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Original Research Article

Effect of thyroxine on initial catch-up growth in children with hypothyroidism

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ABSTRACT

Background: Hypothyroidism is a common endocrinal cause of growth retardation in children. Following adequate treatment with thyroxine, growth resumes at an accelerated rate which is known as catch-up growth. There are few observational studies from India on the growth parameters following treatment with thyroxine in children with hypothyroidism.
Methods: A retrospective study was done in children aged 2-10 years who were newly diagnosed cases of primary hypothyroidism [Total serum Thyroxine (T4) levels <5 µg/dl and serum Thyroid Stimulating Hormone (TSH) levels >15 µU/ml] and treated with oral thyroxine to attain euthyroid state. Height measured before starting treatment and at the time of follow up visits was noted, the Height Standard Deviation Scores (HSDS) were calculated. The effect of thyroxine on linear growth was studied.
Results: There were 23 children who were diagnosed as having primary hypothyroidism of whom 16(69.6%) were females and 7(30.4%) were males. The mean age of the children studied was 7.3±2.3 years. The mean dose of thyroxine required to maintain euthyroid status was 4.6±2.2 µg/kg/day. Mean duration of follow up was 13.7±2.4 months. The initial HSDS was - 2.31±0.9 which improved to a final value of - 1.7±0.76 (ΔHSDS0.61, p value <0.0001). Mean height velocity was 8.1 cms/year.
Conclusions: Following adequate thyroxine replacement therapy catch-up growth occurs and increased growth velocity leads to partial regain of height deficit in the first couple of years of treatment.

Keywords: Catch-up growth, Height standard deviation scores, Height velocity, Primary hypothyroidism, Thyroxine

INTRODUCTION

Hypothyroidism is one of the most common endocrinopathies seen in children and adolescents. Primary hypothyroidism occurs due to deficient functioning of the thyroid gland and manifests as congenital or acquired hypothyroidism. Thyroid hormones are necessary for early brain development, somatic growth, bone and pubertal maturation. They have a profound direct stimulatory effect on bone growth and skeletal maturation.

Beyond the age of 3 years, when thyroid hormone dependent brain development is completed, the effects of thyroid deprivation is more evident on physical growth, metabolic functions and skeletal maturation, with less impairment of intellectual functions. Hypothyroidism in childhood is almost invariably associated with growth failure and short stature may be the presenting feature.[1] Failure of growth is caused by a decrease in the direct effect of thyroid hormones on skeletal growth and by a secondary reduction in growth hormone secretion and concentration of IGF-1 and other growth factors.[2]

Treatment with thyroxine resolves these abnormalities and growth resumes. This growth occurs at a rate greater than the normal rate for age. This period of rapid linear growth is known as catch-up growth which helps the child to reach towards his/ her target height.

Most studies have assessed the growth of infants with congenital hypothyroidism detected by neonatal screening.[3-5] Few studies have been done to assess the catch-up growth in older children with hypothyroidism. Therefore, author undertook this study to assess the catch-up growth in children with primary hypothyroidism following treatment with thyroxine.

METHODS

This retrospective study was conducted in the Endocrine clinic of a tertiary care hospital in Ahmedabad, Gujarat, Western India. Institutional Ethical Committee approval was taken.

Inclusion criteria

- Children aged between 2-10 years who were newly diagnosed as having primary hypothyroidism [Total serum thyroxine (T4) levels <5 µg/dl and serum Thyroid Stimulating Hormone (TSH) levels >15µU/ml] and started on thyroxine therapy were included in the study.

Exclusion criteria

- Children who had secondary hypothyroidism.
- Those who were already on thyroxine therapy before they first visited authors clinic.
- Those who were not able to maintain euthyroid status (serum T4 levels 6.5-14µg/dl and TSH levels 0.7-4µU/ml) during follow up visits.[1]

Case records of the children diagnosed with Primary hypothyroidism between 2014 to 2018, who fulfilled the inclusion criteria were analyzed. Results of the thyroid function tests which led to the diagnosis of hypothyroidism and the dose of thyroxine required to maintain euthyroid status were noted. Baseline height prior to starting treatment and the height at the time of last follow up visit after commencement of treatment with thyroxine were recorded in centimeters (cms). Follow up heights recorded within the first two years after starting treatment were used in the study.

Height Standard Deviation Scores (HSDS) were calculated for the initial height prior to starting treatment and for the final follow up height recorded following treatment. World Health Organization (WHO) growth charts and data tables were used for children between 2-5 years of age and Indian Academy of Pediatrics (IAP) growth charts and data tables were used for children between 5-10 years of age.[6,7] These charts and tables were used for obtaining the mean height, height centiles, z scores and Standard Deviation (SD) values appropriate for age and gender. HSDS was calculated by dividing the difference between the mean height (50th percentile) and the patient's height by the standard deviation of height for that age and gender. Serum total thyroxine and Thyroid Stimulating Hormone (TSH) levels were measured by Electrochemiluminiscent immunoassay method by Elecsys T3 and Cobare analysers, Roche diagnostics, Germany.

Statistical analysis

The data was recorded in a predesigned proforma. The values were presented as mean±standard deviation for continuous variables. Mean of initial HSDS and final HSDS were calculated and compared using paired t test. p value <0.05 was considered as significant. Difference of the mean initial and final HSDS (Δ HSDS) was calculated. The difference between the final follow up height recorded (in cms) and the initial height (in cms) divided by the duration of follow up (in months) gave the individual height velocity (in cms/month). This value was multiplied by 12 to obtain the height velocity in cms /year. Mean height velocity of the patients was calculated.

RESULTS

Total 23 children between 2-10 years of age were newly diagnosed as cases of primary hypothyroidism and included in the study. Mean age was 7.3±2.3 years (Range- 2 years 4 months to 9 years 10 months).

Table 1: Parameters of catch-up growth of the hypothyroid children.

Parameter	Total (n=23)	Girls (n=16)	Boys (n=7)
Mean age at time of diagnosis (years)	7.3±2.3	7.7±2.1	6.2±2.3
Mean duration of follow up (years)	13.7±2.4	13.8±2.3	13.5±2.4
Mean height velocity(cms/year)	8.1	8.0	8.1
Mean Initial HSDS	-2.31±0.9	-2.29±1.01	-2.34±0.57
Mean final HSDS	-1.7±0.76	-1.71±0.87	-1.67±0.40
ΔHSDS	0.61	0.59	0.67
p value	<0.0001	<0.001	<0.001

Data wise 16(69.6%) were females and 7(30.4%) were males. 8(34.8%) patients had a family history of hypothyroidism. The mean dose of thyroxine required to maintain euthyroid state was 4.6±2.2 µg/kg body weight /day. The mean dose was 5.8±1.1 µg/kg/day in children aged 2-5 years and 3.7±0.9 µg/kg/day in children aged 5-10 years. The children were followed up for a mean duration of 13.7±2.4 months. Taking all the 23 patients into consideration, the mean initial HSDS was- 2.31±0.9 which improved to a final follow up HSDS of - 1.7±0.76 (ΔHSDS,0.61and p value <0.0001). Mean height velocity

was 8.1 cms /year. The mean height velocity in children aged 2-5 years was 10.1 cms /year while that of children aged 5-10 years was 7.6 cms /year. The mean initial and final HSDS, ΔHSDS and height velocity of the girls and boys with primary hypothyroidism are shown in table 1.

DISCUSSION

Growth refers to the progressive increase in size of various parts and organs of the body and is characterized by an increase in height from infancy to adulthood. Linear growth can be expressed in terms of change in Height Standard Deviation Score (HSDS) over a period of time and growth velocity. HSDS expresses the height of the child in comparison with the mean height for that age. Height velocity refers to the rate of increase in height over a period of time. A high velocity from birth with a rapid deceleration up to 3 years of age is seen, followed by a period with a lower and slowly decelerating velocity up to puberty. Puberty starts with an increased velocity and after the age of peak velocity a deceleration is observed until growth ceases.[8] While in the first years of life, the length of healthy infants can cross the percentiles towards their genetic target height standard deviation score, height tends to remain within a narrow "channel" on the growth charts between 3 years and the onset of puberty, close to the same percentile or Standard Deviation Score (SDS) position. The tendency to keep to this narrow and predictable track of growth is called "channelization'.[9]

Growth is affected by genetic, nutritional, environmental, socioeconomic and hormonal factors. Thyroid hormones act on the growth plate, bones and growth hormone-IGF-1 axis to modulate growth. Hypothyroidism in childhood is associated with growth failure and short stature (height below 2SD of mean height). Effective neonatal screening has led to early diagnosis and treatment of congenital hypothyroidism. Studies have shown that treatment with thyroxine started soon after birth in these children leads to normal linear growth. The onset and completion of puberty and achievement of adult height have been found to be normal in these children.[3-5] However, delayed diagnosis of congenital hypothyroidism or acquired juvenile hypothyroidism leads to growth retardation. There is a slowing of growth with a downward deviation from the standard growth curve. On starting replacement therapy with thyroxine, exaggerated acceleration in linear growth occurs which is above the statistical limits of normalcy for age and maturity. The term ''catch-up growth" is used to describe this period of rapid growth in children that follows a period of growth inhibition, leading towards their original growth channel. Catch-up growth can be expressed in terms of change in height velocity but since height velocity is highly variable and dependent on the age and height percentile of the child, HSDS and its change over a period of time is a better parameter of catch-up growth, particularly when assessed over the full trajectory. Catch-up growth results in an increase in HSDS over time.[9]

The capacity to catch-up is variable in different phases of growth and among different individuals suffering from the same disease. The major factors influencing catch-up growth include the nature, intensity and duration of the preceding growth disorder, efficacy of therapy, age at onset of therapy and stage of development of the child. Catch-up growth may be complete or incomplete depending on the final height achieved with reference to genetic target height. It is complete if the resultant final height is close to the target height (mid-parental height ±1 SD) or 50th percentile or above for a given population (HSDS ≥0). A catch-up that brings a child to a HSDS >-2 but <0 is considered incomplete. Increase in height velocity is clearly recognizable in the first year after removal of the cause of growth retardation especially in early and mid-childhood. Interpreting catch-up growth during adolescence is difficult because of a large variability in onset, duration and magnitude of pubertal growth spurt. Catch-up-growth is then difficult to distinguish from pubertal growth spurt. In patients with prolonged severe hypothyroidism, catch-up-growth may be incomplete if it coincides with pubertal growth spurt and the final height may be compromised due to too rapid bone maturation.[10]

Growth is controlled by dynamic and complex multisystem interactions that make a child return to its path of growth after any deviation. Two main hypotheses have been proposed to explain the mechanism of catch-up growth- (a) Neuroendocrine hypothesis by Tanner and (b) Growth plate hypothesis. According to the growth plate hypothesis, catch-up growth occurs because growth inhibiting conditions conserve the limited proliferative capacity of the growth plate chondrocytes, thus slowing the normal process of growth plate senescence. When the growth inhibiting condition like hypothyroidism resolves, the growth plates are less senescent and therefore grow more rapidly than normal for age resulting in catch-upgrowth.[11,12]

Catch-up growth occurs either by an increase in growth velocity (Type A catch-up growth) or an increase in the total duration of growth by delayed growth plate closure (Type B) or a combination of both (Type C). Majority of young children with hypothyroidism show Type A catch-up growth following thyroxine therapy. An increase in height velocity occurs to such an extent (up to four times the mean velocity for the corresponding chronological age) that the height deficit is quickly eliminated. Once the original curve is reached, height velocity returns to normal.[8-10]

In this study of 23 hypothyroid children, accelerated growth was noted following thyroxine therapy with a mean height velocity of 8.1cms/year. The mean height velocity in children aged 2-5 years was 10.1 cms/year while that of children aged 5-10 years was 7.6 cms/year. Normal height velocity is 6-7 cms each in the third and fourth year of life, followed by 5 cms/year until the onset of pubertal growth.[1,13] Therefore, the height velocity observed in this study was significantly higher than the normal height velocity for the given age. There was a

height gain of 0.61 SDS over a mean duration of 13.7±2.4 months. This is significant as an SDS change of >0.25 /year is rarely seen in longitudinal growth studies in normal children.[9] Both girls and boys showed significant height gain (p value <0.001) following treatment. Similar results were also noted in other studies.[14,15]

Rajitha et al, who studied catch-up-growth in 36 children with primary hypothyroidism noted that the mean HSDS improved by 0.42 standard deviations from initial -2.01±1.51 prior to treatment to -1.6±1.3 following treatment with thyroxine (p value <0.001).The mean duration of follow up was 14.1±2.5 months and the mean growth velocity on follow up was 7.7 cm/year.[14]

Gutch et al, studied the growth of 87 patients of juvenile hypothyroidism aged between 6-18 years following treatment with thyroxine. They noted that the HSDS increased from -2.9±0.9 at the time of starting treatment to -1.8±0.8 after 12 months (p value <0.001).The height velocity increased from 4.9±0.8 cms/year in the year before treatment to 8.7±1.3 during treatment (p value <0.001).[15]

Ranke et al, studied catch-up-growth in childhood onset primary hypothyroidism following treatment with thyroxine in 20 prepubertal children starting treatment at an average age of 4.4 years and HSDS of -3.1±0.8. They were followed for 3 pre-pubertal years and the change in HSDS score was 1.60±0.56, 0.57±0.33 and 0.28±0.38 at the end of the first, second and third year of treatment. 11 children who were followed to adult height reached a height HSDS of -0.11±1.1 and all were within their target height range. They concluded that catch-up growth in childhood onset primary hypothyroidism is complete.[16]

Soliman et al, studied 15 infants and children with neglected congenital hypothyroidism with an average age of 6.37±4.1 years. At the end of one year of treatment, HSDS increased from -4.3±2.5 to -2.7±2.3. The basal growth hormone and IGF-1 concentrations and peak growth hormone response to Clonidine increased but was significantly lower compared to those of age matched controls.[17]

Long term studies done in older children and adolescents which followed patients till they reached the final adult height have noted that despite catch-up growth, patients with prolonged hypothyroidism partially regained the lost height leading to compromised adult height.[18-20]

Pantsiotou et al, studied long-term growth of 20 girls and 9 boys with juvenile hypothyroidism till they reached final height. They noted that during treatment, the rate of skeletal maturation exceeded the changes in chronological age. The final adult height attained in all patients except one girl was below the 50th percentile. In girls, growth at puberty both in duration and quality was abnormal. They concluded that prolonged severe hypothyroidism may diminish the potential for catch-up growth and that a delay in onset of treatment is a crucial factor in limiting catch-upgrowth.[18]

Similarly, Rivkees et al, studied long-term growth 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 severe primary hypothyroidism. 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 with thyroxine, they noted that the children's skeletal maturation exceeded the maturation expected for their linear growth, regardless of whether or not they were undergoing pubertal development. At maturity, girls and boys stood approximately 2 SD below normal adult stature, at 149±5.0 cm and 168±5.1 cm, respectively. The deficit in adult stature was significantly related to the duration of hypothyroidism before treatment (p<0.01).[19]

Boresma et al, in his study on catch-up growth after prolonged hypothyroidism noted that although the capacity to establish a remarkable catch-up growth spurt was intact, even after a long period of thyroid dysfunction, catch-up growth may be incomplete if treatment has been started shortly before or during puberty.[20] The above studies indicate that there is marked catch-up growth during thyroid replacement therapy but it may not always be complete.

This study has limitations. It was a small study in children between 2-10 years of age for catch-up growth in the initial period following thyroxine replacement therapy. A larger sample size, including children of all age groups with long term follow up till adulthood will give more information regarding factors affecting the extent of catch-up growth and the final adult height achieved.

CONCLUSION

Hypothyroidism is a common treatable endocrinal cause of growth retardation in children. Following adequate thyroxine replacement therapy, catch-up growth occurs and increased growth velocity leads to partial regain of the height deficit in the first few years. Delay in diagnosis may compromise the final adult height attained, therefore early diagnosis and treatment of this disorder is necessary.

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