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Congenital Hypothyroidism: Etiology

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ABSTRACT

The etiology of Congenital Hypothyroidism (CH) is important in determining its severity, prognosis, genetic counseling and clinical management.

***Aims*: investigate the causes of CH and their severity using serum levels of FreeT4 and TSH.**

***Patients and Methods*: 243 neonates with CH (61% were girls) diagnosed by the Neonatal Screening Program of Minas Gerais between 1996 and 2003. The thyroid function was assessed through serum FreeT4 and TSH by chemilumiscence. CH etiology was evaluated by ultrasonography, scintigraphy, potassium perchlorate discharge test and serum thyroglobulin levels.**

***Results*: Out of 243 patients, dysgenesis was found in 114 (47%): 3.3% had athyreosis; 0.4% eutopic dysgenetic gland due to maternal use of ^{131}I; 22% ectopic glands (8.6% an isolated ectopic gland and 13% also an eutopic dysgenetic thyroid); 9% eutopic dysgenesis, 8.6% hypoplasia and 3.7% hemiagenesis. Thyroid in situ was found in 129 (52%): 23.5% had iodide organification defect; 3.7% thyroglobulin synthesis defect; 6.2% other dyshomonogenesis; 0.4% iodide transport defect; 1.2% transient CH and 18% a normal gland. Patients with dysgenesis had a more severe CH than those with thyroid in situ (TSH 248.08 vs. 18.17 μIU/mL and FT4 0.32 vs. 0.95 ng/dL, $p<0.001$).**

***Conclusions*: Some cases had more complex dysgenesis, presenting ectopia associated to a dysgenetic eutopic gland. The ultrasound was the best tool to detect the dysgenetic tissue, but the scintigraphy was the most effective in identifying the functioning tissue. The thyroid hormone synthesis defects were found more frequently than expected, but in some cases they could not be defined.**

KEY WORDS

Thyroid, congenital hypothyroidism, TSH, children

INTRODUCTION

Congenital Hypothyroidism (CH) is a disease provoked by a deficiency or absence in the production of thyroid hormones in case of functional or developmental abnormalities of the thyroid gland or, rarely, by peripheral hormonal resistance. It is considered one of the most common preventable causes of mental retardation provided there is an early diagnosis and immediate treatment, principally within the first two weeks of life. This advancement became possible with the implementation of newborn screening in several parts of the world more than 30 years ago[1-3].

The thyroid development begins in the first weeks of gestation, starting as a thickening of the floor of the primitive pharynx and afterwards migrating to the normal site in front of the trachea. After approximately the 10th week of gestation, the fetal gland is able to concentrate the iodide and synthesize the thyroid hormone. For normal fetal brain development the maternal thyroid hormone is very important, mainly in the first trimester of gestation; later both the maternal and fetal thyroid hormones contribute to it[4,5].

The etiology of CH is very important as it makes it possible to determine the severity of the disease and its prognosis, the need for genetic

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counseling and its clinical management[6-8]. In rare cases, it can be transient[9,10], but mostly it occurs in its permanent form and the most frequent causes are the thyroid organogenesis defects, the dysgenesis (ectopia, hemiagenesis, hypoplasia and athyrosis) that occurs in approximately 85%[11,12] of cases, and the defects in thyroid hormone synthesis (dyshormonogenesis) that occur in approximately 15% of cases[13,14].

The thyroid dysgenesis generally appears sporadically and predominantly in females, and its pathogenesis is still not clear. Recent genetic studies have found mutations in genes involved in the thyroid organogenesis (PAX-8, TTF-1 and FOXE-1) that could be responsible for some cases of these defects. These studies have reported some familial cases affected by either dysgenesis of the thyroid gland[15,16] or by mutations in the TSH receptor gene[17,18]. Therefore there is evidence that genetic factors contribute to defects of the thyroid organogenesis[19,20], but the molecular defects are demonstrated in only a few cases, so there is the possibility of the existence of other mechanisms involved in thyroid dysgenesis that are still unknown[21].

The cases of dyshormonogenesis are generally transmitted by autosomal recessive inheritance. The mutations in the thyroid peroxidase gene present the highest prevalence and mutations in the other genes such as in the thyroglobulin gene, the Pendrin (PDS) gene, sodium iodide symporter (NIS) gene, and thyroid oxidase 2 (THOX2) gene, were described also[13,22-25].

The etiologic evaluation of the CH must be made by means of several examinations, such as thyroid ultrasonography, scintigraphy, the measuring of thyroglobulin and the perchlorate discharge test, because in some cases the diagnosis can be incorrect when only one of the tests is used[26,27]. There are also cases when the results can be inconclusive even if several tests are performed.

The scintigraphy is considered the gold standard in the imaging for etiologic diagnosis of CH[28-31], but it is not good enough for analyses of the thyroid size and morphology. The ultrasound is of limited value in case of ectopic glands[32-35]. However, the advance in technology, the presence of experts in ultrasonography and, more recently, the use of color Doppler ultrasonography have increased the value of this examination in the etiologic diagnosis of the CH[36]. There is a possibility that one apparent athyreosis at scintigraphy could be either an inactivating mutation in the TSH receptor genes or a congenital defect in iodine uptake. They can be distinguished through plasma levels of thyroglobulin or through thyroid ultrasonography which shows either a normal, a hypoplastic or even an enlarged thyroid gland in case of congenital defect in iodine uptake. In these cases, if genetic studies were carried out, the finding of a mutation in the TSH receptor gene or in the NIS gene would define the diagnosis.

The aims of the present study were: 1) to investigate the conditions that led to CH, by researching possible defects in the organogenesis or in the thyroid hormone synthesis; 2) to examine the relationship between biochemical severity, as judged by serum levels of freeT4 (FT4) and TSH of the thyroid defects.

PATIENTS AND METHODS

Patients

This study group consisted of 243 neonates with CH who were diagnosed by the Neonatal Screening Program of Minas Gerais between 1996 and 2003 and were referred for treatment and follow-up at the Hospital das Clínicas of the School of Medicine of the Federal University of Minas Gerais. Out of the 243 children, 148 (61%) were girls and 95 (39%) were boys and 173(71%) children were diagnosed at up to 30 days of life and 70 (29%) at over 30 days. Only two of them had a diagnosis, at 66 and 90 days, respectively.

In all the children an elevated screening TSH was confirmed by the measurement of serum levels of TSH and FT4. The median age at onset of therapy was 24 days, the range was from 9 to 90 days, with the L-T4 median dose of 10 μg/kg/day. The follow up was performed at a 3-month-interval and, at the age of 3 years, the replacement therapy was interrupted for 4 weeks for etiological studies by imaging (ultrasound

exams as well as color Doppler in some children and scintigraphy), perchlorate discharge test and serum Thyroglobulin.

Informed consent was obtained from the parents of the children included in the study and the protocol was approved by the institution's Ethics Committee.

Methods

The screening strategies for detection of CH consisted of measuring TSH in blood spots collected through heel puncture on filter paper on the 5th day of life by an enzyme-linked immunoassay. Values in whole blood below 10 mIU/L were considered normal and when TSH values were over 20mIU/L, the children were referred immediately to the pediatric endocrinologist to be submitted to dosages of serum TSH and serum FT4 to confirm the diagnosis of CH. Children with TSH values between 10mIU/L and 20mIU/L, which suggested a high risk of CH, were recalled immediately for a second test. If the TSH values in this test were over 10mIU/L, they were also referred to the pediatric endocrinologist to be submitted to dosages of serum TSH and serum freeT4 to confirm the diagnosis of CH. As soon as the CH diagnosis is confirmed, the treatment with L-Thyroxine should be prescribed.

Serum FT4 and serum TSH were measured by chemoluminescence methods, using Automated Chemiluminometric System kits (ACS 180™, Chiron, Walpole, MA, USA. The serum Thyroglobulin (TG) was measured by immunoassays using the chemiluminescence method (Beckman-Coulter kit) The reference range was 0.75 to 1.8 ng/dL; 0.30 to 5.0 μIU/mL and 2 to 35 ng/dL, respectively.

Ultrasonography was performed and interpreted by the same experienced professional using a real time linear transducer with an 8 - 10-MHz transducer (SSA-340 instrument; Toshiba, Japan). The patients were examined in a supine position and the entire neck in hyperextension at the anterior cervical area was checked systematically for the presence of any thyroid tissue along the normal pathway from the sublingual region to the top of the sternal manubrium. The ultrasonogram was evaluated for the presence or absence of the thyroid gland or of any additional thyroid tissue and the location of the gland was determined. The volume was calculated by the ellipsoid formula. The volumes of the right and left lobes and the isthmus were combined to obtain the whole thyroid gland volume. The normative ranges for the thyroid volume were those provided by the Ueda D methods, which consider the normal gland volume as a function of the patient's height[38]. A structure was regarded as thyroid tissue if located at the thyroid area or along the normal pathway of the thyroglossal duct. In the last case, it is described as an ectopic gland.

Thyroid scintigraphy with iodine (radioactive iodide, ^{131}I) was performed using a dual head gamma camera (GE Millenium) to identify functional thyroid tissue.

The potassium perchlorate discharge test (KClO4 test) was performed in patients with ^{131}I uptake. The uptake was calculated after 2h of the administration of ^{131}I and it was considered a positive test if a reduction in this uptake was equal or greater than 20% after 2h of the administration of KClO4.

The ultrasonography and the scintigraphy were carried out on different days, but every care was taken so that the professionals who performed these exams were unaware of each other's findings.

All the data were expressed as medians and ranges. Statistical analyses were performed by means of the Wilcoxon and Mann-Whitney tests, using the SPSS version 13.0 and the MINITAB version 15.1.0.0 software. A value of $p \leq 0.05$ was considered significant.

RESULTS

According to the results of the thyroid scintigraphy combined with the results of the ultrasound exams, the KClO4 test and the serum thyroglobulin levels a variety of etiological diagnostics of CH was found and this is shown in Table 1. The biochemical results (serum TSH and FT4 at diagnosis and at the etiological exams) according to the etiological groups are shown in Table 2.

TABLE 1

Etiologycal diagnosis of Congenital Hypothyroidis by ultrasound, scintigraphy, potassium perchlorate discharge test (KClO4 test) and Thyroglobulin(TG) in 243 childrenof neonatal screening of Minas Gerais

Type	n (%)	Scintigraphy	US	#KClO4 test (%)	TG (ng/ml) Median/Range
Thyroid Dysgenesis	114 (47%)				28.9 (0.1-565.0)
Athyreosis	8 (3.3%)	No uptake	No tissue	not perfomed	7.5 (0.5-38.8)
Dysgenetic eutopic Thyroid after maternal 131I	1(0.4%)	No uptake	No tissue	not perfomed	1.1 (0.1-24.6)
Dysgenetic eutopic thyroid	22(9.1%)	No uptake	Small dysgenetic eutopic gland	not perfomed	23.1
Ectopic thyroid	21(8.6%)	Small , rounded or oval area of uptake on base or midline of tongue	Small ectopic gland and in four no tissue not detected, increased colour Doppler in one	negative in ten, positive in two (25 and 22% of discharged), not performed in eight	37.5 (0.4-80.9)
Ectopic with dysgenetic eutopic thyroid	32 (13.2%)	Small , rounded or oval area of uptake on base or midline of tongue and no uptake in 2	Small ectopic gland and small disgenetic eutopic gland	not perfomed in 18; negative in 12 and positive in two (25%, 31% of discharge)	39.3 (1.1-83.0)
Hemiagenesis of left lobe	7(2.9%)	Little uptake on thyroid region without lobe definition	Severe hypoplasia or absence lobe left	negative, positive (45%) in one, no perfomed in one	41.6 (13.6-95.3)
Hemiagenesis of right lobe	2(0.8%)	Little uptake on thyroid region	Right lobe absent	negative in one, positive (21%) in one	66.5 (36.2-96.8)
Hypoplastic thyroid	21(8.6%)	Little uptake on thyroid region without lobe definition; little uptake thyroid on upper cervical region in six	Small eutopic thyroid	Not performed in11. negative in 8, positive (26%) in one	28.9 (0.1-565.9)

Thyroid In Situ	129(52%)				53.79 (0.10-1822.0)
Iodide organification defect	57(23.5%)	Good uptake - Globally enlarged in10; Normal in 47	Large eutopic thyroid in 35; Normal thyroid in 20; Small thyroid in 2	20-50% of discharge in 33 and over 50% in 24	137.5 (11.3 - 947.0)##
Thyroglobulin synthesis defect	9 (3.7%)	Good uptake - Globally enlarged in 6 and Normal in 3	Large eutopic thyroid in 6; Normal thyroid in 3. increased collour Doppler in two	Negative	0.1 (0.1-7.1)
Iodide transport defect	1(0.4%)	Good uptake , eutopic decreased gland, heterogeneous distribution of radiosotope	Large eutopic thyroid, increased colour Doppler	Not performed	195.10
Other defects of hormone synthesis	15(6.2%)	Good uptake - Globally enlarged	Large eutopic thyroid, increased colour Doppler	Negative	73.1 (3.1-1822.0)
Transient hypothyroidism	3(1.2%)	Good uptake, homogeneous distribution of radioisotopic	Normal eutopic thyroid	Negative	37.9/110.0#
Normal thyroid	44(18,1%)	Good uptake, faint uptake in one, homogeneous distribution of radio-isotopic, ectopic in one	Normal eutopic thyroid	Negative	32.8 (0.1-180.0)
TOTAL	243(100%)				36.3 (0.1-1822.1)

missing one patient ## missing two patients

TABLE 2

Median concentrations and range at diagnosis (iTSH, iFT4) and at etiological evaluation (eTSH and eFT4) values in children of neonatal screening programs of Minas Gerais

Type		iTSH (μIU/ml)		IFT4 (ng/dl)		ETSH (μUI/ml)		EFT4 (ng/dl)	
Thyroid dysgenesis	n	Median	Range	Median	Range	Median	Range	Median	Range
Athyreosis	8 (3.3%)	#546.96	#100.00-1212.72	#0.30	#0.1-0.33	397.89	135.00-674.85	0.17	0.12-0.33
Dysgenetic eutopic thyroid after maternal ^{131}I	1 (0.4%)	656.90		0.10		440.38		0.19	
Dysgenetic eutopic thyroid	22 (9.1%)	588.39	91.20-1238.50	0.20	0.03-0.88	259..34	15.76-615.56	0.19	0.10-1.49
Ectopic thyroid	21 (8.6%)	365.97	15.20-942.71	0.40	0.2-1.1	256.32	5.63-542.05	0.36	0.10-1.67
Ectopic with dysgenetic eutopic thyroid	32 (13.2%)	240.09	32.60-964.11	0.60	0.2-1.3	238.12	9.99-596.80	0.37	0.13-1.63
Hemiagenesis of left lobe	7 (2.9%)	156.01	50.61-545.99	0.26	0.1-0.8	10.5	2.96-135.00	1.08	0.51-1.41
Hemiagenesis of right lobe	2 (0.8%)	263.59	221.68-305.49	0.60	0.60-0.63	106.96	38.92-175.00	0.59	0.43-0.74
Hypoplastic thyroid	21 (8.6%)	300.10	50.49=682.4	0.46	0.10-1.21	192.9	3.73-455.47	0.32	0.20-1.60
Subtotal	**114 (47%)**	**[a]341.56#**	**15.2-1238.50#**	**[e]0.36#**	**0.10-1.59#**	**[b]248.08**	**2.96-674.85**	**[f]0.32**	**0.10-1.67**
Thyroid in situ									
Iodide organification defect	57 (23.5%)	350.01	10.13-1122.00	0.29	0.10-1.70	100.91	2.44-515.54	0.63	0.11-1.53
Thyroglobulin synthesis defect	9 (3.7%)	310.70	62.00-674.67	0.20	0.10-0.70	248.01	131.57-571.79	0.23	0.10-0.40
Iodide transport defect	1 (0.4%)	352.63		0.19		604.82		0.15	
Other defects of hormone synthesis	15 (6.2%)	106.71	40.33-678.36	0.51	0.10=1.30	12.72	2.80-330.00	1.18	0.29-1.87
Normal thyroid	47 (19.3%)	192.76	12.77-980.00	0.40	0.10-1.50	9.35	0.75-473.27	1.12	0.21-1.70
Subtotal	**129 (52%)**	**[c]255.66**	**10.13-1122.00**	**[g]0.37**	**0.01-1.70**	**[d]18.17**	**0.75-604.82**	**[b]0.95**	**0.10--1/87**
Total	**243(100%)**	**[i]300.31**	**10.13-1238.50**	**[k]0.36**	**0.01-2.30**	**[j]135.00**	**0.75-674.85**	**[l]0.49**	**0.10-1.87**

#Missing one patient; iTSH = TSH at diagnosis; iFT4 = FT4 at diagnosis; eTSH = TSH at etiological exams; eFT4 = FT4 at etiological exams.

¶Including 3 children with transient congenital hypothyroidism. **a** vs. **b; e** vs **d**; **g** vs **h**; **b** vs **d**; **f** vs **h**; **i** vs **j**; **k** vs **l** = significantly different, $p < 0.0001$. **a** vs **c** = significantly different, $p = 0.039$.

In the group of 243 children, 173 (71%) were given the CH diagnosis within the first 30 days of life. Out of these 173, 90 (52%) had a diagnosis of dysgenesis and 83 (48%) of thyroid in situ. In 70(29%) children the CH diagnosis was given after 30 days; 24/70 (34%) were confirmed to be affected by the dysgenetic gland and the thyroid in situ appeared in 46/70 (66%).

DYSGENESIS

In the group of 243 children thyroid dysgenesis was found in 114 (47%). A percentage of 3.3% (8/243) did not present any functioning thyroid tissue at scintigraphy and at ultrasound scanning, establishing the athyreosis diagnosis. In one patient (1/243-0.4%), who had a history of maternal use of iodine-131(^{131}I) in the pregnancy, the scintigraphy revealed no thyroid gland and the ultrasound showed a severe eutopic dysgenetic gland. An ectopic gland was found in 53/243 (24%); in 21/243 (8.6%) of them both the scintigraphy and ultrasound exams showed an isolated ectopic gland and in 32/243 (13%) an eutopic dysgenetic gland was also found at the ultrasound exam (Fig. 1). Among the 21 patients who had an ectopic gland at scintigraphy, no tissue was detected at the ultrasound in four of them. The color Doppler, used in some patients of this group, provided an additional value to identify the sublingual gland (Fig.2). In 22/243 (9,1%) children no uptake of ^{131}I was detected at scintigraphy, but a small eutopic dysgenetic gland was found at the ultrasound. A small gland located at its normal place was observed by ultrasound in 21/243 (8,6%) children, which indicated a hypoplastic thyroid gland; in these cases the scintigraphy was normal. Hemiagenesis was found in 9/243 (3,7%) patients, in whom the right lobe was absent in two and the left lobe was not detected or was very small in seven.

Additionally, in eight patients (two with ectopic glands, two with ectopic and dysgenetic eutopic thyroid, two with hemiagenesis, one with thyroglobulin synthesis defect and one with hypoplastic thyroid) of the group with thyroid dysgenesis, a positive KClO4 test with low wash-out value (<50%) was observed.

As shown in Table 2, the median TSH values at diagnosis were higher than the median TSH value at the etiological evaluation of all the patients with dysgenesis (341.53μIU/mL vs 248.08μIU/mL; $p<0.0001$). However, the median FT4 values at diagnosis and at the etiological evaluation were similar (0.36ng/dL vs 0.32ng/dL; $p=0.078$).

The patients with athyreosis and those with a dysgenetic eutopic thyroid had the highest median TSH values (546.96μIU/mL and 588.39μIU/mL, respectively) at diagnosis and at the etiological evaluation (397.89μIU/mL and 259.34μIU/mL, respectively), and the lowest median FT4 values at diagnosis (0.3ng/dL and 0.2ng/dL, respectively) and at the etiological

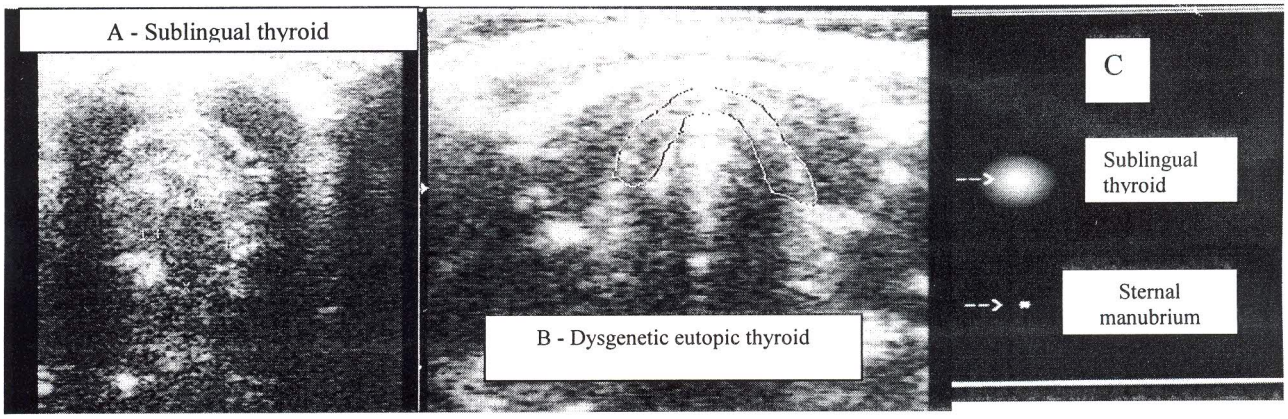

Fig. 1: Ultrasound (A and B) and scintigraphy (C) of one patient with an ectopic and dysgenetic eutopic thyroid

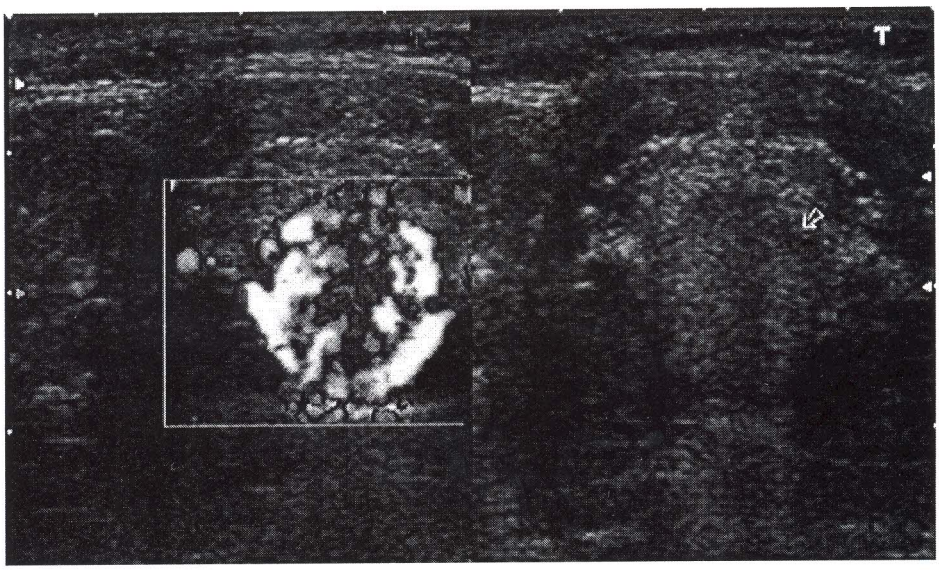

Fig. 2: Ultrasound with colour Doppler of one patient with sublingual thyroid

evaluation (0.17ng/dL and 0.19ng/dL, respectively). The patient with dysgenetic eutopic thyroid after maternal ^{131}I also had very high serum TSH and very low FT4 at diagnosis and at etiological evaluation (Table 2).

The serum thyroglobulin levels in the majority of patients with athyreosis and with eutopic dysgenetic thyroid were almost undetectable and they had the lowest median values (7.5ng/dL and 1.1ng/dL, respectively) found among all the other children with dysgenesis (Table1).

GLAND *IN SITU*

In 129 out of the 243 children (52%) a thyroid gland *in situ* was observed both at scintigraphy and at the ultrasound exam. The iodide organification defect due to a peroxidase deficiency as identified by a positive KClO4 test was found in 57 patients, that is, in 44% of 129 and 23% of all the 243 patients. Twenty-four (42%) out of these 57 patients had a wash-out value of over 50%, with three of them having a wash-out value of over 90%. The other dyshormonogeneses that were possible to be identified were a TG deficiency in 9/243 children (3,7%) and an uptake iodine defect in only 1/243 (0,4%). In 15/243 children (6%) an enlarged gland *in situ* was observed at the ultrasound suggesting another defect of the thyroid hormone synthesis that was impossible to identify.

In the remaining 47/243 children (19%), the scintigraphy and the ultrasound showed a normal gland in morphology and in size besides a negative KClO4 test and a normal serum TG. However, it is important to notice that in 3/243 (1.2%), of these children the normal thyroid function suggested a transient CH and in the other 44/243 (18%) an abnormal thyroid function suggested a permanent CH, but it was impossible to come to a final etiological diagnosis.

The 129 patients in the group of thyroid *in situ* had a higher median TSH value at diagnosis (255.66 μIU/mL, range 10.3 to 1122.0 μIU/mL), than at the etiological exams (18.17 μIU/mL, range 0.75 to 604.82 μIU/mL), $p<0.0001$. The median FT4 values (0.37ng/dL, range 0.01 to 1.7 ng/dL) at the diagnosis were lower than the median values at etiological exams (0.95 ng/dL, range 0.10 to 1.87 ng/dL) in all of the patients with thyroid *in situ*, $p<0.0001$. In the 3 children (1.2%) who had transient CH, the serum TSH values at diagnosis were 189.64 μIU/mL, 236.31 μIU/mL and 492.07 μIU/mL and their serum FT4 values at that time were 0.36 ng/dL 0.33 ng/dL and 0.15 ng/dL.

The median serum thyroglobulin values in patients with iodide organification defect, 137.5 ng/dL (range 11.3-947.08 ng/dL) and the serum

TG in the patient with iodide uptake defect, 195.0 ng/dL, were the highest values in both groups, thyroid *in situ* and thyroid dysgenesis groups (Table1).

The median TSH value in the 243 children at diagnosis, of 300.31 μIU/mL, ranging from 10.33 to 1.238.5 μIU/mL, was higher than at the etiological evaluation, which was of 135.0 μUI/mL, ranging from 0.75 to 674.8 μUI/mL , ($p<0,001$). The median FT4 value at diagnosis, of 0.36 ng/dL, was lower than the 0.49 ng/dL at the etiological evaluation, ranging from 0.01 to 2.30 ng/dL and from 0.10 to 1.87ng/dL, respectively ($p<0.001$) (Table 2).

When comparing the group of patients with thyroid dysgenesis to the one with thyroid *in situ*, the median TSH values at the etiological evaluation (248.08 μIU/mL vs 18.17 μIU/mL) and the median FT4 values also at that time (0.32 ng/dL vs 0.95 ng/dL), the results were different, $p<0.001$ (Table 2).

DISCUSSION

The newborn screening programs for CH were implemented over thirty years ago in several parts of world. Since then, much progress has been made for better understanding of the pathogenesis of this disease. The CH etiology is important for better clinical management, for the identification of either its transient or permanent nature and for genetic counselling. Recent technological progress and an increase in the knowledge of CH has made it possible to identify several causes of the disease but, unfortunately, it is still difficult to reach a final diagnosis in some cases.

The Neonatal Screening Program of Minas Gerais (NSPMG) was implemented at the beginning of 1994 and this study was made with children who were born between 1996 and 2003. In the majority of cases, a diagnosis of CH was given in the first month of life, thus enabling a more favorable evolution of the neurocognitive development of these patients. However, because of the difficulties linked to program implementation, some children could not be diagnosed before 30 days of life. In the population studied, the median age at onset of treatment was 24 days of life, which was slightly older than in some parts of the world where the CH diagnosis is given within the first two weeks of age[1,2].

As in other studies[39-41], several examinations were necessary to get a definitive diagnosis, although this was not possible in 18% of cases in the present study. Three patients showed transient CH as no abnormalities were found at the scintigraphy, ultrasound examinations or per-chlorate discharge test and they had normal TSH, FT4 and TG levels at the time of the etiological diagnosis. In these children all TSH and FT4 levels before the onset of hormonal treatment were very high, thus the initial TSH levels did not determine the transient nature of CH, as demonstrated in previous studies[9].

We observed that some patients, whose gland at scintigraphy was ectopic, at the ultrasound examination were shown to have a eutopic hypoplastic thyroid and in other patients, besides a dysgenetic eutopic gland, an ectopic dysgenetic thyroid was also found. The ultrasound has then been found to be more precise in the identification of dysgenetic thyroid tissue. These cases may provide evidence that the mechanisms of the thyroid follicular cells differentiation and the migration of the thyroid must be more complex. It is not yet clear if thyroid follicular cells disappear through apoptosis after initial thyroid differentiation following migration or if they fail to differentiate during the initial phase of the gland development[5,21]. In some patients who had an ectopic gland at scintigraphy, the ultrasound did not show any thyroid gland. Therefore, the scintigraphy was more accurate than the ultrasound exam in showing functioning glandular tissue. However, in one case of radiodine defect uptake, when no thyroid was seen at scintigraphy as if we had a case of athyrosis, the ultrasonography showed one eutopic gland with an increased volume, therefore suggesting a Sodium-Iodine Symporter (NIS) defect. Thus, in some cases the presence and the volume of the gland can be determined only through the ultrasound exam. These results emphasize that it is very important to use more than one exam to establish the final etiology of the CH, as was done in other studies[26,27].

In the present study, cases of hemiagenesis were found more frequently (3.7%) than in other studies involving schoolchildren with an estimated prevalence of 0.05 to 0.5%[44,45]. This result suggests the presence of specific genetic or geographic factors in the population studied.

Genetic studies have demonstrated the mutations in factors of transcription (TTF-1, FOXE-1, PAX-8)[5,15,16,26]. Consequently, although the majority of cases of thyroid dysgenesis are considered to be sporadic, a small number of patients have been found inside the same family. We have not had any familial cases of dysgenesis. Only two families were found to have a positive history of dyshormonogenesis in siblings. One family had children with TPO synthesis defects and the other had children with TG synthesis defects.

We found dyshormonogenesis in 34% of patients, which is a higher proportion than that reported by other studies[13,14]. In the majority of them, the organification iodine defect could be identified by means of: (1) a positive perchlorate discharge test; (2) a normal or an increased eutopic gland at scintigraphy and at the ultrasound exam and (3) increased levels of serum TG. In the positive perchlorate discharge test, the wash-out value was over 50% in 42% of the patients; and in three of them the wash-out was over 90%, which can be considered a complete form of organification iodine defect. It was found that 6.2% of the patients presented some dyshormonogenesis, based on the presence of an increased eutopic gland *in situ* and elevated TSH levels, but it was not possible to define the defect. The high frequency of thyroid dyshormonogenesis suggests that there are some specific genetic factors in this population, as observed in the other study[22]. It is important to notice that it is possible that some patients with a hypoplastic or an absent gland referred to in this study could present a TSH receptor defect, as has been demonstrated in some recent genetic studies[15-18].

In addition, a positive perchlorate discharge test with wash-out values lower than 50% was found in some patients with thyroid ectopy and hemiagenesis. This fact suggests that these patients have an iodine organification defect associated with abnormal thyroid development, and the lower wash-out values may indicate the presence of a small functioning tissue. However, further studies of these patients are needed to confirm this hypothesis.

This study, as other studies, has demonstrated that thyroglobulin also made a contribution in the identification of some thyroid congenital defects[43]. The TG levels were lower or undetectable in patients with severe dysgenesis or athyrosis and they were higher in severe dyshormonogenesis, except in cases of TG synthesis defects, which we found in 6% of our patients. In these patients, the scintigraphy and ultrasound exams showed a normal or an increased gland *in situ*, a negative perchlorate discharge test and had undetectable or very low thyroglobulin levels, suggesting a mutation in gene of this protein. As was demonstrated by other studies, the measurement of plasma TG was also important to determine the existence of some thyroid tissue in patients with apparent athyrosis at scintigraphy and a dysgenetic gland at the ultrasound exam[43].

A variety of etiological HC diagnoses was identified in the group studied. To summarize, it is important to notice the following points: (1) Dysgenesis, in some cases, apparently was more complex, with an isolated ectopic gland associated to a dysgenetic eutopic gland; (2) The scintigraphy was more precise to show the ectopic gland, but through the Doppler used in some cases, the ultrasound also enabled us to see it; (3) The thyroid hormone synthesis defects were found frequently, but in some cases they could not be defined through the exams used in this study; (4) The ultrasound was the best to evaluate the localization and the gland volume as well as the dysgenetic tissue, but the scintigraphy was superior to ultrasound in the detection of a functioning tissue; (5) The assessment of the CH etiology in this study made it possible to make the diagnosis of transient CH, which is very important for the handling of these children. However, more studies, including genetic studies, are necessary for a better knowledge of the CH pathogenic mechanisms.

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