

Original Article:**Initial catch-up growth in children with hypothyroidism on thyroxine replacement therapy**

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ABSTRACT

Background: There is a paucity of observational data from India on initial catch up growth in hypothyroid children started on thyroxine replacement therapy.

Methods: We retrospectively studied 44 children and adolescents (32 girls) with a diagnosis of primary hypothyroidism i.e., (thyrotropin > 15 μ IU/mL and thyroxine < 55ng/mL). All were started on treatment with oral thyroxine. The dose was adjusted to maintain thyrotropin between 0.5-5 μ IU/mL. Height was measured at baseline and at each follow-up visit and height standard deviation scores (HtSDS) were calculated. We studied the therapeutic benefit of thyroxine replacement therapy on growth in the initial couple of years of treatment.

Results: Dose of thyroxine required to restore euthyroidism was 4.1 ± 2.5 μ g/kg body weight. The dose fell from 9.7 ± 2.4 μ g/kg body weight in infants to 3.0 ± 1.5 μ g/kg body weight in adolescence ($p < 0.001$). Likewise, the dose per unit body surface area also fell consistently from 207 ± 70.3 μ g/m² in infants to only 89.3 ± 17.9 μ g/m² in adolescents ($p < 0.001$). The initial HtSDS was -2.0 ± 1.5 and this improved by 0.4 to final value of -1.6 ± 1.3 ($p < 0.001$) after an average follow up of 14.1 ± 2.5 months. The mean catch-up growth velocity, weighted for the duration of follow-up was 7.7 cm/year.

Conclusions: The HtSDS deficit because of hypothyroidism is partially regained in the first few years after treatment.

Key words: *Catch up growth, Primary hypothyroidism, Thyroxine dose*

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INTRODUCTION

Hypothyroidism is a common and an eminently treatable endocrine cause of growth retardation in children.¹ The disorder may manifest in early childhood, either as congenital or acquired juvenile hypothyroidism. The first clinical manifestation of hypothyroidism may be retardation of the growth; but it often goes unrecognized. Before puberty, thyroid hormone appears to be a major prerequisite for normal growth and maturation of bone.² Childhood hypothyroidism results in growth arrest,

delayed bone age, epiphyseal dysgenesis and short stature. In severe cases, linear growth is almost completely halted. When adequate treatment is given, growth often resumes at a rate faster and beyond the normal rate for age.³ This phase of accelerated growth constitutes the “catch-up growth” phenomenon. Catch up growth should result in an increase in the height standard deviation score (HtSDS) over time. There are very few observational studies on catch-up growth in adequately treated hypothyroid children from South Asia.^{4,5} Hence we decided to take up the present study.

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MATERIAL AND METHODS

In this retrospective study, case records of children and adolescents fulfilling the following inclusion and exclusion criteria were reviewed for data regarding stature, growth and adequacy of thyroid hormone replacement therapy. The study was approved by the Institutional Ethics Committee. Children (age less than 18 years) diagnosed to have overt primary hypothyroidism defined by the presence of low circulating thyroxine i.e. total thyroxine (T_4) <55 ng/mL along with significantly elevated thyroid stimulating hormone (TSH) (> 15 μ IU/mL), were included in the study. Children who were already on treatment when they first visited our hospital, or those who were unable to maintain a euthyroid status (i.e., TSH 0.5-5 μ IU/mL) during follow-up were excluded.

Height standard deviation scores (HtSDS) were calculated from normative data for age and sex, available in the data tables accompanying the Centers for Disease Control (CDC), Atlanta, growth charts⁶ (available at URL: www.cdc.gov/growthcharts/data_tables.htm). The coefficient of variation (CV) available in these gender specific tables was multiplied by the corresponding mean to obtain the standard deviation (SD) for height at each age. The HtSDS was calculated by the formula: $HtSDS = (\text{mean height for age} - \text{patient's height})/SD$.⁷ Weight was measured on a beam balance (Tulaman, Hyderabad) while wearing minimal clothing.

Treatment was started with thyroxine. Dose was adjusted to maintain TSH between 0.5-5 μ IU/mL. The total dose of thyroxine required to maintain euthyroid status was noted. Height and weight were re-measured at each follow up visit. Only heights recorded within the initial 2 years after commencement of thyroxine were used in this study. Girls achieving age of 13 years and boys reaching 15 years of age, anytime within 2 years from the

commencement of thyroxine replacement were excluded from the growth analysis in view of the difficulty in accurately recording height changes during these periods of marked growth deceleration. Children aged less than 2 years at baseline were excluded from growth analysis.

The thyroid hormones were measured using radioimmunoassay (RIA) or immunoradiometric assay (IRMA) kits, manufactured by the Board of Radiation and Isotope Technology (BRIT), Vashi, Navi Mumbai. The total serum T_4 was measured using BRIA Mag 4 RIA kit, and serum TSH was measured by IRMAK-9 (IRMA) kits. The range of measurement for serum T_4 and TSH were 15-240 ng/mL and 0.15-50 μ IU/ml respectively.

Statistical analysis

Data were recorded on a predesigned proforma and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond, USA). All the entries were double-checked for any possible error. The difference between the last height (in cm) recorded and the initial height (in cm) divided by the duration of follow up (in months) was the individuals growth velocity in cm/month. This, multiplied by 12 gave the growth velocity in cm/year. Weighted mean of the growth velocity was calculated by the formula; $\text{mean growth velocity} = \frac{\sum \text{growth velocity} \times \text{duration of follow-up}}{\sum \text{duration of follow-up}}$.

The data are presented as mean \pm standard deviation for continuous variables. Paired t-test was used to compare the means of initial and final HtSDS. One-way analysis of variance (one-way ANOVA) was used to calculate difference in thyroxine dose between different age groups of children. Tukey "Honestly Significant Difference" post-hoc test was done to study inter-group comparisons. A p-value less than 0.05 was considered as significant for all these tests. Statistical software Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

Forty four children and adolescents (mean age 8.8 ± 4 years; range 5 months-17 years; 32 females) with newly diagnosed primary hypothyroidism were included in this study. Family history of hypothyroidism was present in 45% of the patients.

Dose of thyroxine per unit body weight required to restore euthyroidism was 4.1 ± 2.5 $\mu\text{g/kg}$ of body weight. The dose requirement fell (Table 1) from 9.7 ± 2.4 $\mu\text{g/kg}$ in infants to 3.0 ± 1.5 $\mu\text{g/kg}$ in adolescence ($p < 0.001$). Likewise, the dose per unit body surface area (BSA) also fell consistently from 207 ± 70.3 $\mu\text{g/m}^2$ in infants to only 89.3 ± 17.9 $\mu\text{g/m}^2$ in adolescents ($p < 0.001$).

After excluding children less than 2 years of age and also girls achieving 13 years of age and boys achieving 15 years of age during the initial 2 years of follow-up growth assessment was done in 36 patients. Their mean age was 9.4 ± 2.8 years; there were 26 females. The mean duration of follow up was 14.1 ± 2.5 months. The mean growth velocity, weighted by the duration of follow-up was 7.7 cm/year.

The initial mean HtSDS for 36 patients was -2.01 ± 1.51 and this improved by 0.42 standard deviations to a final value of -1.6 ± 1.3 (p value < 0.001). In girls, the initial HtSDS of -2.08 ± 1.68 improved to a final value of

-1.63 ± 1.3 (Δ HtSDS = 0.55; $p = 0.021$). Likewise, in boys HtSDS improved (though not significant statistically) from -2.3 ± 1.9 initially to -2.03 ± 1.7 (Δ HtSDS = 0.22; $p = 0.24$), by the end of the follow-up.

DISCUSSION

Hypothyroidism is the result of the deficient production of the thyroid hormone. Thyroid hormones act on growth plate, bones and the growth hormone (GH) - insulin like growth factor (IGF-1) axis to modulate growth. Early diagnosis and treatment of infants born with congenital hypothyroidism, through neonatal screening, results in normal linear growth and attainment of full growth potential. However, delayed diagnosis and treatment of congenital hypothyroidism and/or acquired juvenile hypothyroidism may result in partial catch-up growth and compromised final adult height of patients.

A catch-up process that brings a child to the 50th percentile or above, for a given population (HtSDS ≥ 0) is considered complete. A catch-up that brings a child to greater than - 2 standard deviation score (HtSDS) but below 0 is considered incomplete. Catch-up growth may be also be considered acceptable when the child attains a final height within the genetic potential range (mid-parental height ± 1 standard deviation).⁸

Table 1: Thyroxine dose requirement in different age groups

Dose	Infants (<1 Years)	Toddlers (1-3 years)	Preschool (3-6 years)	School (6-12 years)	Adolescents 12-18 years)	p-value
$\mu\text{g/kg}$ body weight	9.7 ± 2.4	8.8 ± 1.0	5.7 ± 1.5	3.2 ± 1.1	3.0 ± 1.5	*
$\mu\text{g/m}^2$ body surface area	207 ± 70.3	195 ± 26.1	137 ± 33.5	90.0 ± 26.2	89.3 ± 17.89	†

* Infants vs toddlers $p = 0.9133$; infants vs preschool $p = 0.0079$; infants vs school-going $p < 0.001$; infants vs adolescents $p < 0.0001$; toddlers vs preschool $p = 0.0160$; toddlers vs school-going $p < 0.0001$; toddlers vs adolescents $p < 0.0001$; preschool vs school-going $p = 0.0139$, preschool vs adolescents $p = 0.0265$; and school-going vs adolescents $p = 0.9961$

† Infants vs toddlers $p = 0.9870$; infants vs preschool $p = 0.0627$; infants vs school-going $p < 0.0001$; infants vs adolescents $p = 0.0001$; toddlers vs preschool $p = 0.0666$; toddlers vs school-going $p < 0.0001$; toddlers vs adolescents $p < 0.0001$; preschool vs school-going $p = 0.0586$; preschool vs adolescents $p = 0.1248$; school-going vs adolescents $p > 0.99$

Catch-up growth may be complete or incomplete depending upon many factors including the age at presentation, the severity of hypothyroidism, duration of unrecognized and untreated disease, and the genetic target height.

Three different types of catch-up growth can be distinguished. Type A pattern is common in infancy and early childhood. When growth restriction ceases, height velocity increases up to four times the mean velocity for chronological age in order to compensate rapidly and fully for the height deficit. Once the original curve is re-approached, height velocity returns to normal. A classic example of catch-up growth type A occurs after institution of a gluten-free diet in childhood coeliac disease.

In catch-up growth type B a small or no increase of height velocity occurs after the growth restriction has ceased as compared with the mean velocity for chronological age. However, growth continues for longer than usual, so that ultimately the growth arrest is compensated for. Type C is a mixture of types A and B. When growth restriction ceases, there is an increase in height velocity as well as a prolongation of growth.⁹⁻¹²

Before the neonatal screening was initiated in the 1970s, the percentage of children with congenital hypothyroidism (CH) having a height below the 10th percentile has been shown to range from 19% to 31%.¹³ Adult stature without treatment ranged from 1 to 1.6 metres, depending on severity, gender and other genetic factors.¹³

Growth data were available for 36 patients in our study. The growth velocity in the short-term was robust at 7.7 cm/year, which was higher than that seen at any period of childhood after the initial two years of life, excepting the pubertal growth spurt. This increased velocity accounted for a partial catch-up growth with a

height gain of 0.42 SDS in the whole group over merely 14.1±2.5 months of thyroxine replacement. The data for the girls with hypothyroidism was similar. However for the boys, though there was a trend towards improvement in the HtSDS, the change was not statistically significant. This was most likely due to small sample size (n=10). Similar results were reported in other studies^{14,15} as well.

In a study¹⁴ of 15 children with neglected hypothyroidism (mean age 6.4±4.2 years), patients had HtSDS of -4.3±2.5 and delayed bone age (-4.5±2 years), with defective GH response to clonidine and low IGF-I concentration. After two years of treatment with levo-thyroxine, their HtSDS has increased from -4.3±2.5 to -2.7±2.3. This was associated with a significant improvement in their GH response to clonidine and increased IGF-I generation in response to GH stimulation. HtSDS increments correlated significantly with free T4 concentrations, while the growth velocity standard deviation scores (GVSDS) correlated significantly with increments in IGF-1 concentrations. The capacity to establish a significant, catch-up growth spurt was associated with recovery of GH-IGF-1 axis, even after a long period of thyroid dysfunction.

Studies, which have followed up treated hypothyroid patients till attainment of final height, have shown that despite the presence of catch up growth, the height lost during the period of hypothyroidism is only partially regained, thereby leading to a compromised final adult height.

In one study,³ hypothyroidism was diagnosed in 18 girls (mean age, 11.4±2.7 years; bone age, 6.2±3.1 years) and 6 boys (age, 10.6±4.7 years; bone age, 6.4±2.7 years) with serum thyroxine level 1.1±0.3 µg/dL. At diagnosis, heights were 4.04±0.5 and 3.15±0.4 SD below the mean heights for age of normal girls and boys, respectively. During the first 18 months of therapy, the children's skeletal maturation

exceeded the maturation expected for their statural growth, regardless of whether or not they were undergoing pubertal development. At maturity, girls and boys stood approximately 2 SD below normal adult stature ($HtSDS = -2.1 \pm 0.2$), at 149 ± 5 cm and 168 ± 5.1 cm, respectively with loss of 6-7 cm of the predicted adult height. The deficit in adult stature was significantly correlated to the duration of hypothyroidism before treatment ($p < 0.01$). Delay in therapy was considered to be a critical factor responsible for the deficit in final adult height.

In another study,¹⁵ 20 girls and 9 boys with juvenile primary hypothyroidism were followed up until they reached final height. At presentation the mean age of the boys was 9.5 years (range: 3.7-14.2; mean bone age = 6.3 years) and mean age of girls was 8.8 years (range 3.0-13.0 years; mean bone age = 5.4 years). On adequate treatment of the hypothyroidism, the onset of puberty was 1.2 years later in girls than in the normal population but the duration of puberty was reduced. The pattern of growth in girls with treated hypothyroidism was abnormal as the growth continued after menarche, at a time when normal girls would have almost stopped growing. During the second year after menarche patients still had a mean growth velocity of 4.1 cm/year.

During treatment the rate of skeletal maturation exceeded the change in chronological age. As a consequence at the attainment of final height all the patients except one girl were below the 50th centile. These data suggest that juvenile primary hypothyroidism can result in a permanent height deficit and disharmony between growth and sexual maturation in girls, despite adequate treatment.

Evidence from animal studies suggests that catch-up growth is due, in large part, to a delay in growth plate senescence. Growth plate

senescence refers to the normal, programmed changes that occur in the growth plate over time i.e. growth plate chondrocytes may have a finite proliferative capacity that is gradually exhausted, causing growth to slow and eventually to stop. With increasing age, there is a decrease in the linear growth rate, the chondrocyte proliferation rate, the height of the growth plate, and the number of cells in each growth plate zone.

Hypothyroidism suppresses the rate of growth plate chondrocyte proliferation, but it conserves the proliferative capacity of the chondrocytes and therefore it slows their senescence. Consequently, after transient growth inhibition, growth plates retain a greater proliferative capacity, are less senescent, and, hence, show a greater growth rate than expected for age, resulting in catch-up growth.^{8,16}

In the present study, we also looked at the dose of thyroxine required to maintain euthyroid status (TSH 0.5-5 mIU/L) at different ages. As expected,¹⁷ the replacement dose of thyroxine consistently fell from 9.7 ± 2.4 $\mu\text{g/kg}$ in infants to 3.04 ± 1.5 $\mu\text{g/kg}$ in adolescence ($p < 0.001$) (Table 1). This is usually attributed to the higher body surface area in relation to the body weight in smaller children, particularly infants. If this were the only explanation, then the dose of thyroxine per m^2 body surface area should have been the same irrespective of the age group. However, we have noted an equally consistent dose decrement with age, even when the dose of thyroxine was calculated per unit body surface area (Table 1).

This suggests that the reduced thyroxine dose both per kg as well as per m^2 in older children and adults might be due to either a better bioavailability of thyroxine or a lower rate of metabolic clearance. A pharmacokinetic study of thyroxine at different age groups is needed to clarify this issue.

The height HtSDS deficit because of hypothyroidism is partially regained in the first couple of years after treatment, on account an increased growth velocity. However, follow up till the attainment of final height is needed to conclude about the completeness of the catch up growth. Dose requirement of thyroxine is reduced in older children/adolescents both in terms of dose per unit body weight as well as per unit body surface area.

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