Clinical and laboratory features of children and adolescents with congenital hypothyroidism due to dyshormonogenesis in southern Brazil

*Características clínicas e laboratoriais de crianças
e adolescentes com hipotireoidismo congênito
devido a disormonogênese no sul do Brasil*

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ABSTRACT

Objective: To characterize the phenotype of patients with congenital hypothyroidism (CH) due to dyshormonogenesis, and to hypothesize on the degree of genetic defect. **Subjects and methods:** Patients with dyshormonogenesis were subdivided into G1 (radioactive iodine uptake, RAIU > 15%; n = 62) and G2 (RAIU ≤ 15%; n = 32). Thyroglobulin (TG) was measured in all patients; perchlorate discharge test (PDT) was performed in G1; and saliva-to-plasma radioiodine ratio (I⁻ S/P) in G2. **Results:** Levels of TSH, TT_4, and FT_4 before treatment and upon diagnosis confirmation were significantly different in both groups, but not between groups. In G1, 27 patients developed goiter; 17 had positive PDT (14%-71% discharge), 11 had TG < 2.5 ng/dL (one with high TSH), and one developed thyroid carcinoma. In G2, four patients developed goiter, and three had low I⁻ S/P. **Conclusion:** These data suggest an iodide organification defect in 17 cases; an iodide transport defect (NIS defect) in three, probable TSH resistance in 10, and a TG synthesis defect in two cases. Arq Bras Endocrinol Metab. 2012;56(3):201-8

Keywords
Congenital hypothyroidism; thyroid hormones; goiter; thyroglobulin

RESUMO

Objetivo: Caracterizar o fenótipo de pacientes com hipotireoidismo congênito (HC) por disormonogênese e sugerir o nível do defeito genético. **Sujeitos e métodos:** Pacientes com disormonogênese foram subdivididos em G1 (captação de [131]I > 15%; n = 62) e G2 (captação ≤ 15%; n = 32). Tireoglobulina (TG) foi dosada em todos, teste de descarga do perclorato (TDP) foi realizado no G1 e relação iodo salivar/sérico (I⁻ S/P), no G2. **Resultados:** Os valores de TSH, T_4T e T_4L pré-tratamento e na confirmação do diagnóstico foram significativamente diferentes em ambos os grupos (p < 0,01), mas não entre eles. No G1, 27 pacientes desenvolveram bócio; TDP foi positivo em 17 (descarga de 14%-71%); 11 tiveram TG < 2,5 ng/dL (um com TSH elevado) e um desenvolveu carcinoma de tireoide. No G2, quatro pacientes desenvolveram bócio e três apresentaram baixa I⁻ S/P. **Conclusão:** Esses dados sugerem defeito na organificação do iodeto em 17 casos; defeito no transporte do iodeto (defeito na NIS) em três, provável resistência ao TSH em 10 e defeito na síntese de TG em dois. Arq Bras Endocrinol Metab. 2012;56(3):201-8

Descritores
Hipotireoidismo congênito; hormônios tireoidianos, bócio; tireoglobulina

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common congenital endocrine disease and a preventable cause of mental retardation. The disorder is permanent and results primarily from abnormalities in the development of the thyroid, either dysgenesis or agenesis. The second most common cause of CH is dyshormonogenesis, i.e., inborn errors of thyroid hormone synthesis. Other less frequent etiologies include defects in the binding of thyroid-stimulating hormone (TSH) to its receptor, and pituitary or hypothalamic abnormalities, such as central and secondary or tertiary hypothyroidism.

Recent advances in molecular biology have led to better understanding of the steps involved in thyroid hormone synthesis, and the genes involved in this process. Several genes have been identified and mutations have been recognized as causes of CH (1,2). Dyshormonogenesis is usually transmitted in an autosomal recessive pattern (3). Clinical manifestations of CH caused by dyshormonogenesis are similar to those associated with thyroid dysgenesis, except for a familial incidence and a tendency to develop goiter during the neonatal period or, more commonly, during childhood or adulthood. In order to identify the etiology of the dyshormonogenesis, additional investigation is required, and includes the perchlorate discharge test (PDT), measurement of serum thyroglobulin (TG), iodide saliva-to-plasma ratio (I⁻ S/P) and molecular genetic analysis. The latter test is not easily available in daily practice.

About 10% to 15% of the newborns with CH are affected by dyshormonogenesis. However, due to a decrease in the TSH cutoff values in neonatal screening to 12 or 10 mU/L over the last years, more cases of CH have been detected, mainly caused by milder defects in thyroid hormone synthesis (4). Dyshormonogenesis may occur due to defects in any level of synthesis or secretion of thyroid hormones, such as iodide transport, iodide organification, synthesis of TG, and iodotyrosine deiodination. The most common defect affects thyroperoxidase (TPO) activity, leading to abnormalities in iodide oxidation and organification, and interfering with its binding to the tyrosine molecule (2).

To date, few studies have characterized the phenotype of a large group of patients with thyroid dyshormonogenesis. The aim of this study was to assess the clinical and laboratory features of children and adolescents with CH due to dyshormonogenesis, and to investigate whether the identification of these features could suggest the degree of genetic defect that culminated with dyshormonogenesis.

SUBJECTS AND METHODS

Between June 1991 and May 2008, the Neonatal Screening Program of the state of Paraná identified 759 patients with elevated TSH, and referred these patients to the Pediatric Endocrinology Unit of Federal University of Paraná (UEP-UFPR) for additional evaluation. From 407 patients with a diagnosis of permanent CH, 108 (26,6%) had an *in situ* thyroid with normal morphology on scintigraphy, compatible with dyshormonogenesis. Fourteen patients were excluded for being followed up at another service, interrupting treatment for more than six months, or presenting a concomitant genetic syndrome. The final cohort consisted of 94 patients, of whom 54 (57%) were female.

Initial clinical and laboratory data were retrieved from medical records, and information collected before treatment and at the time of the confirmation of CH diagnosis was included. These data included levels of TSH, total T_4 (TT4), free T_4 (FT4) and 24-hour ^{131}I radioactive iodine uptake (RAIU). Random serum TSH and TG were obtained in all patients. According to the RAIU, patients were divided into two groups. Group 1 (G1) was made up of patients with RAIU greater than 15%, and group 2 (G2) of those with RAIU lower than or equal to 15%. Patients categorized as G1 underwent further evaluation with PDT, whereas those categorized as G2 had salivary and plasma iodine measured for assessment of the serum-to-plasma iodine ratio (I⁻ S/P).

Blood samples for measurement of TSH, TT_4 and FT_4 were collected in the morning of the visit, before the administration of levothyroxine (L-T_4), or in the evening, about six hours after L-T_4 intake. Measurements were performed at the Clinical Analysis Laboratory of the UFPR School Hospital. TT_4, FT_4, and TSH were measured using Immulite 2000® Analyzer (DPC) by chemiluminescence, with analytical sensitivity of 0.3 µg/dL, 0.18 ng/dL, and 0.002 mU/L, respectively. Serum TG was also measured by chemiluminescence (reference value 2 to 60 ng/mL).

Thyroid scan, PDT and salivary iodide measurement were performed at the Nuclear Medicine Service of the UFPR School Hospital. Thyroid scan was performed between 2.5 and 3 years of age. In preparation for the scan, L-T$_4$ was suspended for 30 days. Patients received a dose of 50 µCi of ^{131}I (^{123}I is not available in our institution) followed by RAIU measurement at 24 hours. In 11 patients, the scan was performed using ^{99m}Tc due to a temporary shortage of radioiodine. Uptake was then considered normal or high based on the visual aspect.

In preparation for PDT, L-T$_4$ was suspended for 30 days. For the test, patients received potassium perchlorate at a dose of 10 mg/kg body weight after administration of ^{131}I. Due to a limited availability of potassium perchlorate capsules, the test was not performed in all G1 patients and priority was given to patients with normal or high TG levels. When patients had iodide discharge between 10% and 90%, they were considered to have a partial iodide organification defect (PIOD), and when discharge was above 90%, total iodide organification defect (TIOD) (5).

I$^-$ S/P was calculated by measuring the radioactivity of 1 mL of saliva and 1 mL of blood aliquots collected after an oral radioiodine dose of 500 µCi. The test was considered normal when the plasma-to-saliva iodide ratio was above 25, whereas values close to 1 indicated a complete iodide trapping defect. A I$^-$ S/P ratio of up to 20 represented partial defects (6).

At UEP-UFPR, thyroid ultrasound is performed routinely in patients with CH. However, the exam is performed by different examiners at random ages. As, in this cohort, the exam was performed at different ages, with different degrees of laboratorial control, and by different examiners, thyroid volume ultrasound measurements were not used as a parameter in this study.

Informed consent was obtained from all patients in accordance with the guidelines of the Ethical Committee of the Federal University of Paraná School Hospital.

Statistical analyses were performed using the software Statistica (Statsoft, version 7.1). For all analyses, nonparametric Mann-Whitney test for between-group comparisons was applied, and a minimum level of 5% was considered significant ($p < 0.05$).

RESULTS

Overall, median age at first evaluation was 25.5 days (range: 4 to 88 days).

Description of G1

G1 was made up of 62 patients (65.9%). All subjects in this group had a normal or enlarged thyroid on scintigraphy. The scan was performed with radioactive iodine in 51 patients of this group, whereas in 11, ^{99m}Tc was used, resulting in normal or increased uptake. Most patients in this group were female (n = 38; 61.2%). Median age at first evaluation was 26.5 days (range: 4 to 88 days). Six patients had consanguineous parents, and in four of these cases (two siblings), parents were first-degree cousins. Goiter was absent in all children at the initial visit and developed during follow-up in 27 of them. Other prevalent clinical signs were umbilical hernia (48%), abdominal distension (42%), prolonged jaundice (38.7%), depressed nasal bridge (30.6%), large posterior fontanel (22.5%), hoarse cry, and constipation (both 19.3%).

As shown in table 1, there were significant differences on TSH, TT$_4$, and FT$_4$ levels measured before treatment and upon diagnosis confirmation ($p < 0.01$).

Random serum TG ranged from 0.5 to 168 ng/mL (mean 27.2 ng/mL, standard deviation 37.8 ng/mL; median 11.3 ng/mL). As shown in table 2, eleven patients had TG below 2.5 ng/mL, and only one of these patients had an elevated TSH (10.2 mU/L). Eight patients had TG levels above 60 ng/mL, three of them with normal TSH.

PDT was performed in 30 patients (46.8%). The test was normal in 13 cases, whereas in 17, it was considered positive with an iodide discharge ranging from 14% to 71%, compatible with PIOD. Among patients with positive PDT, nine had goiter (53%). There were no significant differences in iodide discharge values among patients with and without goiter ($p = 0.38$). The three patients shown in table 2 who presented high TG with normal TSH levels had goiter and positive PDT.

Median pretreatment TSH levels were lower in patients with normal PDT compared with those with positive PDT (75.0 mU/L *versus* 100.0 mU/L, respectively; $p = 0.03$). However, there were no differences in TSH levels between these two groups when measured upon diagnosis confirmation (14.5 mU/mL *versus* 28.8 mU/mL, respectively; $p = 0.10$), and during PDT (15.1 mU/mL *versus* 23.0 mU/mL, respectively; $p = 0.64$).

One patient in this group developed a follicular variant of papillary carcinoma at the age of 15 years.

Throughout follow-up, mean serum TSH in this patient was 1.54 mU/L (range 0.02 to 4.71 mU/L). Goiter was observed at the age of seven, which developed together with the thyroid nodule, in spite of the fact that TSH levels remained within the normal range.

Description of G2

G2 was made up of 32 patients with normal thyroid morphology and RAIU less than 15%. Half of the patients (n = 16) were male. Median age at first evaluation was 21.5 days (range 11 to 80 days). Only one patient in this group had consanguineous parents (first-degree cousins). At initial evaluation, goiter was present in only one child, whereas the most prevalent clinical signs were umbilical hernia, abdominal distension and prolonged jaundice (50%), depressed nasal bridge (43.7%), and hoarse cry (40.6%).

Table 1 shows the levels of TSH, TT_4, and FT_4 measured before treatment and upon diagnosis confirmation in this group. There was a significant difference in TSH and TT_4 levels (both $p < 0.01$), but not in FT_4 ($p = 0.81$) measured before treatment and upon diagnosis confirmation.

Serum TG levels ranged from 0.5 to 460 ng/mL (mean 45.9 ng/mL, standard deviation 90.6 ng/mL; median 13.5 ng/mL). Four patients had TG below 2.5 ng/mL but normal TSH, whereas six patients had high TG associated with high TSH, except for one patient in whom TSH was not available (Table 2).

I^- S/P was calculated in 13 patients. Low I^- S/P was found in three of them (Table 3). None of these patients had consanguineous parents and only one showed goiter on the first evaluation (21 days) that persisted throughout childhood.

Table 2. Serum TG (ng/mL) and TSH (mU/L) in patients of G1 and G2

Patient	TG (ng/mL)	TSH (mU/mL)
G1		
8	0.5	1.70
18	0.5	2.70
19[(1)]	0.5	10.20
22	0.5	1.25
35	0.5	3.46
39	0.5	2.54
48	1.6	4.10
49	0.5	1.27
56	1.6	2.24
58	0.5	0.34
62	1.3	0.42
9	162.0	Not available
17	74.4	6.58
21[(2)]	129.0	2.57
25	112.0	5.72
36	81.5	100.00
45[(2)]	81.3	3.90
50[(2)]	168.0	3.30
57	64.1	7.91
G2		
4	1.7	1.13
17	0.5	3.46
29	0.5	1.49
30	0.9	0.90
7	71.9	Not available
11	77.5	8.31
15	164.0	15.40
21	93.1	8.61
31	460.0	100.00
32	230.0	17.10

(1) Patient with low TG and high TSH; (2) Patients with high TG and normal TSH.

Table 1. Serum levels of TSH, TT_4, and FT_4 in G1 and G2 patients measured before treatment and upon diagnosis confirmation

Parameter	G1 – Pretreatment	G1 – Diagnosis confirmation	p-value	G2 – Pretreatment	G2 – Diagnosis confirmation	p-value
Median TSH (mU/L)	75.00 ± 161.70 (25.20-813)[(a)] (n = 62)	35.70 ± 78.58 (7.18-472)[(b)] (n = 62)	< 0.01	107.46 ± 208.73 (8.7-822)[(a)] (n = 32)	30.04 ± 77.68 (6.11-331)[(b)] (n = 32)	< 0.01
Median TT_4 (ng/dL)	2.33 ± 3.38 (0.06-15.50)[(c)] (n = 61)	6.58 ± 3.02 (1.00-12.40)[(d)] (n = 58)	< 0.01	2.35 ± 3.53 (0.09-13.40)[(c)] (n = 32)	5.55 ± 3.89 (0.35-11.97)[(d)] (n = 28)	< 0.01
Median FT_4 (µg/dL)	0.35 ± 0.44 (0.01-1.95)[(e)] (n = 22)	0.93 ± 0.35 (0.20-1.56)[(f)] (n = 34)	< 0.01	0.40 ± 0.63 (0.01-1.66)[(e)] (n = 5)	0.51 ± 0.44 (0.20-1.36)[(f)] (n = 17)	0.81

Comparison between G1 and G2: (a) pretreatment TSH: $p = 0.31$; (b) diagnosis confirmation TSH: $p = 0.95$; (c) pretreatment TT_4: $p = 0.42$; (d) diagnosis confirmation TT_4: $p = 0.13$; (e) pretreatment FT_4: $p = 0.85$; (f) diagnosis confirmation FT_4: $p = 0.05$.

Table 3. Laboratory characteristics of G2 patients with low I⁻ S/P

Patient	Pretreatment TSH (mU/mL)	Diagnosis confirmation TSH (mU/L)	RAIU (%)	Serum TG (ng/dL)	I⁻ S/P
2	312	7.1	3.7	28	13
5	280	31.8	13.6	31	4.9
27[1]	60	75	1.3	5.7	1.3

(1) Patient with goiter.

Goiter was observed in four patients: I⁻ S/P was normal in one of them, low in another one, and it was not calculated in the other two patients.

Comparison between G1 and G2

Compared with G1, G2 patients were more likely to have some of the clinical manifestations of CH in the first evaluation, such as hoarse cry and pallor (p = 0.03), hypotonia and ocular hypertelorism (p = 0.01), as well as hypoactivity (p < 0.01). Statistical analysis showed no significant difference between G1 and G2 in relation to TSH levels measured before treatment and upon diagnosis confirmation. However, FT_4 levels upon diagnosis confirmation were higher in G1 than in G2, with borderline significance (p = 0.05), as shown in table 1.

DISCUSSION

We found a prevalence of dyshormonogenesis equal to 26.6% among patients screened for CH by the Neonatal Screening Program of the State of Paraná. These patients were subsequently followed up at the UEP-UFPR. This prevalence was higher than the one classically described in the literature, which is about 15%. However, more recent studies have shown increased incidence of CH and higher prevalence of milder forms of dyshormonogenesis due to lower cutoff values of TSH in the screening for the disease (4,7).

Because of the lack of a reference values for RAIU in the pediatric population, we chose a cutoff value of 15% for patient classification, based on reports showing RAIU of up to 15% in patients with congenital I⁻ transport defects (10).

Several patients were older than 30 days at the first visit. This reflects deficiencies in the Screening Program during the first years of its implementation. The area of coverage of the Brazilian National Screening Program varies among states. Coverage in the southern region of the country, where Paraná is located, is 87.1%, the best national average. The state of Paraná has a coverage rate of 88%, according to a 2008 report, and the average age at the onset of treatment in this state is 15 days (8,9).

Overall, 57% of the patients were female, similar to other reports in the literature that show similar sex distribution for dyshormonogenesis, unlike thyroid dysgenesis which shows higher prevalence in females, with a ratio of 2:1 (2).

Unfortunately not all patients underwent all tests. If available, molecular study would have added more information and enabled further conclusions about this population. So far, we understand that patients with dyshormonogenesis present wide phenotypic variability, which limits the definition of the etiology based only on clinical and laboratory data. The type of the genetic defect may be related to some prognostic features, such as goiter development, neurological outcome, hearing loss, and even thyroid cancer. This knowledge will be of great importance for a more specific clinical follow-up, and for familial counseling.

Before treatment, G2 patients had higher levels of TSH than those in G1, although this difference was not statistically significant. There was no significant difference between the groups in relation to TSH levels measured upon diagnosis confirmation, but levels of FT_4 measured at this moment were higher in G1 than in G2. Furthermore, some signs and symptoms of hypothyroidism described at first evaluation were more frequent in G2, suggesting that patients with impaired I⁻ uptake, probably as a result of *NIS* mutations or TSH resistance, have more severe hypothyroidism.

In both groups, pretreatment levels of TSH and TT_4 were significantly higher and lower, respectively, when compared with levels found upon diagnosis confirmation. Lower TT_4 at birth suggests that hypothyroidism may be more severe at birth, and that thyroid function may recover at least partially with age.

As for TG values, it was not possible to consider all results, since in most patients, TSH levels were normal. Low TG level associated with high TSH was found only in one patient in whom a TG synthesis defect was suspected, although no goiter development has been observed yet. This patient had a pretreatment TSH level of 325 mU/L, RAIU of 30.5%, and normal PDT. Absence of synthesis and secretion of TG was confirmed by absence of an increment in

serum TG (serum TG 0.8 ng/dL) in a sample collected during PDT with maximum TSH stimulation (TSH > 100 mU/L). The parents of this child are first degree cousins and the brother also has CH. Interestingly, the phenotype of the brother is slightly different: he presented a pretreatment TSH level of 75 mU/L, high ^{99m}Tc uptake, normal PDT, goiter, and serum TG in the lower limit, which did not increase with high TSH stimulation, either. Defective TG synthesis usually results in goitrous CH (11-13). Nevertheless, it would be interesting in both cases to search for mutations in the TG gene.

There were three patients (patients 21, 45 and 50) who had high serum TG and normal TSH, all of them with goiter and positive PDT (iodide discharge of 58%, 71% and 55%, respectively), compatible with PIOD.

Unfortunately PDT was performed in only 58% of the patients in G1, because of the limited availability of potassium perchlorate capsules. All positive PDT results were compatible with PIOD. Among these 17 patients, only nine had goiter (53%), a lower incidence compared with 70% (49 out of 71) reported by Cavarzere and cols. (14). This discrepancy may be related to geographic, ethnic and molecular differences, number of patients evaluated, or even to the fact that, in our study, the presence of goiter was considered based only on physical examination, whereas in the study of Cavarzere and cols., goiter was defined based on scintigraphic data.

There was no difference between the results of PDT in patients with and without goiter, reflecting no tendency in patients with higher iodide discharge to develop goiter. Similarly, there was no correlation between the presence of goiter and levels of TSH measured before treatment or upon diagnosis confirmation. This observation is different from the report of Cavarzere and cols., who described significantly higher TSH levels in patients with goiter (14). This difference was probably due to the lower number of patients in our study (17 patients *versus* 71) and to the reasons mentioned above.

The wide phenotypic variation among patients with PIOD, also reported by Cavarzere and cols. (14), is linked to the diversity of genetic disorders. PIODs are more commonly associated with TPO gene mutations (about 50% of cases), especially when goiter is present (15,16). Therefore, PIOD may also be caused by mutations in other genes that encode proteins associated with any of the steps involved with iodide organification. In the 17 patients with PIOD in our

study, the genetic etiology of the defect has not been defined yet. However, in 9 of these patients who presented goiter, the hypothesis of a *TPO* mutation is reasonable. Another possible etiology to be considered is Pendred syndrome. Patients with CH at UEP-UFPR are now referred to hearing screening, which will probably help to direct the search for an etiological diagnosis. However, since both Pendred syndrome and defects in TPO may be present with goiter, hypothyroidism and positive PDT, no definitive etiologic diagnosis is possible without molecular evaluation of patients who show concomitant hearing loss.

Tonacchera and cols. described a patient with CH and no goiter who was followed up until 14 years of age. This patient had mildly elevated TSH (32 mU/L on diagnosis, and 6 mU/L after six weeks of treatment), normal serum TG and a 13% iodide discharge at PDT. The authors found, in this patient, two novel mutations in *DUOX2*, which were responsible for the PIOD. This finding showed that inactivating mutations of *DUOX2* may be responsible for PIOD-related mild cases of CH (17). In our study, three subjects had clinical and laboratory features similar to this patient.

Although we had no cases compatible with TIOD, this diagnosis is still possible in our cohort, considering that there are still 20 patients in G1 in whom we intend to perform PDT.

PDT was normal in 14 patients and in six of them, goiter was present. All these patients, except for one, had normal TG with normal or slightly elevated TSH. In half of them, TSH-stimulated TG was measured during PDT, and in all of these patients, TG levels were high, reflecting its ability to accumulate in the colloid, since its synthesis is not impaired. The identification of the degree of molecular defect in these patients based on their clinical and laboratory characteristics is challenging: normal or high RAIU, normal or elevated serum TG, normal PDT, and goiter. Considering patients with normal PDT, the main hypothesis for them would be TG defects, since serum levels may vary from undetectable to normal or even high, in these cases. However, patients with TG defects typically present congenital large goiter. Pendred syndrome is a possible diagnosis in this scenario, since it typically presents positive PDT, although there have been reports of patients with normal PDT and *SLC26A4* mutation (18). Hearing screening would be important in these patients. Other diagnoses to consider are defects in iodotyrosine deiodinase, as

they have been described in association with mild cases of hypothyroidism with goiter (19).

RAIU below or equal to 15% is highly suggestive of iodide transport defects (NIS defects). The clinical characteristics of patients with NIS mutations include goiter, in most cases, and hypothyroidism in variable degrees, usually related to iodine intake.

The diagnosis of iodide transport defects is based on I⁻ S/P. In our study, goiter was observed in only four patients who had wide variation in laboratory parameters. Only two of these patients underwent salivary iodine measurement, and only one had a low I⁻ S/P, confirming a defect in NIS protein. Two other patients, described in table 3, had low I⁻ S/P. It would be of particular interest to have molecular analysis of *NIS* in order to define the genetic defect in these patients. In the other subjects with low RAIU and normal I⁻ S/P, we suspect the occurrence of TSH resistance. Iodine contamination, which frequently interferes with thyroid scan, was not considered, since iodine intake in our region is within the established parameters for iodine sufficiency (20).

More than ten cases of thyroid cancer in patients with goiter and dyshormonogenesis have been described in the literature. Prolonged stimulation by high levels of TSH may play a role in the development of the goiter and/or tumor progression, since all cases have been reported in patients with elevated TSH and long-term inadequate treatment (21). Most cases reported are related to defects in TG synthesis, in one case a mutation was found in the *PDS* gene and in another, in the *TPO* gene (22). Recently, Raef and cols. described the first case of a metastatic follicular variant of papillary carcinoma associated with a p.R2223H *TG* gene mutation (23). One of our patients also presented a follicular variant of papillary carcinoma, but had no signs of metastases. Also, unlike all cases described, this patient had always maintained normal TSH levels, contradicting the hypothesis that the development of the tumor could be influenced by elevated TSH. It would be of great importance to search for a *TG* mutation in this patient and to analyze possible mutations in oncogenes and tumor suppressor genes.

CONCLUSION

Patients with CH due to dyshormonogenesis presented wide phenotypic variability, limiting the de-

finition of the etiology based only on clinical and laboratory information. However, a suggestion of etiological diagnosis was possible in 32 patients: 17 with iodide organification defect, three patients with iodide transport defect, 10 patients with probable TSH resistance, and two patients with probable TG synthesis defect.

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