the same issue on two separate sessions or two distinct complaints on a single visit) or if the participant chose to stop taking Ox/Pl as a result of the incident. The last three of four measures were averaged and represented as SDS after taking into account the age, gender and height.

Blood samples were collected before to initiating GH, six months later, annually, and six months after GH+Ox/Pl discontinuation. Determinants included

plasma, glycosylated hemoglobin (HbA1c), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), TSH and free T4.

RESULTS

Throughout the 16 years, twenty-eight TS cases were discovered. Of them, 15 cases were with classical Turner karyotype and 13 had karyotype indicative of one of the TS variants. Median follow-up duration was 6.6 years (1–18 years). In group A (n=11), range of age at time of diagnosis were 15-18 years-old with mean age of 16.5 years at presentation presented with short stature
and amenorrhea. The mean height was 136.18 (131-146.5 cm) and the height SD score was 2.64±0.47 (2–3 SD). There bone age was going with chronological age. They received growth hormone for the mean duration of 1.6 years when they reached their final height 135-147.5. Estrogen therapy started after age of 14 years-old and growth velocity for this group was 3 cm/year. In group B (n=10), range of age at diagnosis were 10-15 years-old with median age of 12 years at presentation presented with short stature, 2 patients were with hypothyroidism and 1 patient were with coeliac disease with median height (122.5 cm) ranging (106-131 cm) and height SDS was
(< 3 SDS), there bone age was delayed they received growth hormone for the median duration of 3.4 years, but they did not reach their final height yet (121-147 cm) and growth velocity for this group was 4.4 cm/year. In group C(n=7), they are below 10 years with median age at presentation of 4.2 years-old presented with stigmata of TS, one had hyperthyroidism, one had hypothyroidism, one AV canal and polycystic kidneys. The mean height was 92.5 (48-116 cm), age (1-10 years-old), growth hormone therapy duration was 5 years with growth velocity of 6 cm/year and estrogen was not started for this group Five Patients with primary thyroid disease, one patient had hypothyroidism which were handled, to maintain the fT4 and TSH levels in the normal range, with levothyroxine administration. There were two patients had hyperthyroidism and anti-thyroidal drugs were prescribed. All cases were under the 3rd percentile on the typical female growth chart for height velocity at presentation. Recombinant human GH was initiated at a dose of 0.375 mg/kg. These participants were monitored for 18 months and 5 years during which period height velocity was documented. Mean gain in height in group 1,2 and 3 was 3 cm/year, 4.4 cm/year and 6cm/year, respectively. There In addition, mean duration in growth hormone 1.6 year, 3.4 years and 5.1 years, respectively.

TS women were shorter and had higher BMI than the age-matched BMI in group A (22), in group B (19) and in group C (17).

GH doses were modified every 6 months and completely discontinued when height velocity was less than 1 cm per 6 months or because patients chose to quit because their height was satisfactory. Following this, patients were monitored for two following years after GH discontinuation to assess growth. The baseline results across the dose groups were comparable as indicated in Table 1, which displays the height of SDS before, during and after GH treatment and shows the individual heights of the 28 girls at starting GH therapy as well as after reaching adult height. As regard adult height gain, measured 1.9±0.8 year after discontinuing GH, was greater than zero in each dosage group.

Puberty not started spontaneously in girl's turner syndromes; estrogen therapy was started at a mean age of 12. ±0.9 yr. In the years thereafter, During the study, none of the adverse effects were deemed GH-related.

Table 1: Distribution of Turner Syndrome Variants according to Karyotypes in 28 Women

Karyotype group	Karyotype	No. of patients
46XX Mosaic	45X/46XX	8
Ring X Mosaic	45X/46Xr(X)	1
Isochromosome X	46Xi (Xq)	5
45XO classic turner	45XO	12
45XO/46X, y chromosome	45XO/46X, y chromosome	2

Table 2: Clinical features of Group 1 and 2 patients Turner syndrome

Clinical Features	Classic Turner (n=12)	Turner variants (n=16)
Primary Amenorrhea	11	16
High arched palate	12	7
Wide Carrying angle	12	6
Short Metacarpals	1	4
Pigmented Neavi	9	3
Primary hypothyroidism	2	3
Coarctation of Aorta	2	1
Bicuspid Aortic valve	2	0
Renal Anomalies	2	0

DISCUSSION

In this study, 42.86% of patients had classic karyotype while the remaining had one of karyotype variants. Group 2 was more frequent in structural abnormalities of X chromosomes than 45, X/46, XX karyotype. In earlier investigations by Khadilkar et al.4 and Suri et al.5 The TS variants have shown structural abnormalities incidence rate of 72.7% and 56% correspondingly. These variations are attributable to the lack of population-based research. Median levels of TSH (p=0.028) were significantly higher among TS patients owing to the classical karyotype than the variant karyotype. One of the earlier investigations of thyroid autoimmunity in TS revealed that women with isochromosome-X karyotype had an increasing prevalence of thyroid autoimmunity and primary hypothyroidism in comparison with other karyotypes.

TS diagnosis was established later when low height and primary amenorrhea were examined. Karyotyping was then conducted and revealed 45 X/47XXX/47XXX. The median presentation age of Group A was 16.5 years (8-18 years) and the median age of diagnosis confirmation by karyotyping was 17 year (8-32 year), the delay between the time of presentation to diagnosis was 3 years. This delay not only leads to a delayed start in treatment to promote development and puberty but also a failure to promptly detect any heart, kidney, thyroid, auditory, psychosocial and intellectual dysfunctions that may possibly occur in TS.

In this analysis, patients initiating GH therapy had an average height increase of 3 cm/year while the height gain of group B was 4.4 cm/year and C 6 cm/year in group.

In the study carried out by Khadilkar et al , when GH therapy was administered for 1 year in 16 females with TS, the height increase was around 2.4 cm. Our patients who received GH therapy for 5 years had final height gain of 10.56 cm than her predicted height before treatment.

Accurate early diagnosis of TS can assist to improve the quality of life of these patients by possibly increasing their adult height in respondents to GH therapy and by starting sex hormone substitution. Also, for these cases, early identification and treatment of coexisting diseases (such as coarctation) may save lives.

Several studies have shown that adding Ox to GH had a beneficial effect on females' adult height with TS [11-12]. Blind research has demonstrated that GH coupled with Ox modestly improves adult height growth with a previously unstudied low dose (0.03 mg/kg/d) and has a satisfactory safety profile apart from minor slowdown in breast development.

The administration of the traditionally conventionally administered dose of Ox (0.06 mg/kg/d) does not enhance the adult height growth substantially and induces virilization in many cases.

TS patients are at elevated insulin resistance risk and GH treatment may rise this in particular in combination with Ox 0.06 mg/kg/d or higher [11,12, 13]. This impact, though, was reversible once the treatment was stopped [14].

Prior literature has similarly shown inconsistent effects of Ox on IGF-I and IGF-I to IGFBP-3 levels [15, 16]. Ox is not the sole method for increasing adult height among TS patients. Adult height increase can as well also be enhanced by adding GH doses instead of introducing Ox (17). However, greater GH dosages

would raise IGF-I levels besides costs, while our statistics indicate that Ox can reduce expenses related to GH. Another reason for adding Ox is that it may lead to a better physiologic hormonal condition given the inadequate androgen level of untreated cases with TS (18, 19). The launch of GH treatment at a very early age is another approach to enhance adult height gain. Our results demonstrated that GH increased adult height by 5.8 cm, 9.4 cm and 6.3 cm in age groups A, B and C respectively, confirming that early detection and initiation of GH administration have a favorable effect on the increase in adult height.

Long-term safety assessment would need a longer follow-up. Secondly, we haven't studied wellbeing and quality of life. We assume that a latency in breast growth could impact these parameters adversely, while the rise in height and length of GH therapy (i.e., sc injections) can have some beneficial impacts.

Equalizing androgenic deficiency in TS can also show some beneficial benefits comparable to the impacted wellbeing in adult androgen-treated TS patients [20].

Lastly, in the evaluation of virilizing adverse events, no consistent grading methodology was employed. Accordingly, measured virilization might misrepresent the actual frequency of virilization. Since we could not compare participants to healthy females in puberty, it is further uncertain whether the observed virilization can be considered genuine virilization or androgen-insufficient normalization.

CONCLUSION

GH treatment initiated at an early age increases the final AH and height gain in patients with TS. In our study, the height outcome in Turner syndrome patients after treatment depended on: 1- Height SDS at the start of treatment. 2- The chromosomal karyotype classic turner or variant Turner, 3- Genetically determined (MPH, SDS). 4- Earlier replacement of estrogen. 5- A low-dose of Ox (0.03 mg/ kg/d) added to GH can moderately improve adult height gain and has a rather excellent safety profile, with the exception of a minor breast growth slowdown. In patients believing this decline is less significant than the height gain increase, Ox 0.03 mg/kg/d can be added to GH to increase height.

Disclaimer

The article has not been previously presented or published and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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