Height prognosis in children with late - diagnosed congenital hypothyroidism

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It is a general belief that early and adequate thyroid hormone replacement achieves normalization of growth as well as disappearance of clinical sings and symptoms of hypothyroidism. Due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroidic children. The limited number of previous studies have suggested permanent height deficit in these children.

In this study we present longitudinal growth and final height of 20 children (14 females and 6 males) in whom the duration of hypothyroidism before onset of therapy varied from three to 12.6 years. The etiological distribution of cases revealed ectopic thyroid tissue in nine cases, agenesis in seven, and dyshormonogenesis in four cases. At the time of the diagnosis all hypothyroidic children had severe growth retardation (mean height SDS ± SD -3.95 ± 1.07) due to prolonged hypothyroidism. Although the catch-up spurt corrected an important part of the initial height deficit in all patients, only nine patients reached or exceeded their target height, and the final height of five patients remained below 2 SD of mean. Despite treatment, prolonged hypothyroidism may result in compromised adult height in some patients. The contributing factors to this height deficit may include the duration of hypothyroidism, the height deficit at the time of the diagnosis, etiological differences and the diminished potential for catch-up growth in late-diagnosed hypothyroidism.

Key words: congenital hypothyroidism, short stature.

Thyroid hormone action is essential for normal growth and bone maturity. It is established that growth is normal in children with congenital hypothyroidism (CH) detected by screening and treated from the early neonatal period[1-3]. However, due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroidic children. The limited number of previous studies have suggested permanent height deficit in children with late-diagnosed congenital and acquired hypothyroidism[4-6].

In this study we present longitudinal growth and final height of late-diagnosed children with CH.

Material and Methods

Twenty children (14 females and 6 males) in whom the duration of hypothyroidism before onset of therapy varied from three to 12.6 years were included in the study. Hormonal determination of T_3, T_4 and TSH were made by radioimmunoassay. Etiological diagnosis was based on the results of technetium-99 scan. The etiological distribution of cases revealed ectopic thyroid in nine cases, agenesis in seven and hyperplastic thyroid in four. All patients were given thyroid hormone replacement therapy ($L\text{-}T_4$) at a dose of 100-125 $\mu g/m^2$/day and were followed every 3-6 months during the therapy.

The height and weight were determined and serum thyroid hormone tests performed at each visit, and the dose of $L\text{-}T_4$ was adjusted accordingly. Bone age was determined every six months or yearly using Greulich and Pyle standards[7]. Height SDS was calculated as follows:

$\frac{X-M}{SD}$ with X the height of the patient expressed in centimeters, M the mean height for the patient's chronological age

and SD the standard deviation of the mean height according to Tanner's standard[8]. Target height was calculated using standard equations for boys) [1/2 (maternal + paternal height + 13)] and girls [1/2 (maternal + paternal height-13)].

Statistical analysis was performed using tests Statistical Package for the Social Sciences, update 1996, version 7.5 (SPSS, Chicago). Results were expressed as mean ± SD. Differences between mean values were tested using Mann-Whitney U test for non-paired samples and Wilcoxon test for paired samples. Pearson or Spearman's correlation analysis was used accordingly.

Results

The clinical characteristics of the hypothyroidic children are shown in Table I. The mean pretreatment chronological age was 5.7 ± 3.2 years, the mean bone age was 1.9 ± 1.8 years, and the mean height SDS for chronological age was -3.95 ± 1.1 in all patients. The mean pretreatment T_4 level was 1.8 ± 1.1 µg/dl and TSH level was 102.2 ± 47.6 mIU/L (normal T_4 4.5-12 µg/dl and normal TSH 0.49-4.67 mIU/L). During treatment, serum T_4 levels were in normal range in all patients; however, serum TSH levels remained high in some patients (Figs. 1, 2).

The mean final height in both boys and girls was less than the mean target height, although the difference was not statistically significant ($p > 0.01$). (Table II). Only nine patients reached or exceeded their target height, and the final height of five patients remained below 2 SD of mean (Fig. 3). The final height SDS was correlated with height SDS at diagnosis ($r = 0.453$, $p < 0.05$) but not with age at diagnosis ($r = -0.098$, $p > 0.05$). There were no correlation between the deficit in adult height and chronological age, height age or bone age at diagnosis ($r = 0.253$, $p = 0.282$; $r = 0.025$, $p = 0.920$; $r = 0.240$, $p = 0.322$, respectively).

Table I. Clinical Characteristics of 20 Children With Congenital Hypothyroidism at the Time of Diagnosis

	Agenesis n=7	Ectopic thyroid n=9	Hyperplasia n=4
Age*	6.4 ± 3.8	5.7 ± 3.0	4.6 ± 2.9
Height SDS*	-4.6 ± 1.3	-3.8 ± 0.8	-3.3 ± 0.9
Bone age*	2.6 ± 2.6	1.8 ± 1.5	1,3 ± 0.9
T_4*(µg/dl)	1.2 ± 0.8	2.3 ± 1.3	1.8 ± 0.7
TSH* (mIU/L)	117.7 ± 51.6	94.1 ± 42.4	93.2 ± 58.1

* mean ± SD, year.

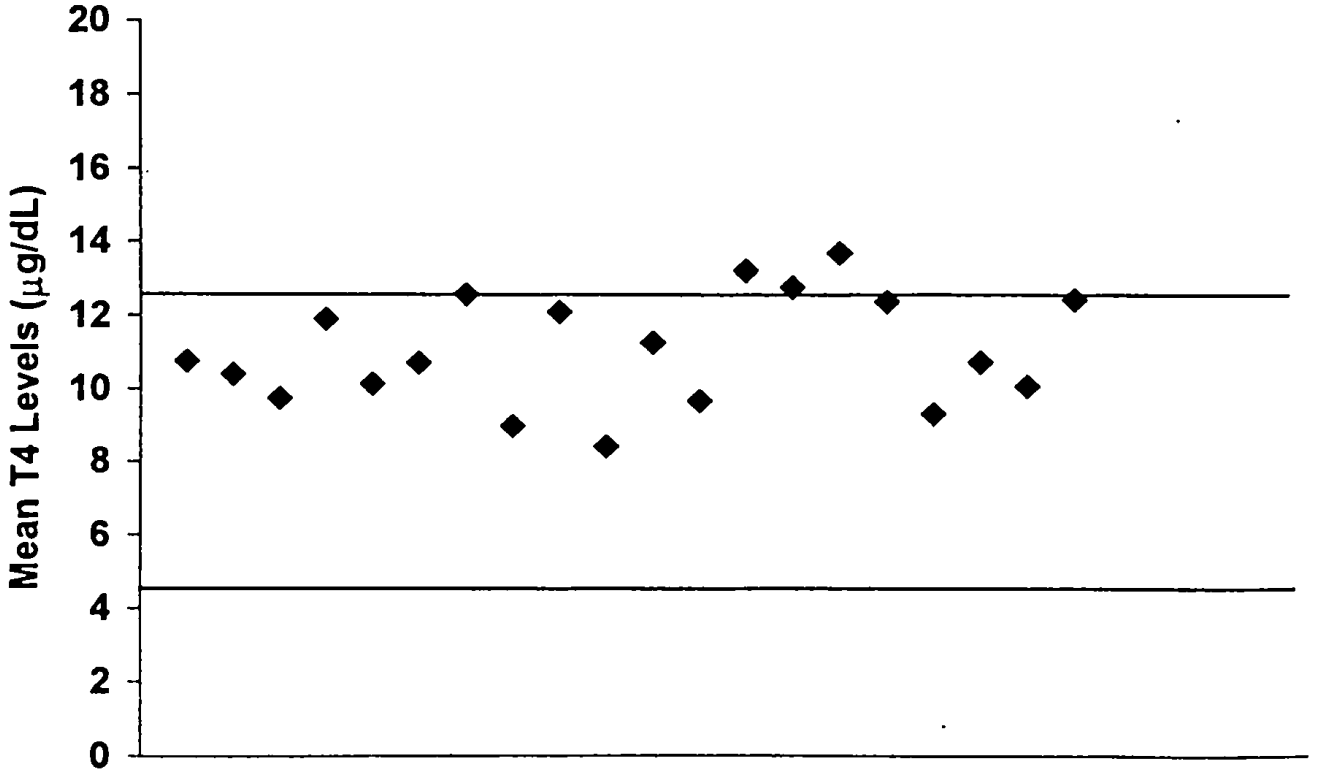

Fig. 1. The mean serum T_4 levels of 20 patients with congenital hypothyroidism during L-T_4 replacement therapy.

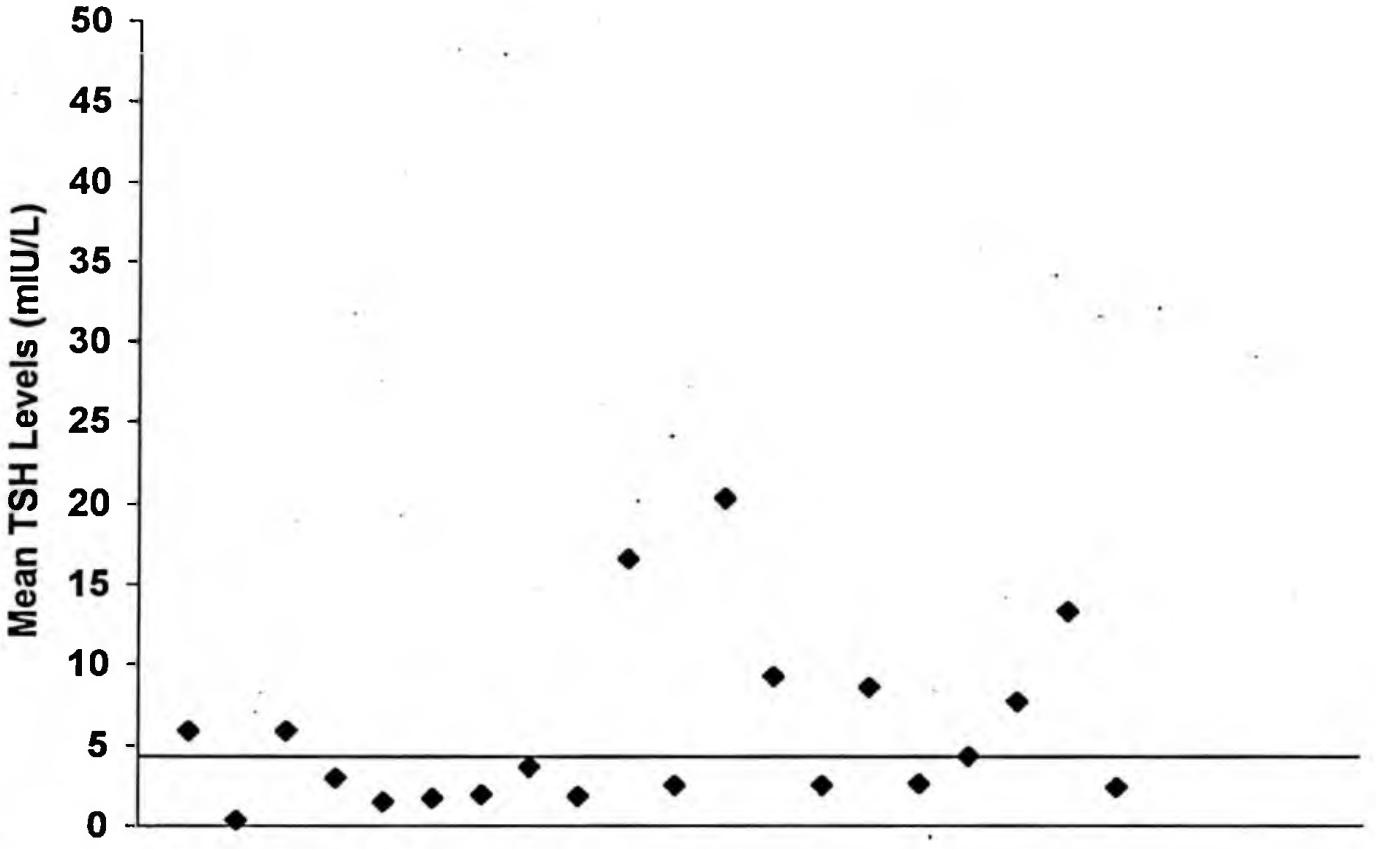

Fig. 2. The mean serum TSH levels of 20 patients with congenital hypothyroidism during L-T_4 replacement therapy.

Table II. Height Prognosis of the Patients With Congenital Hypothyroidism

	Girls (n=14) (mean ± SD)	Boys (n=6) (mean ± SD)
Target height (cm)	155 ± 4.7	168.3 ± 3.2
Final height (cm)	152.7 ± 4.3	166.3 ± 4.97
Target height SDS	-1.2 ± 0.8	-0.9 ± 0.5
Final height SDS	-1.6 ± 0.7	-1.2 ± 0.8
Final height vs target height	$p > 0.01$	$p > 0.01$

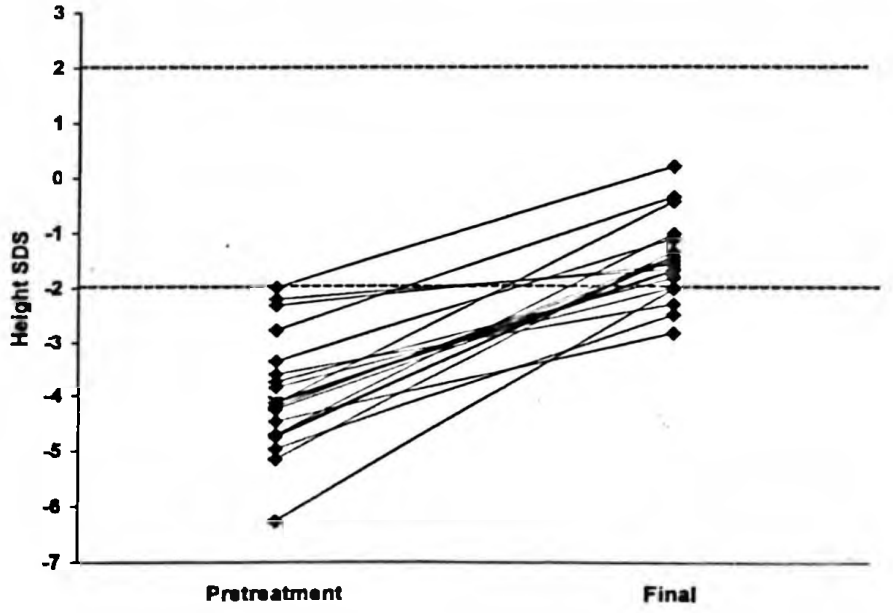

Fig. 3. The pretreatment and final height SDS of children with congenital hypothyroidism.

The final height SDS was -1.42 ± 0.34 (min -2.0, max. -1.0) in children with thyroid agenesis, -1.7 ± 0.8 (min -2.8, max -0.4) in the ectopic thyroid group and -1.15 ± 0.96 (min -2.0, max -0.2) in patients with hyperplastic thyroid tissue. Final height SDS did not show significant difference according to the etiology of hypothyroidism ($r = -0.104$, $p = 0.662$). The deficit in adult height also did not correlate with the etiology of hypothyroidism ($r = -0.102$, $p = 0.668$).

Discussion

The introduction of a neonatal screening program for CH during the past two decades has enabled early diagnosis and prompt initiation of L-T_4 treatment in infants with CH. It is well known that early diagnosis and appropriate daily doses of L-T_4 result in normal growth, normal puberty and achievement of normal adult height[1-3]. Unfortunately, a nationwide neonatal screening program for CH has still not been implemented in many countries, including Turkey, where screening is performed only in certain local centers[9]. Therefore, severe growth retardation (together with mental and motor retardation) is still a problem in these late-diagnosed patients.

Due to the lack of comprehensive growth studies, height prognosis has remained controversial in late-diagnosed hypothyroid children. The limited number of previous studies have suggested permanent height deficit in children with late-diagnosed CH or juvenile acquired hypothyroidism[4-6]. Although the catch-up spurt corrected an important part of the initial height deficit, prolonged hypothyroidism resulted in compromised final height. Bucher et al.[4] reported normal growth only when therapy was begun before the first year of life. Pantsiotou et al.[10] and Rivkees et al.[6] reported that despite treatment, prolonged juvenile acquired hypothyroidism results in a permanent height deficit related to the duration of thyroxine deficiency before treatment. Although the precise mechanism by which adult stature is compromised was not identified in these studies, several explanations were suggested: Firstly, hypothyroidism may directly diminish the potential for catch-up growth; Rivkess et al.[6] reported that permanent height deficit is related to the duration of thyroxine deficiency before treatment. Secondly, overtreatment with L-T_4 may stimulate skeletal maturation too much in the study of Casado de Frias et al.[11] progressive acceleration of bone age limited final height in some children. Administration of replacement therapy too soon before or during puberty may also limit catch-up growth and loss of normal harmony between growth and sexual maturation.

In this study, the correlation between the final height SDS and height SDS at the time of diagnosis suggested that the initial height deficit is an important factor for the deficit in final height. Due to the limited number of patients in each etiological group, the role of etiological differences could not be examined in this sudy.

We conclude that adequate replacement treatment with thyroxine does not lead necessarily to the normalization of growth. Early diagnosis improves normal growth and final height in children with congenital hypothyroidism.

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