ORIGINAL ARTICLE

Evaluation of the hypothalamic–pituitary–thyroid axis in children with Down syndrome

Ana Tereza de A. Oliveira[1], Carlos A. Longui[2], Luis Eduardo P. Calliari[3], Eduardo de A. Ferone[4], Fábio S. Kawaguti[5], Osmar Monte[6]

Abstract

Objective: to determine the thyroid stimulating hormone (TSH) secretion in children with Down syndrome (DS), who do not present clinical and laboratory evidence of classical hypothyroidism and concomitant undetectable antibodies.

Methods: fourteen children with DS with a mean age of 3.4 (±1.8) years were studied. Patients with classical hypothyroidism or hyperthyroidism or those with positive antithyroid antibodies were excluded. The DS group was compared to a control group of 16 children with a mean age of 11.8 (±3.8) years, diagnosed as having familial short stature or constitutional growth delay. Both groups underwent hormonal measurements at basal condition to determine serum TSH, T3, T4, free T4 and prolactin concentrations and after stimulation with thyrotropin releasing hormone (TRH). Thyroid hormones concentrations were also compared when children with DS were subdivided into two groups according to their basal TSH levels.

Results: basal TSH and prolactin levels were significantly higher in DS group. After stimulation with TRH, TSH peak was higher in the DS group. The number of patients presenting basal TSH levels higher than 5 μU/mL and TSH peaks higher than 30 μU/mL were significantly higher in the DS group.

Conclusions: children with Down syndrome present frequent increase in basal TSH concentrations, despite the presence of normal basal thyroid hormones levels and negative antithyroid antibodies. Most of them (65%) show early intense response after TRH stimulation. Our data demonstrate that in spite of the absence of classic hypothyroidism and/or antithyroid antibodies, an abnormal pattern of TSH secretion occurred in patients with Down syndrome, possibly related to hypothalamic dysfunction.

J Pediatr (Rio J) 2002; 78 (4): 295-300: hypothyroidism, Down syndrome, TSH.

1. Resident Doctor, Unit of Pediatric Endocrinology, Department of Pediatrics - Santa Casa de Misericórdia de São Paulo (SCMSP).
2. Assistant Professor, Unit of Pediatric Endocrinology, Department of Pediatrics, SCMSP
3. Assistant Professor, Unit of Pediatric Endocrinology, Department of Pediatrics, SCMSP.
4. Undergraduate student, Medical Sciences College, SCMSP.
5. Undergraduate student, Medical Sciences College, SCMSP.
6. Director of the Unit of Pediatric Endocrinology, SCMSP.

Introduction

The hypothalamic-pituitary-thyroid (HPT) axis is an important part of endocrine and metabolic control, since it allows for proper adaptation to environmental conditions and to energy supply. In children with Down's syndrome, thyroid disorders are quite common, especially Hashimoto's thyroiditis and thyroid dysgenesis.[1]

Thyroid hormones are important for the CNS, since they are concerned with neuronal migration and differentiation, activation of the sympathetic nervous system, synthesis and secretion of neurotransmitters, myelination, in addition to the regulation of the gene expression of neuronal cells.[2] The association of thyroid hormone deficiency potentially aggravates the neurological disorders observed in patients with Down's syndrome.

Depending on the level of the disorder, hypothyroidism can be classified into primary (thyroid), secondary (pituitary) or tertiary (hypothalamic). The concept of hypofunction of the HPT axis includes a severity that goes from total deficiency of thyroid hormones, determining a classic clinical status of hypothyroidism, to a milder status in which T3 and T4 are normal due to greater pulsatility and increased TSH secretion. This way, primary hypothyroidism can be classified into different levels.[3] Level I is characterized by clinical symptoms, decreased concentration of thyroid hormones, elevated TSH baseline value and early hyperresponsiveness to the TRH test. In Level II, the clinical signs and symptoms are discreet, the concentration of thyroid hormones is normal, but the TSH baseline value is high, with hyperresponsiveness to the TRH test as well. In Level III, signs and symptoms are nonexistent, the concentration of thyroid hormones is normal and TSH baseline is at the upper limit of normal values or slightly elevated, with hyperresponsiveness to the TRH test. In the latter group, patients who do not have goiter or positive antithyroid antibodies might not correspond to actual hypothyroidism, but instead, these patients could have CNS disorders and abnormal release of TRH by the hypothalamus. The term clinical hypothyroidism is associated with level I while the term subclinical hypothyroidism refers to levels II and III. Individuals with normal T4 and T3 serum concentrations but with high TSH serum levels can evolve into classic hypothyroidism, with gradually lower concentrations of T4 and T3 and additional increase of TSH levels. In other individuals, TSH levels can remain unchanged or normalize after clinical follow-up.[4,5] Therefore, not all individuals who have normal T4 and T3 levels and elevated TSH can be said to have subclinical hypothyroidism, since longitudinal follow-up studies have identified patients who have normal thyroid function for a long period, apparently adjusted to a slightly elevated concentration of TSH.[6]

With regard to the control of the HPT axis, TRH is known to stimulate the biosynthesis, secretion and glycosilation of TSH, whereas thyroid hormones act as TSH inhibitors by blocking the transcription of its genes and reducing TRH secretion and its pituitary action.

Dopamine is a catecholamine that acts both at the hypothalamic level and on D2 receptors of pituitary thyrotrophs inhibiting the secretion of TSH[7] and prolactin. TRH acts as a secondary agent in the stimulation of prolactin secretion. Due to the similarity between the controlling factors of TSH and prolactin secretion, both hormones are often quantified by the assessment of the HPT axis. Therefore, dysfunctions of the HPT axis in patients with Down's syndrome can be associated with primary thyroid diseases or with disorders of TSH secretion dependent on insufficient dopaminergic control of pituitary secretion.

The aim of the present study was to assess the frequency of disorders associated with the regulation of the HPT axis in children with Down's syndrome who did not show a characteristic clinical or laboratory status of hypothyroidism.

Patients and methods

Fourteen patients (nine males and five females) with Down's syndrome (DS), followed up at the Unit of Pediatric Endocrinology of the Department of Pediatrics and Child Care of Hospital Santa Casa de Misericórdia de São Paulo, were studied. The age of patients ranged between 1.2 and 6.5 years (mean = 3.4 and SD±1.8).

Individuals with classic diagnosis of hypothyroidism or hyperthyroidism who presented positive antiperoxidase or antithyroglobulin antibodies were not included in the study, since the presence of such antibodies could directly interfere with thyroid function and mask possible changes in the HPT axis that are characteristic of Down's syndrome.

The control group consisted of 16 patients, eight males and eight females, who had low stature, but whose growth hormone (GH) concentration was normal, that is, GH concentrations greater than 7 ng/mL in the insulin tolerance test. This group was assessed with combined test and quantification of TSH, prolactin, GH and cortisol, according to the routine of assessment of patients with low stature. The final diagnosis of the patients in the control group was abnormal low familial stature or constitutional growth delay. Other characteristics observed in the control group were: chronological age between 5.5 and 15.4 years (mean = 11.8 and SD±3.8) and normal baseline serum concentrations of T3, T4 and free T4 (FT4).

The baseline serum concentrations of T3, T4, FT4, prolactin, antiperoxidase and antithyroglobulin antibodies were determined by means of a radioimmunoassay.

The TRH test was carried out with the IV bolus administration of 7 μg/Kg. and with blood samples collected at 0, 20, 40, 60 and 90 minutes for the determination of TSH and prolactin concentrations. The serum concentration of TSH was determined by an immunoradiometric assay (IRMA).

The values considered normal for each one of the hormones assessed at baseline were: TSH: 0.3-5 μU/mL (Active™ TSH IRMA DSL-5300, DSL,Inc. Texas,USA); T3: 80-215 ng/dL (Active™ Triiodothyronine(T3) RIA DSL-3100, DSL,Inc. Texas,USA); T4: 5-12 μg/dL

(Active™ Thyroxine DSL-3200, DSL,Inc. Texas,USA); T4L: 0.8-2 ng/dL (Coat-a-Count™ FreeT4, DPC™, Los Angeles, USA); prolactin: 4.3-23.3 ng/dL (RIA-gnost™ Prolactin, CIS bio international, France); antithyroperoxidase antibody: < 50 UI/mL (Anti-TMS Bridge, Biodata Diagnostics S.p.A., Rome, Italy) and antithyroglobulin antibody: < 100 IU/mL (Anti-HTG Bridge, BioChem ImmunoSystems Italia S.p.A., Diagnostics Division, Rome, Italy).

SigmaStat for Windows version 2.03 (SPSS Incorporation) was used for the statistical analysis. Student t-test or Mann-Whitney test was used when the distribution of the samples was respectively parametric or nonparametric. The mean baseline values of TSH, T3, T4, FT4 and prolactin obtained from the group with DS and the control group were compared.

The means of maximum peak TSH obtained from both groups after TRH stimulation were also compared. As to the response of TSH, hyperresponsiveness to TRH was considered when TSH peaks were greater than 30 µU/mL. Hyperresponsiveness was considered to be early when TSH peak occurred between 15 - 20 minutes and late when TSH values between 60 - 90 minutes were greater than those at 15-20 minutes.[8]

The group of patients with DS was subdivided into two groups, one with normal TSH baseline values and another one with elevated TSH baseline value (baseline TSH > 5µU/mL), and the means of the baseline concentrations of T3, T4, FT4 and prolactin were compared.

All the procedures were approved by the Ethics and Research Committee of the Santa Casa de Misericórdia de São Paulo.

Results

The mean baseline concentrations of patients with DS and controls are shown in Table 1. A significant elevation ($P = 0.03$) of TSH baseline values was observed in patients with DS, mean 7.2 µU/mL (SD±4.2) in relation to the mean TSH value of the control group. However, significant differences were not found between the mean values of T3, T4 and FT4 between the two groups.

The baseline values of prolactin are significantly lower ($P = 0.017$) in the control group when compared to those observed in children with DS.

Table 2 describes the results of the TRH test and shows a significantly higher increase ($P = 0.01$) of the peak TSH values observed in individuals with DS, whose mean was 37.3 µU/mL (SD±18.8), in relation to the control group, whose mean was 20.2 µU/mL (SD±8.8). All patients with DS had early hyperresponsiveness (between 15 - 20 minutes after the TRH test). In the control group, only two patients

Table 1 - Baseline serum concentrations of TSH, T3, T4, T4L and prolactin (PRL) in patients with Down syndrome (n=14), and in controls (n=16)

	TSH µU/mL	T3 ng/dL	T4 µg/dL	T4L ng/dL	PRL ng/dL
DS	7.2±4.2	147±46	9.8±2.1	1.7±0.4	13.1±5.5
Control	3.8±2.4	162.3±57.7	8.9±2.6	1.3±04	7.0±3.0
P	0.03	ns	ns	ns	0.017

Data is expressed as means ± standard deviation.
ns = not significant.

had hyperresponsiveness during the test: one at 20 minutes and another one at 30 minutes.

In addition, Table 2 shows that the number of patients with baseline TSH values greater than 5µU/mL in the group with DS (nine of 14 patients) is significantly higher ($P = 0.03$) than that observed in the control group, in which only three of 16 patients had a high TSH baseline value. The number of patients with DS and peak TSH after TRH greater than 30 µU/mL (nine of 14 patients) is significantly higher ($P = 0.01$) than that observed in the control group (two of 16 patients).

No difference as to the prolactin peak after TRH was found between the control group and the group with DS.

Figure 1 shows the individual variation of TSH levels during the TRH test. Most patients with DS initially show TSH baseline values greater than 5 µU/mL and most of them also reach a TSH peak greater than 30 µU/mL; in this group, of the nine patients with TSH baseline value greater than 5 µU/mL, seven showed hyperresponsiveness. Another two patients who did not have a high TSH baseline value also had hyperresponsiveness.

In the control group, most patients had normal TSH baseline values and did not reach a TSH peak after the TRH test greater than 30 µU/mL. In this group, two of the three individuals who had a TSH baseline value higher than 5 µU/mL showed hyperresponsiveness.

By looking at Table 3, which compares the mean baseline values of T3, T4, FT4 and prolactin between the subgroups of patients with DS, classified as to their TSH baseline values, we find no significant difference in terms of thyroid hormones and prolactin between the subgroup of individuals with normal TSH baseline values and the subgroup with elevated TSH baseline values.

Discussion

In this study, the children with DS, when compared to the control group, had elevated TSH values even when normal baseline values of thyroid hormones and negative

Table 2 - TSH results during the TRH test in patients with Down syndrome (n=14), and in controls (n=16)

	BaselineTSH μU/mL	TSH baseline>5 μU/mL	Peak TSH μU/mL	TSH peak>30 μU/mL
DS	7.2±4.2	9 / 14 patients	37.3±18.8	9 / 14 patients
Control	3.8±2.4	3 / 16 patients	20.2±8.8	2 / 16 patients
P	0.03	0.03	0.01	0.01

Data is expressed as means ± standard deviation.
ns = not significant.

antithyroglobulin and antithyroperoxidase antibodies were present. On top of that, most patients with Down's syndrome (9/14 or 65%) showed hyperresponsiveness to TSH during the TRH test.

Some hypotheses could justify the elevated TSH values observed in children with DS:

1) The studied cases may represent individuals with initial and still subclinical primary hypothyroidism. Nevertheless, some peculiarities of these patients observed during a longer period of follow-up are contrary to this hypothesis, for instance: the values of T3, T4 and FT4 are normal in the long run, and the antithyroglobulin and antithyroperoxidase antibodies remain negative; these children's stature is adjusted according to the growth curves of DS with a stable percentile and some treated cases did not
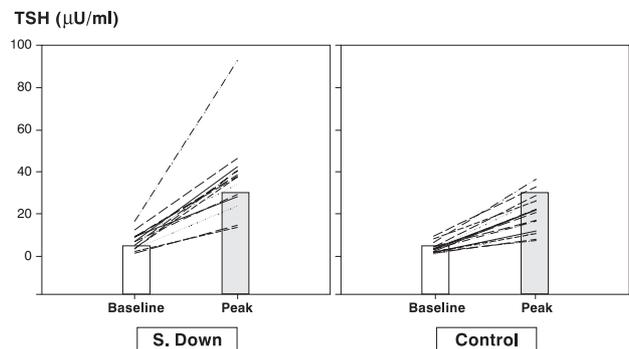

Figure 1 - Individual secretion of TSH during the TRH test (7μg/kg) in patients with Down syndrome, and controls

Table 3 - Baseline serum concentrations of T3, T4, T4L and prolactin (PRL) in patients with Down syndrome classified according to the baseline TSH value

	TSH μU/mL	T3 ng/dL	T4 μg/dL	T4L ng/dL	PRL ng/dL
TSH b<5 (n=5)	3.0±0.9	125.5±42.7	9.3±0.9	1.5±0.1	12.15±5.27
TSH b>5 (n=9)	9.5±3.3	158.9±45.6	10±2.6	1.7±0.6	13.69±6.01
P	ns	ns	ns	ns	ns

Data is expressed as means ± standard deviation.
ns = not significant.

show clear clinical evidence when compared to the pretreatment period.

2) The TSH values of these patients could present some biological inactivity. However, Konings et al.[9] found normal biological inactivity of TSH in patients with DS with AMPc produced by the stimulation of human TSH receptors expressed in ovarian hamster cells. The amount of AMPc obtained by the stimulation of receptors with in vitro use of TSH from individuals with DS was not significantly different from that obtained from the TSH of control individuals who did not present the syndrome. It is worth mentioning that the ovarian hamster cells were transfected with human gene, which codifies TSH receptors of normal individuals and not of those with DS.

3) Patients with SD could show thyroid resistance to the level of TSH receptors or even a post-receptor event. Up to the moment, no study that confirms this hypothesis has been made.

4) Another hypothesis is the reduction of the dopaminergic tonus on the hypothalamus and the pituitary gland. This causes an increased secretion of TSH which, if associated with the down regulation of thyroid receptors of TSH, provides normal baseline values of T3, T4 and FT4.

The elevation of baseline values of prolactin observed in the group of patients with DS (mean = 13.1 and SD ± 5.5) in relation to the control group (P = 0.017) reinforces this hypothesis. In spite of this, no significant difference was found between the group of patients with DS and the control group in terms of prolactin peak during the TRH test. Still regarding the TRH test, although the TSH peak values in patients with DS is remarkably higher than the mean observed in the control group (which is in agreement with the hypothesis of reduced dopaminergic tonus), patients with DS with a TSH peak greater than 30 µU/mL showed early responsiveness. The hyperresponsiveness of hypothalamic cause, usually described as late response, was not observed in our patients. However, we have found that early hyperresponsiveness is a frequent finding in patients with GH deficiency of hypothalamic origin (unpublished data).

Previous studies conducted on patients with DS reinforce the hypothesis of reduced secretion of dopamine in the CNS and describe atrophy and reduction of the number of dopamine-producing cells in the substantia nigra at the base of the brain[10] and ventral tegmental area.[11,12] These findings are common in individuals with DS who are over 40 and occur as dementia similar to that found in Alzheimer's disease. Just like the substantia nigra and the ventral tegmental area (important dopamine-producing areas in the brain), the arcuate nuclei of the hypothalamus (dopamine producers that act as inhibitory hormone upon TSH secretion) could also be compromised.

Studies of response induction by visual, auditory and somatosensory stimuli show that these responses are more commonly present in children with DS than in healthy individuals, with loss of the characteristic reduction of age range, as observed in control individuals, thus suggesting deficiency of inhibitory pathways in DS[13] and strengthening the hypothesis of deficient dopaminergic tonus.

Our conclusion is that children with DS often have elevated TSH baseline values even if the baseline values of thyroid hormones are normal or autoimmunity is absent. We also observed that most of these children (65%) show hyperresponsiveness to the TRH test. This suggests that there may be a hypothalamic-pituitary dysfunction of TSH secretion in patients with Down's syndrome, whose etiology is still unknown.

Therefore, pediatricians should carefully follow up patients with DS who have an elevated TSH level and normal T3 and T4. These patients should not be immediately considered as having hypothyroidism. A careful clinical and laboratory workup is necessary in order to decide whether hormone restoration is required and, if so, when it should be implemented.

References

1. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annerén G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. Arch Dis Child 1998;79:242-5.

2. Bernal J, Nunez J. Thyroid hormones and brain development. Eur J Endocrinol 1995;133:390-8.

3. Sullivan PF, Wilson DA, Mulder RT, Joyce PR. The hypothalamic-pituitary-thyroid axis in major depression. Acta Psychiatr Scand 1997;95:370-8.

4. Rubello D, Pozzan GB, Casara D, Girelli ME. Natural course of subclinical hypothyroidism in Down's syndrome: prospective study results and therapeutic considerations. J Endocrinol Invest 1995;18:35-40.

5. Selikowitz M. A five year longitudinal study of thyroid function in children with Down syndrome. Dev Med Child Neurol 1993;35:396-401.

6. Kabadi UM, Cech R. Normal thyroxine and elevated thyrotropin concentrations: evolving hypothyroidism or persistent euthyroidism with reset thyrostat. J Endocrinol Invest 1997;20:319-26.

7. Wilber JF. Control of thyroid function: The hypothalamic-pituitary-thyroid axis. In: Degroot LJ, Jameson JL, editores. Endocrinology. 3rd ed. Philadelphia: Saunders; 1995.p.602-16.

8. Milner RDG, Herber SM. Response to TRH in suspected hypopituitarism. Arch Dis Child 1983;58:195-7.

9. Konings GH, van Trotsenburg AS, Ris-Stalpers C, Vulsma T, Wiedijk BM, de Vijlder JJ. Plasma thyrotropin bioactivity in Down's syndrome children with subclinical hypothyroidism. Eur J Endocrinol 2001;144:1-4.

10. Yates CM, Simpson J, Gordon A, Maloney AF, Allison Y, Ritchie IM, et al. Catecholamines and cholinergic enzymes in pre–senile and senile Alzheimer-type dementia and Down's syndrome. Brain Res 1983;280:119-26.

11. Mann DM, Yates PO, Marcyniuk B. Dopaminergic neurotransmitter systems in Alzheimer's disease and in Down's syndrome at middle age. J Neurol Neurosurg Psychiatry 1987;50:341-4.

12. Godridge H, Reynolds GP, Czudek C, Calcutt NA, Benton M. Alzheimer-like neurotransmitter deficits in adult Down's syndrome brain tissue. J Neurol Neurosurg Psychiatry 1987;50:775-8.

13. Dustman RE, Callner DA. Cortical evoked responses and response decrement in nonretarded and Down's syndrome individuals. Am J Ment Defic 1979;83:391-7.

Correspondence:
Dr. Carlos A. Longui
R. Cesário Mota Junior, 112 – Vila Buarque
CEP 01122-021 – São Paulo, SP, Brazil
Phone/Fax: +55 11 3220.2008
E-mail: fisiolab@santacasasp.org.br