ORIGINAL ARTICLE

Growth Recovery in Acquired Hypothyroidism Presenting with Height Velocity Decreasing

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Abstract

Introduction: Hypothyroidism is a common endocrinopathy in pediatrics. In severe cases, the most prevalent clinical manifestation is the decrease of growth velocity. The present study aimed to evaluate the height recovery after treatment, in children with primary acquired hypothyroidism associated with growth deceleration.

Methods: Analytical cross-sectional retrospective study. The study sample consisted of patients with primary acquired hypothyroidism and decreased height velocity, followed in a tertiary hospital. Variables studied were age of crossing downward the height percentile, disease duration, Tanner stage, target height and stature before and after treatment.

Results: Fourteen patients were included (71% females). Median age at diagnosis was 10 years and at the growth deceleration was 7 years. The total stature gain was 1.3 ± 0.46 standard deviation score (p = 0.012) in males and 0.8 ± 0.54 standard deviation score (p = 0.002) in females, presenting direct correlation with duration of the levothyroxine therapy (Pearson correlation 0.9, p < 0.001). There was a recovery of growth potential in both genders, occurring between second and third of treatment in males and in fourth year in females. The stature gain was statistically significant regardless of the pubertal stage at diagnosis, but the family target height was reached only in the prepubertal group (prepubertal final stature -0.6 ± 1.07 standard deviation score; target height -0.6 ± 0.69 standard deviation score).

Discussion: Levothyroxine therapy had a positive impact in linear growth in both genders, and lead to achievement target height, despite the severity of hypothyroidism presentation. The recovery of family target height occurred only in the group with diagnosis at prepubertal age.

Keywords: Body Height; Child; Growth Disorders; Hypothyroidism/complications; Hypothyroidism/drug therapy; Portugal; Thyroxine/therapeutic use.

Introduction

Thyroid hormones play a crucial role in normal growth and development.[1-3] Hypothyroidism can be due to a functional compromise of the thyroid gland (primary hypothyroidism), or a hypothalamic/pituitary anomaly, with consequent thyroid repercussion (central hypothyroidism).[1] With regard to primary hypothyroidism, it may be congenital or acquired.[1]

Acquired hypothyroidism is a common pediatric condition with an estimated prevalence of 1.2%.[4] The main cause in children is autoimmune thyroiditis,[1,2,4] which results from an inflammatory response mediated by T cells against to thyroid autoantigens, with consequent inflammation, fibrosis and loss of function.[1]

Thyroid hormones influence growth through local actions at the level of the growth plate, as well as at the central level, interfering with the hypothalamic-pituitary axis.

At the central level, thyroid hormones induce the synthesis and secretion of growth hormone by the somatotrophs of the anterior pituitary,[5] and in hypothyroidism this process is compromised. On the other hand, uncontrolled primary hypothyroidism has been described as a cause of pituitary hyperplasia.[2,6,7] Hypersecretion of thyrotropin-releasing hormones (TRH) due to a decrease in thyroxine levels leads to hypertrophy of thyrotropes and consequent increase in the circulating levels of thyroid-stimulating hormone (TSH) and prolactin.[2] The transformation of somatotrophs into thyrotropes leads, in turn, to a decrease in growth hormone secretion.[2]

In addition to the central effects, the deficit of thyroid hormones also influences growth through actions at the level of the growth plate, namely deceleration of the growth of conjugation cartilages and decrease in the synthesis of hepatic insulin growth factor 1 (IGF1), due to a decrease in growth hormone secondary to hypothyroidism.

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Since hypothyroidism is a well-known cause of growth retardation and development in pediatric age,[8] its early treatment is essential to control symptoms and minimize the repercussion at these levels.[1]

The aim of the study was to evaluate the stature recovery after initiation of replacement therapy with levothyroxine in children with acquired primary hypothyroidism associated with growth deceleration.

Methods

Analytical cross-sectional retrospective study of children with primary acquired hypothyroidism and growth deceleration, followed in a Portuguese tertiary hospital. The data was collected from January 1998 to December 2017 by consulting the clinical process.

The variables studied were age of crossing downward the height percentile, disease duration, Tanner stage, target height and stature before and after treatment with levothyroxine. Statistical analysis was performed using SPSS®; significance level was 0.05.

Results

The sample consisted of 14 patients, of which 10 (71%) were female. The median age at the statural deceleration was 7 years (minimum 3 years and maximum 14 years) and the median age at diagnosis was 10 years (minimum 4 years and a maximum 16 years). The hand bone age at diagnosis was 8.6 ± 3.7 years. The median duration of follow-up was 4 years (minimum 1 year and maximum 7 years).

At diagnosis, eight (57%) adolescents of the sample were prepubescents and six (43%) were pubescents; 12 (86%) had positive antithyroid antibodies: 10 (84%) anti-thyroglobulin (TG) + anti-peroxidase (TPO); one (8%) anti-TPO; one (8%) anti-TG. Target height was 173 ± 7.78 cm [-0.4 ± 1.04 standard deviation score (SDS)] for males and 158 ± 3.32 cm (-1.0 ± 0.5 SDS) for females. The characterization of the sample is summarized in Table 1**.** At diagnosis, the mean height was 136.2 ± 18.8 cm in the male sex (-1.3 ± 1.17 SDS) and in the female sex was 128.3 ± 15.93 cm (-1.9 ± 0.87 SDS). At the end of follow-up, after the establishment of levothyroxine therapy, the mean stature was 168.1 ± 12.58 cm (-0.04 ± 1.21 SDS) in the male sex and 147.4 ± 11.86 cm (-1.1 ± 0.69 SDS) in the female sex, corresponding to a statural increase of 1.3 ± 0.46 SDS (p = 0.012) and 0.8 ± 0.54 SDS (p = 0.002), respectively.

The statural increase correlated directly with the duration of therapy (Pearson correlation 0.9, $p < 0.001$). According to Table 2, there was a statistically significant increase throughout the follow-up, namely in the first four years of treatment in the females, as well as between the second and fourth year of treatment in the males. The recovery of the growth potential in males occurred between the second and third year of treatment, when the z-score of height (-0.1 ± 1.32 SDS) exceeded the target height (-0.4 ± 1.04 SDS). In females, the recovery of the growth potential occurred at the end of the fourth year of treatment. The statural increase observed during follow-up is shown in Figs. 1 and 2.

Parallel to the statural increase, there was a statistically significant reduction in body mass index (BMI) in both genders at the end of follow-up (Table 2). In the male sex, the BMI at diagnosis was 23.2 ± 3.75 kg/m^2 (2.2 ± 1.21 SDS) and at the end of the follow-up was 22.8 ± 4.9 kg/m^2 (0.6 ± 0.69 SDS), corresponding to a differential of -1.6 ± 0.79 SDS (p = 0.027). In females, the BMI at diagnosis was 19.6 ± 4.16 kg/m^2 (0.9 ± 1.21 SDS) and at the end of the follow-up was 19.8 ± 3.51 kg/m^2 (0.1 ± 1.07 SDS), corresponding to a differential of -0.8 ± 0.78 SDS (p = 0.009).

There was a statistically significant statural increase regardless of the pubertal stage at the time of diagnosis, corresponding to a similar increase in both groups. In the pre-pubertal group, there was a total gain of 0.9 ± 0.64 SDS (p = 0.006) and in the group whose diagnosis occurred at pubertal age there the gain was 0.9 ± 0.44 SDS (p = 0.001). However, when comparing the z-score of the stature at the end of the follow-up (pre-pubertal -0.6 ± 1.07 SDS, pubertal -1.1 ± 0.95 SDS) with the z-score of the target height (pre-puberty -0.6 ± 0.69 SDS, puberty -0.7 ± 0.76 SDS), we observed that the recovery of growth potential was achieved only in the group that started treatment in the pre-pubertal period. Statural growth along the treatment, depending on the pubertal stage, is represented in Figs. 3 and 4.

Table 1. Characterization of the sample

Gender	71% female, 29% male
Age at diagnosis	Median 10 years (min. 4 years, max. 16 years)
Age at the statural deceleration	Median 7 years (min. 3 years, max. 14 years)
Duration of follow-up	Mean 3.9 ± 1.9 years (min. 1 year, max. 7 years)
Target height	**Male:** Mean 173 ± 7.78 cm (z-score -0.4 ± 1.04) **Female:** Mean 158 ± 3.32 cm (z-score -1.0 ± 0.5)
Antithyroid antibodies	86% (12) positive: 84% (10) anti-TG + anti-TPO, 8% (1) anti-TPO, 8% (1) anti-TG

Anti-TG - anti-thyroglobulin; anti-TPO - anti-peroxidase; max. - maximum; min. - minimum.

Table 2. Evolution of the stature and body mass index in both genders (mean ± standard deviation)

Male	Diagnosis (n = 4)	1st year (n = 4)	2nd year (n = 4)	3rd year (n = 4)	4th year (n = 4)	5th year (n = 1)	6th year (n = 1)	7th year (n = 1)
Mean stature (*z*-score)	-1.3 ± 1.17	-0.9 ± 1.38	-0.6 ± 1.54	-0.1 ± 1.32	-0.04 ± 1.21	NA	NA	NA
Stature differential (*z*-score / *p*)	-	0.4 ± 0.33 (*p* = 0.113)	0.7 ± 0.43 (*p* = 0.046)	1.2 ± 0.42 (*p* = 0.011)	1.3 ± 0.46 (*p* = 0.012)	NA	NA	NA
Mean BMI (*z*-score)	2.2 ± 1.21	0.9 ± 0.86	0.7 ± 0.68	0.6 ± 0.78	0.7 ± 0.79	NA	NA	NA
BMI differential (*z*-score / *p*)	-	-1.3 ± 0.56 (*p* = 0.018)	-1.5 ± 0.81 (*p* = 0.035)	-1.6 ± 0.81 (*p* = 0.029)	-1.5 ± 0.56 (*p* = 0.013)	NA	NA	NA
Female	**Diagnosis (n = 10)**	**1st year (n = 10)**	**2nd year (n = 8)**	**3rd year (n = 7)**	**4th year (n = 6)**	**5th year (n = 2)**	**6th year (n = 2)**	**7th year (n = 1)**
Mean stature (*z*-score)	-1.9 ± 0.87	-1.5 ± 0.66	-1.4 ± 0.73	-1.1 ± 0.66	-1.0 ± 0.71	-1.1 ± 0.56	-1.1 ± 0.69	NA
Stature differential (*z*-score / *p*)	-	0.4 ± 0.41 (*p* = 0.008)	0.6 ± 0.55 (*p* = 0.015)	0.8 ± 0.61 (*p* = 0.011)	0.8 ± 0.59 (*p* = 0.022)	0.5 ± 0.95 (*p* = 0.616)	0.4 ± 0.86 (*p* = 0.602)	NA
Mean BMI (*z*-score)	0.9 ± 1.21	-0.1 ± 1.06	-0.4 ± 0.72	-0.1 ± 1.06	0.03 ± 0.9	0.5 ± 0.56	0.1 ± 0.98	NA
BMI differential (*z*-score / *p*)	-	-0.9 ± 0.48 (*p* < 0.001)	-0.9 ± 0.73 (*p* = 0.009)	-0.7 ± 0.96 (*p* = 0.096)	-0.8 ± 0.98 (*p* = 0.095)	-2.6 ± 0.66 (*p* = 0.111)	-1.4 ± 0.24 (*p* = 0.078)	NA

BMI - body mass index; NA - not applicable.

Discussion

Thyroid hormones act synergistically with somatotropin in bone growth and maturation.[5] Hypothyroidism is therefore a recognized cause of growth retardation in the child.[8]

Among the causes of acquired primary hypothyroidism, Hashimoto's thyroiditis is the most frequent, being more common in females.[1,3] The incidence increases with age, being rare before 3 years and becoming progressively more frequent in childhood and adolescence.[1,4,8] In a recent epidemiological study, the prevalence of Hashimoto's thyroiditis is 3.2% among 12 and 16 years, 1.2% between 6 and 12 years and 0% between 1 and 6 years.[8,9]

Like described in the literature, more than half of our sample was female, with a mean age in adolescence and a minimum age at diagnosis of 4 years.

The predominant clinical manifestation of hypothyroidism is goiter. Other manifestations are often nonspecific in the child, such as fatigue, cold intolerance, weight gain, constipation or pubertal delay.[1,4] Statural deceleration may be the form of presentation in severe cases and underdiagnosis of hypothyroidism may influence final height in adulthood.[7] In our sample, the mean time between the onset of statural deceleration and the diagnosis was 2.5 ± 1.61 years. Despite the delay in diagnosis, target height was reached, especially in the group whose diagnosis was made at pre-pubertal age.

Figure 1. Statural increase in males.

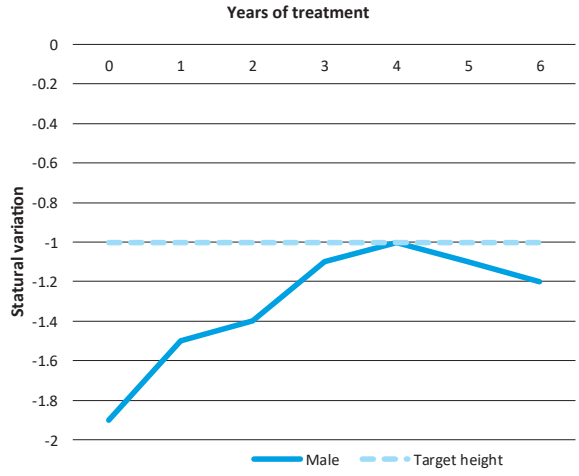

Figure 2. Statural increase in females.

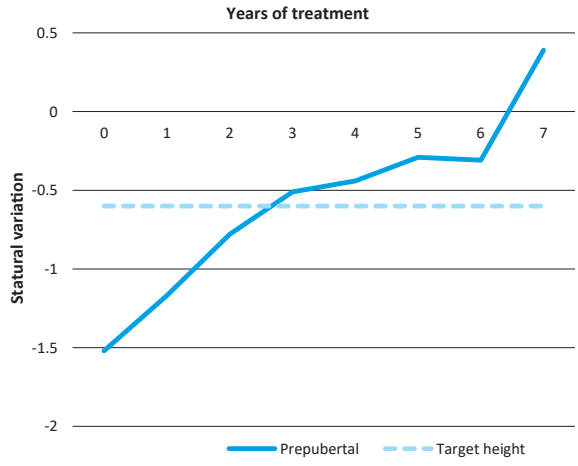

Figure 3. Statural growth in the group with treatment onset in the prepubertal period.

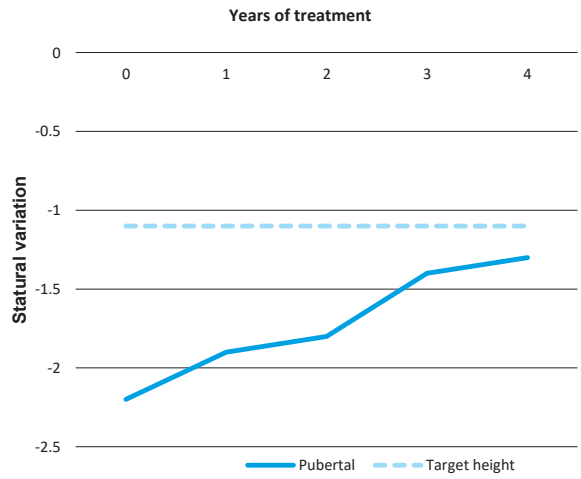

Figure 4. Statural growth in the group with treatment onset in the pubertal period.

Thus, screening for hypothyroidism is mandatory for a child with short stature,[1] especially in the presence of concomitant overweight or obesity, which points to an underlying endocrine cause of growth retardation.

Diagnosis is based on the clinic associated with changes in thyroid function - elevation of TSH, with normal and low triiodothyronine (T3) and thyroxine (T4). In cases of autoimmune thyroiditis, anti-thyroid antibodies (anti-peroxidase and anti-thyroglobulin) are positive in 95% of the cases.[1,4] The imaging study complements the diagnosis, being characteristic the presence of a heterogeneous echo structure in cases of autoimmune thyroiditis,[1] allowing also the exclusion of nodules.

In our study, in 12 of the 14 cases (86%), the cause of hypothyroidism was autoimmune thyroiditis, with at least one of the antibodies positive, which corroborates what has been described in the literature.

Catch-up growth is defined as a growth rate higher than normal for the age, which follows a period of growth inhibition, conditioned by several situations, such as hypothyroidism.[10] When the suppressive condition is resolved, there is usually a recovery of the growth rate.[10] However, according to some literature, in hypothyroidism, catch-up growth is not always observed, despite the institution of therapy.[11] This fact can be justified by the overtreatment with levothyroxine, the long evolution time of the disease prior to initiation of therapy or the complete bone maturation after treatment, preceding catch-up growth.[11]

Some studies advocate that sustained statural deceleration results in a loss of opportunity, which is not compensated after institution of substitute therapy.[1,11] However, in our study, we observed a progressive increase in stature after levothyroxine therapy in both genders. This growth was statistically significant in the first four years of therapy, in the female sex, and between the second and fourth years in the male sex. In addition to the statistically significant increase in stature, there was a recovery of growth potential in both genders, as a result of the *z*-score of the target height, which occurred between the second and third year of therapy, in the male, and at the end of the fourth year of treatment, in the female sex.

Similarly, to stature evolution, replacement therapy with levothyroxine also had a positive impact on BMI in both genders, with a statistically significant reduction at the end of follow-up.

Regarding the statural evolution according to the pubertal stage at diagnosis (pre-pubertal and pubertal), there was a favorable evolution in both groups. However, the recovery of the genetic potential occurred only in the group whose diagnosis was made at the pre-pubertal stage.

Similarly, a recent study found that growth during puberty was normal and final height achieved after replacement therapy was greater than target height.[12] It shows that the potential for genetic growth was achieved after adequate treatment. Hence, the hypothyroidism that is installed and diagnosed in pre-puberty allows the early institution of therapy, which contributes to optimize the child's growth,[1] minimizing the negative impact of the disease. Pubescent children deserve particular attention, as the prevalence of the disease in this age group is high and growth may be compromised if diagnosis and treatment are not timely established.

In summary, in our study, replacement therapy with levothyroxine had a positive impact on the statural evolution, allowing the recovery of genetic growth potential in the group whose diagnosis was established at pre-pubescent age. In addition to the statural growth,

the recovery of growth potential in this group suggests that the efficacy of replacement therapy is as greater as earlier the diagnosis and treatment of the disease occurs. Thus, in the case of a child with short stature, the investigation of growth hormone deficiency must take place only after exclusion and treatment of other causes of statural deceleration, including hypothyroidism.[8] Having a high degree of suspicion is the key to diagnosis and early treatment is a predictor of success.

Despite the results obtained with statistical significance, the small sample size does not allow the extrapolation of the results. We suggest that the study should be replicated with a larger and more representative sample in order to better understand the impact of levothyroxine therapy on stature recovery and its influence on BMI, which this study has indicated.

WHAT THIS STUDY ADDS

- Replacement therapy with levothyroxine in primary acquired hypothyroidism allows statistically significant growth to be achieved in the first four years of treatment.
- The recovery of height potential is more likely if the diagnosis and treatment are instituted at pre-pubertal age.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Study presented at the 18º Congresso Nacional de Pediatria, Porto, 2017.

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Recuperação do Crescimento no Hipotiroidismo Adquirido que se Apresenta com Desaceleração Estatural

Resumo:

Introdução: O hipotiroidismo é uma endocrinopatia frequente em idade pediátrica. Nos casos graves, a desaceleração do crescimento estatural é a manifestação clínica predominante. O objetivo foi avaliar a recuperação estatural após o início da terapêutica, em crianças com hipotiroidismo primário adquirido associado a desaceleração estatural.

Metodologia: Estudo retrospetivo descritivo. Amostra constituída por doentes com hipotiroidismo primário adquirido e desaceleração estatural, seguidos em consulta de um hospital central. As variáveis estudadas foram a idade de cruzamento de percentil, duração da doença, estádio de Tanner, estatura alvo familiar e estatura antes e após tratamento.

Resultados: Foram incluídos 14 doentes (71% do sexo feminino). A idade mediana ao diagnóstico foi de 10 anos e a idade mediana da desaceleração estatural foi de 7 anos. Registou-se um ganho total de 1,3 ± 0,46 desvio padrão (p = 0,012) no sexo masculino e de 0,8 ± 0,54 desvio padrão (p = 0,002) no sexo feminino, que se correlacionou diretamente com a duração da terapêutica (correlação de Pearson 0,9, p < 0,001). Registou-se uma recuperação do potencial de crescimento em ambos os géneros, ocorrendo entre o segundo e o terceiro ano de tratamento no sexo masculino e ao quarto ano no sexo feminino. O aumento estatural foi estatisticamente significativo, independentemente do estádio pubertário ao diagnóstico, mas com atingimento da estatura alvo familiar apenas no grupo pré-púbere (estatura final pré-púberes -0,6 ± 1,07 desvio padrão; estatura alvo familiar -0,6 ± 0,69 desvio padrão).

Discussão: A terapêutica de substituição com levotiroxina teve um impacto positivo na recuperação estatural em ambos os géneros, permitindo atingir o potencial de crescimento genético, apesar da gravidade à apresentação. A recuperação da estatura alvo familiar apenas ocorreu no grupo com diagnóstico em idade pré-púbere.

Palavras-Chave: Criança; Estatura; Hipotiroidismo/complicações; Hipotiroidismo/tratamento farmacológico; Portugal; Tiroxina/uso terapêutico; Transtornos do Crescimento