0021-7557/05/81-01/79
Jornal de Pediatria

Etiological assessment of hyperthyrotropinemia in children with Down's syndrome

Vera M. A. Dias,[1] Júlio C. R. Nunes,[2] Sabrina S. Araújo,[2] Eugênio M. A. Goulart[1]

Abstract

Objective: To study the prevalence of increased TSH level and its probable cause in children with Down's syndrome treated at Policlínica Antônio Cândido.

Methods: The data were colleted using medical records of 169 patients. Of these, 46 patients, whose TSH increased at some time during their follow-up, were re-evaluated. In these patients, TSH, free T4, total T4 and thyroid peroxidase autoantibody (anti-TPO) levels were measured. Thyroid ultrasound, iodine-131 scintigraphy, and a perchlorate discharge test were performed.

Results: In 169 children, 86 (50.8%) of whom were male, aged between 1-16 years (median 4 years), 67 (39.6%) presented increased TSH levels. Out of these 67 patients, 46 were prospectively studied. In 31 (67.4%) of them serum TSH returned to normal levels; in 11, TSH remained between 5 and 10 µU/ml, three (6.5%) had a TSH level over 10 µU/ml and one (2.2%) had hyperthyroidism. The diagnoses in 34 patients who were fully studied were: goiter in five (14.7%); Hashimoto's thyroiditis in four (5.9%); hypoplasia in three (8.8%) and iodide organification defect in one (2.9%). The increased TSH levels had a statistically positive relationship with anti-TPO ($p = 0.02$), but not with gender, abnormal ultrasound or scintigraphy findings. TSH levels did not have any relationship with persistent hyperthyrotropinemia.

Conclusions: In patients with Down's syndrome, slightly elevated and transient TSH levels are frequently detected. Positive anti-TPO antibody test is a key factor in the follow-up of these patients because of its potential risk of progression to manifest thyroid disease.

J Pediatr (Rio J). 2005;81(1):79-84: Down's syndrome, hyperthyrotropinemia, autoimmune thyroid disease, thyrotropin, hyperthyroidism.

Introduction

Down's syndrome (DS) is the most frequent chromosome anomaly, and there is a still unclear association between it and thyroid disorders. The prevalence of thyroid dysfunction in DS is higher than in the general population, ranging from 20 to 66%, depending on the study design, sample size, geographical region, age group and on whether cases of hypothyroidism and/or hyperthyroidism were analyzed.[1-10] These studies conclude that, due to such high prevalence, it is necessary to assess the thyroid function in the follow-up of DS patients.

The most common finding in these patients is the isolated elevation of thyroid-stimulating hormone (TSH) levels, but normal thyroid hormone levels, known as subclinical hypothyroidism, with TSH levels slightly greater than the reference values (between 5 and 10 µU/ml) and, in many cases, with no detectable etiology.[8,11-13]

Studies have demonstrated an increased response of TSH to thyrotropin-releasing hormone (TRH) in DS patients,[14] and this response pattern persists up to the age of three years.[15]

1. Adjunct professor, Department of Pediatrics, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
2. Medical student, Department of Pediatrics, School of Medicine, UFMG, Belo Horizonte, MG, Brazil.
Financial support: Fundação de Amparo à Pesquisa do Estado de Minas Gerais – FAPEMIG.

Manuscript received Feb 17 2004, accepted for publication Oct 27 2004.

Suggested citation: Dias VM, Nunes JC, Araújo SS, Goulart EM. Etiological assessment of hyperthyrotropinemia in children with Down's syndrome. J Pediatr (Rio J). 2005;81:79-84.

The transient elevation of TSH levels has been documented in children with DS.[7,10] Controversy exists over whether such elevation is a risk factor for impaired intellectual outcome in these children[11] and the cause for such elevation has not been clarified yet.[16-19]

Culter et al.[2] suggest that the isolated elevation of TSH levels in children with DS, even in the absence of thyroid peroxidase autoantibody (anti-TPO), might be an early sign of primary autoimmune hypothyroidism. Cases with positive anti-TPO are expected to have a frequent progression to overt thyroid disease.[7]

The age and sex of patients with DS and positive anti-TPO varied in comparison to patients with autoimmune thyroiditis without DS. The incidence was higher among females, and there was a large number of patients with elevated TSH levels, which increased with age. Several studies have shown an increased incidence of positive anti-TPO and/or T4 and TSH variation with the advance of age.[9,20-22] Rubello et al.[7] found a high prevalence of circulating anti-TPO at all ages in DS patients, including very young ones, and a similar distribution in both sexes. Pueschel & Pezzullo[11] observed a significant increase in TSH levels among male patients with DS. Sare et al.[23] noted that female patients with DS, younger than 20 years of age, presented hypothyroidism more often than their male counterparts.

The aim of the present study was to assess the prevalence of elevated TSH levels and investigate their probable etiology among children with DS treated at the Division of Genetics of Policlínica Antônio Cândido, which belongs to the health system of Belo Horizonte, state of Minas Gerais, Brazil.

Patients and methods

All patients with DS, confirmed by karyotyping, treated at the Division of Genetics of Policlínica Antônio Cândido, in Belo Horizonte, between 1994 and 2001, were included in the study. Patients' medical records were reviewed in order to assess the prevalence of thyroid dysfunction. Of all patients, 169 children, median age of four years (range of 1 to 16 years), had a documented history of thyroid dysfunction. Of these patients, 86 were male and 83 female.

Children with elevated TSH levels (above 5 μU/ml) in at least one test, as reported on the medical chart, were called for a new assessment of their thyroid function. Forty-six children, aged between 1 and 16 years (mean of 5.04±2.88 years) presented themselves for reassessment. In cases in which thyroid dysfunction proved persistent, attempts were made to determine its etiology. Patients who were receiving hormone therapy due to hypothyroidism had their thyroid function reassessed after discontinuation of the treatment for four weeks.

The following tests were employed to assess thyroid function:

- Measurement of serum TSH: use of immunometric assay methodology, with IMMULITE analyzer (normal values range from 0.4 to 5.0 μU/ml).
- Measurement of thyroid hormones: an analogous competitive immunoassay using IMMULITE analyzer was employed to measure free T4 levels. Normal values were those ranging from 0.8 to 1.9 ng/dl. A competitive immunoassay employing IMMULITE analyzer was used to measure total T4 levels. Normal values were those between 4.5 and 12.5 μg/dl.
- Measurement of thyroid autoantibodies: a sequential immunometric assay using EDTA in serum and plasma and IMMULITE analyzer was used to measure anti-TPO. Levels greater than 35 U/ml were regarded as positive.
- Thyroid ultrasound: used to determine the size, shape, texture, and echogenicity of the thyroid gland and presence of nodules (position, size and aspect). Ultrasonography was performed using an ultrasound unit with 256 gray-scale gradations equipped with a 10-MHz linear transducer. Thyroid volume was calculated according to the method proposed by Ueda (1990).[24]
- Iodine-131 scintigraphy: the scintigraphic assessment of the thyroid gland was made using an ADAC VERTEX PLUS camera, 24 hours after the oral administration of iodine-131. Anterior and anterior oblique images were obtained.
- Perchlorate discharge test: the assessment of iodine organification in the thyroid gland was made by measuring thyroid iodine uptake two hours after the administration of iodine-131 and by performing serial uptake measurements preceded by the oral administration of 1 g of perchlorate (normal values < 20%).

Children with TSH levels greater than 5 μU/ml were called to undergo the tests described above. A cross-sectional study was carried out to verify whether there was some association of the variables with the persistence of elevated TSH levels. The patients were placed in two groups: Group 1 – patients with normal TSH levels and Group 2 – those whose TSH levels were greater than 5 μU/ml. Group 1 was compared to Group 2 with regard to sex, ultrasound findings, scintigraphic findings, and positive anti-TPO. A patient with hyperthyroidism and positive anti-TPO was excluded from this analysis. The abnormal TSH level described on the medical records was compared with the TSH level measured when patients were reassessed, in an attempt to establish a relationship between TSH levels and the tendency of these levels to remain elevated. The statistical analysis was made using Epi-Info 6.0, and Student's t test was used to compare the means, whereas the chi-square test and Fisher's exact test were used for the frequency distributions. Statistical significance was established at 5% ($p < 0.05$). The study protocol was approved by the Ethics and Research Committee of Universidade Federal de Minas Gerais (UFMG). Parents or those legally representing study participants signed an informed consent form giving their permission for laboratory testing.

Results

Of the 169 medical records, 67 showed elevated TSH levels (above 5 µU/ml), indicating a prevalence of 39.6%. Of these 67 patients, 46 could be tracked; the remaining 21 patients could not be found because the addresses informed on their records had not been updated. All 46 patients were submitted to TSH, total T4, free T4, and anti-TPO measurements. Forty of these patients underwent ultrasonographic (US) examination and 34 were submitted to iodine-131 scintigraphy and to the perchlorate discharge test. Two patients were lost to follow-up because their families did not agree with their participation in the study, one died from complications after a surgery for congenital heart disease and other losses occurred due to problems traveling to and from the places where the tests were performed, since many patients lived in other towns. The main difficulty involved scintigraphy and the perchlorate discharge test, which took three days.

Of the 46 children who participated in the study, eight (4.7%) were being treated for hypothyroidism with hormone replacement therapy. After discontinuation of levothyroxine for four weeks, two of them showed TSH levels greater than 10 µU/ml, whereas four had TSH levels between 5 and 10 µU/ml with normal free T4 levels (which characterizes hyperthyrotropinemia), and two exhibited normal TSH levels.

Of the remaining 38 children, whose previous TSH levels were greater than 5 µU/ml, 29 (76.3%) spontaneously normalized their TSH levels, seven (18.4%) still showed TSH levels between 5 and 10 µU/ml, and only one (2.6%) had a TSH level greater than 10 µU/ml. On the other hand, one of the patients developed hyperthyroidism. In this group of 38 patients, the median TSH level was 3.60 µU/ml, with minimum values ranging from 0.01 (patient who developed hyperthyroidism) to 0.81 µU/ml and maximum values of 13.70 µU/ml. The mean (4.08 µU/ml) was close to the median, with a standard deviation of 2.56 µU/ml.

Therefore, considering the 46 patients who were reassessed, now including those who were being treated with hormone replacement but had discontinued the treatment for four weeks, we observed that TSH levels returned to normal in 31 (67.4%) children, 11 (23.9%) still showed values between 5 and 10 µU/ml, three (6.5%) revealed TSH values greater than 10 µU/ml and one developed hyperthyroidism, with a TSH of 0.01 µU/ml.

With regard to anti-TPO, six (13%) had positive results (56.6 to 1,000 U/ml), three of whom belonged to the group of eight patients who were being treated with levothyroxine replacement therapy. TSH levels were elevated (5.55 to 16.6 µU/ml) in four patients, normal (4.27 µU/ml) in one and suppressed (0.01 µU/ml) in one.

Among 40 patients submitted to thyroid ultrasound, 13 (32.5%) showed some dysfunction. Enlargement of the thyroid gland was the most common finding. The thyroid gland was enlarged in seven (17.5%) patients, and two patients of this subgroup also showed abnormal thyroid gland texture and one presented with suspected colloid goiter (the same patient treated with levothyroxine and positive for anti-TPO - 365 U/ml). Hypoplasia was observed in three patients (7.5%), and one of them had only hypoplasia of the left lobe. One patient (2.5%) presented with abnormal thyroid gland texture only. The US of another patient suggested Hashimoto's thyroiditis. This patient was not receiving any kind of therapy, TSH levels returned to normal (4.27 µU/ml) and anti-TPO was positive (142 U/ml).

Of the 34 patients submitted to thyroid scintigraphy, seven (20.6%) showed some kind of dysfunction, a low thyroid uptake in three and enlargement in the other cases. The six-hour iodine uptake had minimum and maximum values of respectively 3% and 19%, with a median of 8%. The 24-hour iodine uptake was 5% and 20% (minimum and maximum values, respectively), with a median of 11%.

As for the perchlorate discharge test, only one child had a positive result (> 20%) without detectable anti-TPO, suggesting a congenital defect in thyroperoxidase synthesis. This patient had normal thyroid US findings and normal TSH levels.

By analyzing only the 34 patients submitted to hormone level measurements, thyroid ultrasound and iodine-131 scintigraphy, we found the following diagnoses: five (14.7%) cases of goiter; three (8.8%) cases of hypoplasia; Hashimoto's thyroiditis in two patients (5.9%), and iodine organification defect in one patient (2.9%).

Among 10 children with elevated TSH levels, submitted to all tests, no diagnosis could be established in five (50%).

Table 1 shows the results regarding the association of sex, US findings, scintigraphy findings, and positive anti-TPO with elevated TSH levels. In this analysis, 45 children were placed in two groups: Group 1 – those with normal TSH levels and Group 2 – those whose TSH levels were still greater than 5 µU/ml. The child who presented with suppressed TSH and positive anti-TPO was excluded from this study.

No association was observed between sex and elevated TSH levels.

Abnormal US findings were not correlated with the persistence of elevated TSH levels in any of the 39 children evaluated.

The 36 patients submitted to scintigraphic examination did not show any association between abnormal results in this exam and elevated TSH levels.

However, when we compared the presence of anti-TPO with TSH values, we noted that high serum levels of this antibody (> 35 U/ml) were correlated with persistently high TSH levels ($p = 0.0270$).

Group 1 was compared to Group 2 in terms of TSH levels described on the medical records. The mean TSH level found on the medical records was 7.91±2.90 µU/ml (range of 5.1 to 15.9 µU/ml) for the children whose TSH levels returned to normal (Group 1) and 11.37±7.60 µU/ml (range of 5.6 to 29.9 µU/ml) for those whose TSH remained high (Group 2), with no statistical difference between the means ($p = 0.22$). Therefore, the variation of previous TSH levels was not related to a tendency towards persistent hyperthyrotropinemia.

Table 1 - Comparison of the results regarding the association of sex, US findings, scintigraphy findings, and positive anti-TPO with elevated TSH levels of children with Down's syndrome

	Elevated TSH	Normal TSH	Total*	Statistical test	p
Sex					
Female	7	17	24		
Male	7	14	22	Chi-square	0.98
Total	14	32	46		
Ultrasound					
Abnormal	5	7	12		
Normal	5	22	25	Fisher	0.23
Total	10	29	39		
ATPO					
Positive	4	1	5		
Negative	10	30	40	Fisher	0.03
Total	14	31	45		
Scintigraphy					
Abnormal	2	5	7		
Normal	8	19	27	Fisher	1.00
Total	10	24	34		

* One patient with suppressed TSH and positive ATPO was excluded.

Discussion

The close relationship between thyroid disorders and DS has been largely described in the literature. The present study showed a significant prevalence (39.6%) of thyroid dysfunction in DS patients, which concurs with other studies that regard elevation in TSH levels as a thyroid dysfunction. TSH levels were not so elevated (5.1 to 29.9 μU/ml), as observed in several studies.[1-10] There was no difference in sex distribution in our patient population, similarly to what has been described in other studies.[12,13,21] The fact that only eight (4.7%) of 169 patients were following a treatment suggests that most of them had an isolated elevation of TSH levels – hyperthyrotropinemia; corroborating the results found by several authors who studied DS patients.[8,11-13]

Of the children who showed elevated TSH levels sometime during the follow-up period, 67.4% returned to normal levels after new tests. This demonstrates that hyperthyrotropinemia in DS patients is often transient. This result is consistent with studies on DS patients.[7,10] Selikowitz[10] pointed out the inappropriate release of TSH resulting from a central dysfunction, production of a less active type of TSH or some form of unresponsiveness of the thyroid gland to TSH as possible explanations for this transient elevation. However, the study carried out by Konings et al.[19] showed normal bioactivity of TSH in the plasma of children with DS who had subclinical hypothyroidism. An increased response of TSH to TRH is observed in DS patients.[14,15] In the cross-sectional study by Sharav et al.,[15] this increased response of TSH to TRH showed a gradual decrease, returning to normal at the age of three years. This was explained as being a consequence of delayed maturation of the hypothalamic-pituitary-thyroid axis in children with DS, which might be the cause for isolated elevation of TSH levels in a large number of these patients. Other reasons for this transient elevation in TSH levels have been suggested by other studies, namely, low serum levels of zinc,[16,17] which is implicated in some endocrine and immunological processes; and low serum levels of selenium, which is found in proteins responsible for thyroid hormone synthesis.[18]

In this study, no significant difference was observed between the means of initial TSH serum levels of patients who normalized their TSH levels and of those in whom these levels were persistently high during the reassessment. Among the patients with totally normal thyroid function, three presented goiter and one Hashimoto's thyroiditis after a more comprehensive evaluation using ultrasound and scintigraphy. These facts suggest that the persistence of elevated TSH levels or progression to thyroid disease is not related to serum TSH levels.

Autoimmune factors might be implicated in the pathogenesis of hyperthyrotropinemia in DS. Some mechanisms have been suggested, such as greater sensitivity of cells in trisomy 21 to interferon; presence of a certain HDR antigen closely associated with autoimmune thyroiditis in cells of DS patients; or the presence of three superoxide dismutase-1 genes. This enzyme is believed to cause excessive production of hydrogen peroxide and to be involved in high levels of anti-TPO, since peroxidase is the substrate for peroxidase iodine.[6] However, the studies conducted by

Zori et al.[5] did not find any correlation between HLA (human leukocyte antigen) system and the presence of thyroid autoantibodies. The pathogenetic mechanism of subclinical hypothyroidism without anti-TPO still remains unclear in DS patients.

The fact that TSH levels in eight children who had been previously treated for hypothyroidism returned to normal after discontinuation of levothyroxine therapy for four weeks stresses the fact that hypothyroidism may be transient. Therefore, it has been suggested that hormone replacement therapy should be discontinued during the clinical follow-up of these patients in order to determine whether it is necessary to maintain it or not.

The present study allowed demonstrating that children with positive anti-TPO have a higher probability of showing persistently elevated TSH levels, whereas those with negative anti-TPO tend to normalize their TSH levels. It was also observed that anti-TPO proved to be an isolated factor, since other variables such as sex, ultrasound or scintigraphy findings were not associated with the persistence of elevated TSH levels. It should be considered that the absence of detectable anti-TPO in many of these children (including those presenting only goiter) could result from the fact that low serum levels were not detected by the laboratory methods used or from the fact that it could be a case of Hashimoto's thyroiditis with negative autoantibodies commonly observed in children. Rubello et al.,[7] in a longitudinal study about patients with DS and subclinical hypothyroidism without anti-TPO, found that the isolated elevation of TSH levels does not seem to predispose to the development of a clinically overt thyroid disease, since spontaneous normalization of TSH levels was frequently observed in these cases.

Congenital hypothyroidism (CH) also is observed more often in DS patients (1-2%) than in the general population.[7,8,10] In an extensive study on the prevalence of CH in neonatal screening by van Trotsenburg et al., DS patients showed a higher frequency of thyroid dysfunctions. These dysfunctions show significantly high TSH levels and low T4 levels, compared to newborns without DS.[25] In the present study, we detected four cases (8.7%), three of them concerned hypoplasia of the thyroid gland and one constituted an iodine organification defect. Also, a significant number of cases of goiter (14.3%) of unknown etiology was observed. CH due to hormone synthesis defect, which causes enlargement of the thyroid gland, cannot be ruled out in these patients.

One patient with elevated anti-TPO levels developed hyperthyroidism, probably due to Graves' disease. This indicates that, although this thyroid dysfunction is less frequent in DS patients,[3,7,10,26] hyperthyroidism may be present. Occurrence of asymptomatic transient hyperthyroidism also has been reported in DS patients without detectable antibodies. The mechanism of this thyroid dysfunction has not been clarified yet.[26]

The results of the present study show a high prevalence of thyroid dysfunctions in children with DS, the most common of which is the transient elevation of TSH levels without evident pathological consequences. It was not possible to establish a clear etiology for these dysfunctions. However, children with higher anti-TPO levels had greater difficulty in spontaneously normalizing their TSH levels. Therefore, it is important to perform a regular thyroid examination, at least once a year, in children with DS, focusing on those with positive anti-TPO, due to their increased risk of developing clinically overt thyroid disease.

Acknowledgments

Thanks to Dr. Letícia Lima Leão, physician and geneticist at *Policlínica Antônio Cândido*, in Belo Horizonte, for explaining the importance of the study to the patients. Also thanks to Foundation for the Support of Research of the state of Minas Gerais – FAPEMIG – for the financial support.

References

1. Sare Z, Ruvacalcaba RH, Kellwy VC. Prevalence of thyroid disorder in Down syndrome. Clin Genet. 1978;14:154-8.
2. Culter AT, Benezra-Obeiter R, Brink SJ. Thyroid function in young children with Down Syndrome. Am J Dis Child. 1986; 140:479-83.
3. Friedman DL, Kastner T, Poud WS, O'Brien DR. Thyroid dysfunction in individuals with Down Syndrome. Arch Intern Med. 1989;149:1990-3.
4. Pozzan GB, Rigon F, Girelli ME, Rubello D, Busnardo B, Baccichetti C. Thyroid function in patients with Down syndrome: preliminary results from institutionalized patients in the Veneto region. Am J Med Genet. 1990;Suppl 7:S57-8.
5. Zori RT, Schatz DA, Ostrer H, Williams CA, Spillar R, Riley WJ. Relationship of autoimmunity to thyroid dysfunction in children and adult with Down Syndrome. Am J Med Gen. 1990;Suppl 7:S238-41.
6. Kennedy RL, Jones TH, Luckle HS. Down Syndrome and the thyroid. Clin Endocrinol. 1992;37:471-6.
7. Rubello D, Pozzan GB, Casara D, Girelli ME, Boccato S, Rigon F. Natural course of subclinical hypothyroidism in Down Syndrome: prospective study results and therapeutic considerations. Endocrinol Invest. 1995;17:35-40
8. Tüysüz B, Beker DB. Thyroid dysfunction in children with Down's syndrome. Acta Paediatr. 2001;90:1389-93.
9. Ali FE, Bayoumy HA, Mohammad AS, Al-Busairi WA, Al-Othman AN. Thyroid function in Kuwaiti subjects with Down's syndrome. Med Princ Pract. 2002;11:206-9.
10. Selikowitz M. A five-year longitudinal study of thyroid function in children with Down Syndrome. Dev Med Child Neurol. 1992;35:396-401.
11. Pueschel SM, Pezzullo JC. Thyroid dysfunction in Down Syndrome. AJDC. 1985;139:636-9.
12. Jiménez-López V, Arias A, Arata-Bellabarba G, Vivas E, Delgado MC, Paoli M. Concentration of thyrotropic hormone and free thyroxin in children with Down's syndrome. Invest Clin. 2001;42:123-30.
13. Gruñeiro de Papendieck L, Chiesa A, Bastida MG, Alonso G, Finkielstain G, Heinrich JJ. Thyroid dysfunction and high thyroid stimulating hormone levels in children with Down's syndrome. J Pediatr Endocrinol Metab. 2002;15:1543-8.
14. Oliveira ATA, Longui CA, Calliari LE, Ferone EA, Kawaguti FS, Monte O. Evaluation of hypothalamic-pituitary-thyroid axis in children with Down syndrome. J Pediatr (Rio J). 2002;78:295-300.
15. Sharav T, Landau H, Zadik Z, Einerson TR. Age-related patterns of thyroid-stimulating hormone response to tyrotropin-releasing hormone stimulation in Down Syndrome. AJDC. 1991;256:172-5.
16. Napolitano G, Palka G, Lio S, Bucci I, De Remigis P, Stuppia L, et al. Is zinc deficiency a cause of subclinical hypothyroidism in Down syndrome? Ann Genet. 1990;33:9-15.

17. Bucci I, Napolitano G, Giuliani C, Lio S, Minnucci A, Di Giacomo F, et al. Zinc sulfate supplementation improves thyroid function in hypozincemic Down children. Biol Trace Elem Res. 1999;67:257-68.
18. Kanavin OJ, Aaseth J, Birketvedt GS. Thyroid hypofunction in Down's syndrome: is it related to oxidative stress? Biol Trace Elem Res. 2000;78:35-42.
19. Konings CH, 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.
20. Pueschel SM, Jackson IM, Giesswein P, Dean MK, Pezzullo JC. Thyroid function in Down syndrome. Res Dev Disabil. 1991;12:287-96.
21. 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.
22. Rooney S, Walsh E. Prevalence of abnormal thyroid function tests in a Down's syndrome population. Ir J Med Sci. 1997;166: 80-2.
23. Sare Z, Ruvalcaba RH, Kelley VC. Prevalence of thyroid disorder in Down syndrome. Clin Genet. 1978;14:154-8.
24. Ueda D. Normal volume of the thyroid gland in children. J Clin Ultrasound. 1990;18:455-62.
25. van Trotsenburg AS, Vulsma T, van Santen HM, Cheung W, de Vijlder JJ. Lower neonatal screening thyroxine concentrations in Down syndrome newborns. J Clin Endocrinol Metab. 2003;88:1512-5.
26. Tambyah PA, Cheah JS. Hyperthyroidism and Down syndrome. Ann Acad Med Singapore. 1993;22:603-5.

Corresponding author:
Rua Expedicionário Alício, 476, Mangabeiras
CEP 30315-220 – Belo Horizonte, MG
Brazil
Phone: +55 (31) 9654.3737