Outcome of linear growth and onset of menarche following therapy in children with Turner syndrome followed up at a tertiary care referral centre: An interim report from Sri Lanka

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Abstract

Introduction: Short stature and primary gonadal failure are characteristic features of Turner Syndrome (TS). Both these aspects need to be addressed in the care of these patients for a satisfactory outcome. This is the first report from Sri Lanka documenting the short term outcome on linear growth and puberty following treatment with growth hormone (GH) and hormone replacement therapy (HRT).

Method: A prospective analysis was done on 20 patients from a cohort of patients with TS followed up at the University Paediatric Unit at the Lady Ridgeway Hospital, Colombo. An interviewer-administered questionnaire was used to record the relevant information including details and outcome of treatment with GH and HRT. Ethics Review Committee of the Faculty of Medicine, University of Colombo approved the study.

Results: Thirteen (65%) patients had a 45, X karyotype. Their mean (SD) age at presentation was 10.06 (2.83) years with a range of 3.16 to 13.58 years. Their heights at presentation were all <75th percentile on the TS specific growth chart and ranged from 84.0 to 129.8 cm with a mean (SD) of 113.6 (12.13) cm. Growth hormone (n=20) and HRT (n=14) were started at mean (SD) ages of 10.19 (2.72) and 13.41 (1.13) years respectively. Time to menarche after HRT in 9 patients ranged from 0.42 to 2 years with a mean (SD) of 1.26 (0.46) years. The gain in height with GH alone (n=12) was 3.5 to 26.4 cm and at the time of reporting at a mean (SD) age of 13.89 (2.86) years the heights of 7 patients were ≥75th percentile on the TS specific growth chart.

Conclusion: A satisfactory response to GH therapy was observed despite the mean (SD) age of presentation being 10.06 (2.83) years and thus initiating definitive therapy at a mean (SD) age of 10.19 (2.72) years.

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(Key words: Turner syndrome, outcome of linear growth, growth hormone and hormone replacement therapy, Sri Lanka)

Introduction

Turner syndrome (TS) is a common genetic disorder affecting females and is characterized by complete or partial X chromosome monosomy. It occurs in 1 in 1500 to 1 in 2500 live births and it is estimated that 3% of all females conceived are affected and approximately 99% of 45, X foetuses are aborted[1,2,3]. Short stature and primary gonadal failure are characteristic features of this condition[1,4] and treatment with recombinant human growth hormone (rhGH) and hormone replacement therapy (HRT) are important aspects in the management. The objectives of this study were to assess the effect of treatment on linear growth and onset of menarche in children with TS.

Method

A prospective analysis was performed on a cohort of 27 patients with TS followed up from April 2009 till the current analysis in September 2015, in the University Paediatric Unit at the Lady Ridgeway Hospital, Colombo. From this cohort 7 were excluded because of treatment interruptions. An interviewer-administered questionnaire was used to record socio-demographic data, age of commencing GH, duration of HRT prior to onset of menstruation (menarche) and age at menarche.

GH was given as a daily subcutaneous injection at a dose of 9.5mg/m^2/week in the evening[5]. Regular clinical assessments and anthropometric measurements were carried out by one investigator.

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The patients' heights were measured using a wall mounted stadiometer. Biochemical monitoring involves regular IGF-1 estimations to ensure optimal therapy[6]. Dose increments depend on continuous monitoring and are tailored to the needs of the patients. In our study, the dose of GH was adjusted periodically based on the clinical assessment and IGF-1 levels.

HRT was offered at an age based on several factors taking into account the wishes of the patient, age of onset of puberty of the mother, elder siblings and peers and the bone age of the patients[1,6]. A synthetic oestrogen preparation was started with a low dose and gradually increased over 2 to 3 years to simulate normal physiological puberty and a progestogen preparation was introduced during the course of treatment[1,4,7,8]. Onset and progression of puberty was monitored clinically in respect to thelarche, adrenarche and menarche. The growth of the uterus was monitored ultrasonically recording the shape of the uterus, ratio of the uterine body to cervical length and the endometrial thickness by demonstrating an endometrial echo.

The patients' serial anthropometric measurements were obtained by perusing their clinic records maintained by a single investigator. Data were analysed using descriptive statistics expressed as means, standard deviations and percentages. Ethics Review Committee of the Faculty of Medicine, University of Colombo, approved the study.

Results

The parents of the 20 selected patients gave consent for the study. Nineteen were referred for evaluation while one was a self-referral. Majority of them were from the Western Province (Table 1). Thirteen (65%) had a 45, X karyotype (Table 2). All were negative for the SRY gene.

Table 1: ***Province of residence of patients*** *(n=20)*

Province	Number of patients (%)
Western	8 (40)
Southern	3 (15)
Northern	1 (05)
North Western	4 (20)
Sabaragamuwa	1 (05)
Central	3 (15)

Table 2: ***Karyotype of the patients*** *(n=20)*

Karyotype	Number of patients (%)
45,X	13 (65)
Mosaics	04 (20)
Deletions	03 (15)

At initial presentation their ages ranged from 3.16 to 13.58 years with a mean (SD) of 10.06 (2.83) years and the heights ranged from 84.0 – 129.8 cm with a mean (SD) of 113.6 (12.13) cm. GH was started at a mean (SD) age of 10.19 (2.72) years. HRT was started in 14 patients at a mean (SD) age of 13.41 (1.13) years. The mean (SD) duration of HRT prior to menarche (n=9) was 1.26 (0.46) years with a range of 0.42 to 2 years. The mean (SD) age at menarche in 11 patients was 14.18 (1.65) years. Height gain with GH prior to HRT (n=12) was 3.5 to 26.4cm with a mean (SD) of 11.7 (6.67) cm. At the last assessment at a mean (SD) age of 13.89 (2.86) years, 7 patients had reached a height >75th percentile on the TS specific growth chart but only one of them had reached the target height (TH) based on their parents' heights. Table 3 gives a description of the patients and Table 4 is a summary of the outcome of therapy. Table 5 gives the height percentiles on the TS specific growth chart prior to treatment and Table 6 is a description of the height percentiles reached at the time of reporting.

Table 3: ***Characteristics of the study population*** *(n=20)*

	Number of patients	Mean (SD)	Range
Age at presentation (years)	20	10.06 (2.83)	3.16 – 13.58
Height at presentation (cm)	20	113.6 (12.13)	84.0 – 129.8
Bone age at presentation (years)	20	7.26 (2.34)	1.5 – 12.0
Age at starting GH treatment (years)	20	10.19 (2.72)	3.41 – 13.58
Duration of GH therapy (years)	20	3.38 (1.21)	1.33 – 5.75
Height gain with GH before HRT (cm)	12	11.7 (6.67)	3.5 – 26.4
Age at starting HRT (years)	14	13.41 (1.13)	12.0 – 15.16
Bone age at starting HRT	11	11.53 (1.34)	10.0 – 13.83
Age at menarche (years)	11	14.18 (1.65)	11.08 – 16.58
Duration of HRT prior to menarche (years)	09	1.26 (0.46)	0.42 – 2.0
Age at last assessment (years)	20	13.89 (2.86)	7.08 – 17.5
Height at last assessment (cm)	20	131.88 (10.74)	105.5 – 146.0

GH: Growth hormone; HRT: Hormone replacement therapy

Table 4: ***Effect of GH* and HRT# on the heights of the patients***

	No. of patients	Mean (SD)	Range
Height velocity prior to GH treatment (cm/year)	08	3.84 (1.55)	0.93 – 5.7
Height velocity during first year of GH treatment (cm/year)	20	6.09 (1.63)	2.33 – 9.08
Height gain with GH before starting HRT	12	11.7 (6.67)	3.5 – 26.4
Height velocity during first year after commencing HRT (cm/year)	13	4.68 (1.34)	3.0 – 7.95
Height velocity during the year prior to menarche (cm/year)	10	4.85 (1.57)	2.66 – 7.36

** GH – Growth hormone; # HRT – Hormone replacement therapy*

Table 5
Patients' heights on the Turner syndrome specific growth chart prior to treatment *(n=20)*

Height percentile prior to therapy at presentation	Number of patients (%)
<3	3 (15)
3 - <10	2 (10)
10 - <25	6 (30)
25 - <50	6 (30)
50 - 75	3 (15)

Table 6
Patients' heights on the Turner syndrome specific growth chart at the time of reporting *(n=20)*

Height percentile reached at the time of reporting	Number of patients (%)
10 - <25	6 (30)
25 - <50	4 (20)
50 - <75	3 (15)
75 - <90	6 (30)
90 - <97	1 (05)

Discussion

TS is a chromosomal disorder resulting from complete or partial X chromosome monosomy[1]. The karyotype is 45, X in approximately 50% of TS patients and 20-30% demonstrate mosaicism while Y chromosome material is reported to be found in 3-6% of them[2,3,6]. In our cohort of patients, 65% had a karyotype of 45, X and mosaicism was seen in 20% (Table 2). All these patients were negative for the SRY gene. Of the 7 patients who were excluded from this analysis due to treatment interruptions, one was positive for the SRY gene giving a rate of detection of 3.7% in our cohort.

Short stature and primary gonadal failure being inherent associations of TS, this report describes the short term outcome of therapy of these two aspects and is the first such report from Sri Lanka. TS is an indication for GH therapy[1,6]. Being a condition demonstrating GH resistance, the therapeutic dose of GH required is twice the amount that is needed in GH deficiency[9]. Untreated adult height is 136 to 147cm and is approximately 20cm less than the female average of the corresponding ethnic group[1,9]. GH therapy is indicated as early as possible when the height is below the 5th percentile of the normal female growth chart[1,3] or below the 95th percentile on a TS specific growth chart[4] which usually occur between 3-5 years of age[3,4]. Additional benefit has been reported when GH is commenced late in girls older than 9-12 years of age, by combining GH with a non aromatizable anabolic androgenic steroid such as oxandrolone[1,2,3,9]. However, the possible virilization with clitoromegaly and potential risk of hepatotoxicity and glucose intolerance, are reasons for concern[4,6]. GH is recommended to be continued till the bone age is above 14 years and the height velocity is <2cm/year[1,2,3,6,9].

Although the majority of our patients were referred for treatment, they presented late at a mean (SD) age of 10.06 (2.83) years with a mean (SD) height of 113.6 (12.13) cm. Therefore we started GH therapy at approximately 10 years of age (Table 3). Oxandrolone was not used in our patients. The mean (SD) height velocity prior to treatment of 3.84 (1.55) cm/year increased up to 6.09 (1.63) cm/year during the first year of GH therapy (Table 4). With treatment the final height increments are reported to vary from 5-15 cm with the achievement of a final adult height of approximately 150-153 cm[1,3,4]. At the time of reporting our patients were still on GH ± HRT and had not reached the adult height. But we were able to demonstrate a mean (SD) gain in height of 11.7 (6.67) cm with GH therapy in 12 patients after treatment for 1 year 6 months to 5 years 9 months, prior to commencing HRT (Table 4).

Primary gonadal failure occurs in almost 90% of girls with TS. Spontaneous puberty is seen in approximately 30-40% and 2-5% will have spontaneous menarche while 1% is spontaneously fertile. However, induction of puberty and/or maintenance oestrogen therapy will be required by the majority[1,4,6,7]. An oestrogen preparation is recommended to be started at 12-13 years of age and not later than 14 years[1,4]. Natural oestrogen is preferred over a synthetic preparation due to fewer side effects[4].

None of our patients went into spontaneous puberty and at the time of reporting HRT had been started in 14 patients at a mean (SD) age of 13.41 (1.13) years. During the first year of HRT in 13 patients, the height velocity ranged from 3.0–7.95 cm/year with a mean (SD) of 4.68 (1.34) cm/year. With the combined therapy, in spite of delay in initiating treatment in some patients due to late presentation, at the time of reporting at a mean (SD) age of 13.89 (2.86) years, 7 patients had reached a height $\geq 75^{th}$ percentile on the TS growth chart. This was a satisfactory improvement as the heights of all the patients prior to therapy were below the 75^{th} percentile. Although only one had reached the TH based on their parents' heights, there is further room for improvement as the measurements at the time of reporting were not the final adult heights.

Conclusion

A satisfactory response to GH therapy was observed despite the mean (SD) age of presentation being 10.06 (2.83) years and thus initiating definitive therapy at a mean (SD) age of 10.19 (2.72) years.

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