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Congenital hypothyroidism: the clinical profile of affected newborns identified by the Newborn Screening Program of the State of Minas Gerais, Brazil

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Abstract

Objective: To evaluate the clinical profile of newborns with congenital hypothyroidism identified by the Newborn Screening Program of the State of Minas Gerais, Brazil, between 2000 and 2006.

Methods: Analysis of factors involved in this profile, including: TSH and FT4 levels (determined by chemiluminescence, with limits of normality set at 0.3-5.0 µUI/mL and 0.8-1.8 ng/dL, respectively), age at diagnosis and age at treatment. The study sample consisted of 443 children, 55.8% were female and 95% were seen before completing 60 days of life.

Results: The most prevalent clinical signals were: umbilical hernia (51%), enlarged anterior fontanel (50.3%), and open posterior fontanel (47.2%). Hypotonia, macroglossia and feeding difficulties were the clinical signs most frequently associated with the biochemical severity of the disease. A delay in bone age was present in 32.1% of the children at diagnosis. The median of serum TSH and FT4 was 120 µUI/mL and 0.62 ng/dL, respectively. The median age at start of treatment was 28 days.

Conclusion: There are some early clinical signs that suggest a diagnosis of congenital hypothyroidism. Therefore, when presented with a child exhibiting these signs, serum TSH and FT4 should be assayed in order to confirm or rule out the disease, irrespective of the result of screening. Age at start of treatment remains high, but strategies are being implemented to reduce it.

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Introduction

Congenital hypothyroidism (CH) is considered a pediatric emergency, since severe consequences may result if it is not treated promptly. Early diagnosis and treatment initiated during the first weeks of life are of fundamental importance to the normal intellectual development of affected children.[1,2]

The natural history of CH has been changing drastically over recent years thanks to neonatal screening programs that offer early detection of the disease in apparently healthy newborn infants.[3] A number of such programs were set up in Brazil during the 1980s,[4] and the Neonatal Screening Program of the State of Minas Gerais (PETN-MG) was launched in 1993 to screen for CH and phenylketonuria.

The incidence of CH is four to five times that of phenylketonuria, for which the screening programs were originally developed.[1] It affects approximately 1:3,000 to 1:4,000 live births,[5] and is more common in Hispanics and rarer among

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blacks.[1] Some variations in incidence between different geographic regions appear to be more related to iodine deficiency than to the ethnic characteristics of populations.[3] There is a predominance of females (2:1), and children with Down syndrome are at increased risk.[1]

Before the screening programs were implemented, children were diagnosed clinically and the reported incidence of CH was considerably lower, varying from 1:5,800 to 1:6,900. A Danish study found that just 10% of affected children were diagnosed clinically during their first month of life, 35% by 3 months and 70% by the age of 1 year. The remaining affected children were not diagnosed until their third or fourth years of life.[6] A retrospective analysis of 1,000 cases of CH in Turkey found a mean age at clinical diagnosis of 49 months. Just 3.1% of cases were diagnosed during the neonatal period and 55.4% were diagnosed after 2 years of age.[7]

The majority of affected children exhibit signs and symptoms that are highly nonspecific, and in only 5% of cases is diagnosis possible based on clinical examination during the first days of life.[5,8] The absence or reduced expression of symptoms at the start of life can be explained by transplacental migration of maternal thyroid hormone and the increased cerebral deiodinase levels in newborns.[9,10]

Despite the existence of screening programs and the lack of sensitivity and specificity of the clinical manifestations of CH, diagnosis of symptomatic children should be clinical.[11] The classical symptoms of this disease should not be ignored.

The objectives of this study were to: 1) evaluate the clinical profile of newborn infants identified with CH by the PETN-MG, taking note of the age at diagnosis and biochemical severity of the disease; 2) to make pediatricians aware of the importance of giving due value to the clinical signs and symptoms of CH; and 3) to evaluate the performance of the PETN-MG during this period, on the basis of an analysis of the age at which these children began to receive treatment.

Methods

Data were collected by means of an analysis of the medical records of children screened by the PETN-MG between 2000 and 2006 and requested to attend a first CH consultation. Only children with confirmed congenital hypothyroidism took part in the study. Diagnosis of congenital hypothyroidism was based on a confirmatory serum thyroid stimulating hormone (TSH) assay result at > 10 µUI/mL, indicating cases requiring treatment. Children who were already receiving hormone therapy on the occasion of their first consultation were excluded from the analysis.

During the period being studied, the PETN-MG was using TSH analysis on filter paper to diagnose CH, with blood ideally being taken on the fifth day of life and using < 10 mUI/L as the cutoff for normality. All children with TSH > 25 mUI/L were summoned for emergency medical consultations. Children with borderline results (10 to 25 mUI/L) had a fresh sample taken on filter paper as soon as possible and were referred if the second result confirmed a TSH level over 10 mUI/L.

All of the children were treated at the pediatric endocrinology clinic at the Hospital das Clínicas at the Universidade Federal de Minas Gerais (UFMG). During the first consultation, after taking detailed patient history, children were examined by one of three physicians on the clinic's staff. The following signs and symptoms were systematically confirmed or ruled out: umbilical hernia, enlarged anterior fontanel, open posterior fontanel, dry and rough skin, mottled skin, wide sutures, edema, jaundice for more than 10 days, hoarseness, macroglossia, cold extremities, pallor, lethargy, protruding tongue, intestinal constipation, hypotonia, feeding difficulties, pondero-statural deficits, heart murmur, delayed neuropsychomotor development and goiter. Objective criteria defining the clinical signs were not established, but were determined based on the experience of the examiner.

On the same day as the examination, all patients had blood taken and TSH and FT4 were assayed in serum. After blood had been taken, treatment with levothyroxine was initiated (10 to 12 µg/kg/day), although treatment was later discontinued in cases in which the diagnosis was not confirmed (serum TSH < 10 µUI/mL). The children on treatment were followed-up every 3 months until the age of 3 years, at which age the levothyroxine was withdrawn in order to determine the etiology and permanent or transitory character of the disease (Figure 1).

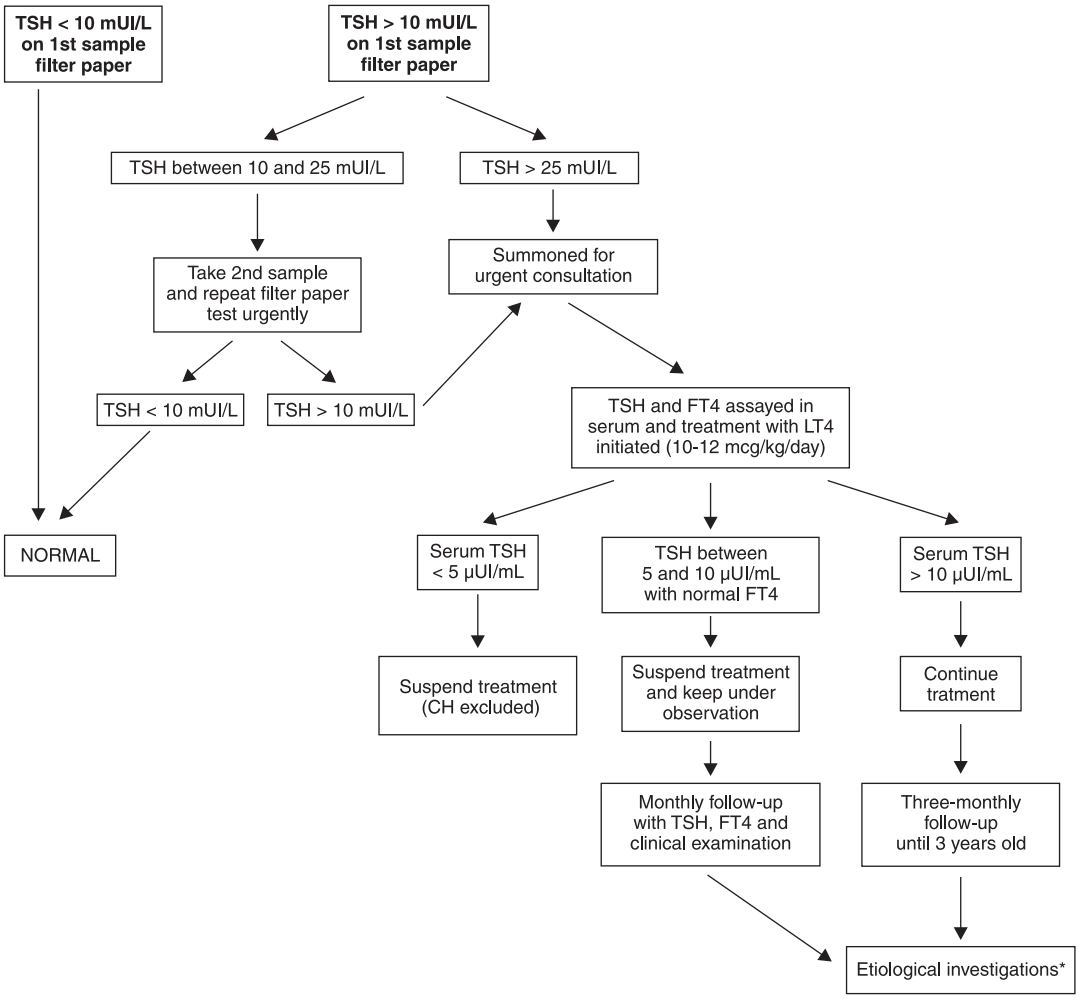
The TSH was assayed on filter paper using the ELISA method (enzyme linked immunosorbent assay) (normal values are < 10 mUI/L) and serum TSH and FT4 were assayed by chemiluminescence (normal values are 0.3 to 5.0 µUI/mL and 0.8 to 1.8 ng/dL, respectively).

This study analyzed the following data, obtained from the datasheet filled out at the first consultation: age of child, sex, clinical signs and symptoms suggestive of CH (described above), bone age, age at screening, screening TSH result, first serum TSH and FT4 results, age at start of treatment and whether there had been a clinical suspicion of hypothyroidism prior to screening.

Bone age was determined from X-rays of the knees of newborn infants and was defined as retarded when the nucleus of the distal femoral epiphysis was absent in children born full term or with corrected gestational age of more than 37 weeks.[12]

This study was approved by the Research Ethics Committee at UFMG. Parents or guardians gave written consent for the children to take part, after being informed about the study.

Statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences). Associations were tested using Pearson's chi-square test or Fisher's exact test and means were compared using the Mann-Whitney



LT4 = levothyroxine.
* Ultrasound of thyroid, thyroid scintigraphy, perchlorate discharge test, serum thyroglobulin assay.

Figure 1 - Protocol used by PETN-MG for congenital hypothyroidism between 2000 and 2006

non-parametric test. The significance level adopted was 5% ($p < 0.05$).

Results

A total of 1,874,055 children were screened by the PETN-MG between 2000 and 2006, achieving a 99% coverage of the municipalities in the state of Minas Gerais. A total of 852 children were referred to attend a first CH consultation during this period. Data were analyzed from 553 of these children (the number of medical records that were available during the period established for data collection, which was from July to December of 2007) and 464 of these had their diagnosis of congenital hypothyroidism confirmed. Of these, 443 patients were selected for analysis, since the remaining 21 were already on levothyroxine when they presented for their first consultation.

Two hundred and forty-seven (55.8%) of the 443 children analyzed were female and 7 (1.6%) had Down syndrome. Their median age on the day of neonatal screening was 8 days of life, and 75% of them were screened aged less than 12 days. At their first consultation, 17 children (3.8%) were already more than 2 months old, the youngest child was 5 days old on presentation and the oldest was 107 days old (median of 28 days).

A total of 184 children had already been taken to see a physician, but a clinical suspicion of hypothyroidism had only been aroused in 20 of these cases (4.5% of the total number of cases analyzed).

At the first consultation at the clinic, the physical examination was suggestive of hypothyroidism in 55.3% of the children assessed, on the basis that they exhibited more than one of the disease's clinical signs. The most commonly identified clinical signs were: umbilical hernia (51%), enlarged anterior fontanel (50.3%) and open posterior fontanel (47.2%). The least often identified signs were: heart murmur (2.9%),

Table 1 - Clinical signs and symptoms of congenital hypothyroidism found in 443 children at their first consultation

Signs and symptoms	Frequency (n = 443)	%
Umbilical hernia	226	51.0
Enlarged anterior fontanel	223	50.3
Open posterior fontanel	209	47.2
Dry and rough skin	181	40.9
Mottled skin	160	36.1
Wide sutures	130	29.3
Edema (infiltrate)	125	28.2
Jaundice for more than 10 days	124	28.0
Hoarseness	103	23.3
Macroglossia	94	21.2
Cold extremities	85	19.2
Pallor (anemia)	85	19.2
Lethargy	52	11.7
Protruding tongue	46	10.4
Intestinal constipation	42	9.5
Weight deficit	32	7.2
Hypotonia	26	5.9
Feeding difficulties	25	5.6
Statural deficit	16	3.6
Heart murmur	13	2.9
Delayed neuropsychomotor development	6	1.4
Goiter	5	1.1
Signs/symptoms absent	35	7.9

delayed neuropsychomotor development (1.4%) and goiter (1.1%) (Table 1). In 7.9% of the children with CH, no signs or symptoms suggestive of the disease were found at the first consultation.

Bone age was determined for 280 children, 90 (32.1%) of whom had retarded bone age for their chronological age. The highest serum TSH result was 1,122 µUI/mL and in 25% of the children TSH was less than 36 µUI/mL, but greater than 10 µUI/mL (median of 120 µUI/mL). In 285 children (64.3%), FT4 was below normal (< 0.8 ng/dL) with the lowest FT4 result being 0.01 ng/dL (median 0.62 ng/dL). More than 80% of the children with hypotonia, macroglossia, feeding difficulties, wide sutures, lethargy and hoarseness had serum FT4 below 0.8 ng/dL (Table 2).

Certain signs and symptoms were significantly more common among children who presented for their first consultation with less than 30 days of life, in comparison with the older children (more than 30 days) (Table 3). The children presenting with less than 30 days of life had significantly more abnormal thyroid function and a higher incidence of retarded bone age with relation to the children over 30 days old (median serum TSH was 135 µUI/mL vs. 71 µUI/mL and retarded bone age in 41 vs. 21%, respectively) ($p < 0.05$).

The median age at start of treatment was 28 days and 53% of the children started treatment with less than 30 days and 3% with less than 15 days of life.

Discussion

Due to the prevalence, severity and initially asymptomatic presentation of CH, routine neonatal screening has been

Table 2 - Relationship between clinical signs and symptoms and FT4 results

Signs and symptoms	Frequency (%)		Total
	FT4 < 0.8 ng/dL	FT4 > 0.8 ng/dL	
Hypotonia	22 (84.6)	4 (15.4)	26
Macroglossia	79 (84.0)	15 (16.0)	94
Feeding difficulties	21 (84.0)	4 (16.0)	25
Wide sutures	105 (80.7)	25 (19.3)	130
Lethargy	42 (80.7)	10 (19.3)	52
Hoarseness	83 (80.5)	20 (19.5)	103
Cold extremities	67 (78.8)	18 (21.2)	85
Jaundice for more than 10 days	96 (77.4)	28 (22.6)	124
Open posterior fontanel	160 (76.5)	49 (30.5)	160
Pallor (anemia)	64 (75.2)	21 (24.8)	85
Dry and rough skin	136 (75.1)	45 (24.9)	181
Edema (infiltrate)	92 (73.6)	33 (26.4)	125
Enlarged anterior fontanel	163 (73.0)	60 (27.0)	223
Mottled skin	115 (71.8)	45 (28.2)	160
Umbilical hernia	158 (69.9)	68 (30.1)	226
Total	285 (64.3)	158 (35.7)	443

Table 3 - Prevalence of signs and symptoms among children less than 30 days old *vs.* those more than 30 days old at first consultation

Signs and symptoms	Frequency (%)	
	Less than 30 days (n = 238)	More than 30 days (n = 205)
Dry and rough skin	134 (56.3)	47 (23.0)
Enlarged anterior fontanel	132 (55.4)	91 (44.4)
Open posterior fontanel	130 (54.6)	79 (38.5)
Jaundice	94 (39.4)	30 (14.6)
Edema	94 (39.4)	31 (15.1)
Wide sutures	92 (38.6)	38 (18.5)
Macroglossia	76 (31.9)	18 (8.7)
Hoarseness	73 (30.6)	30 (14.6)
Lethargy	40 (16.8)	12 (5.8)

recommended and instituted all over the world and is nowadays responsible for detecting the majority of newborn infants with the disease. Nevertheless, some children with CH present the classic symptoms of the disease soon after birth and should be diagnosed clinically.[11,13]

The clinical signs and symptoms of hypothyroidism are related to a generalized immaturity of organs and systems and with reduced metabolism resulting from lack of thyroid hormone. They depend on the degree of hormone deficiency and the age at which diagnosis is made.[2]

In this study it was possible to observe that clinical suspicion of CH was only aroused prior to screening results in 4.5% of the children who had the disease. In contrast, a little over half of them (55.3%) had findings from the clinical examination that the pediatric endocrinology team considered suspicious at first consultation. This discrepancy can be explained by the fact that the positions in the endocrinology team have more training in the identification of the clinical signs of CH and also because they are more alert to the possibility, since they are treating children who are known to have had abnormal screening results. None of the 21 children excluded from

the analysis because of prior hormone therapy had been diagnosed clinically. These were children born premature or with other conditions and who started treatment while still in the maternity unit, since their screening results were obtained while still in hospital.

What can be observed is that nowadays pediatric physicians are giving less value to the clinical manifestations of CH, possibly because they are completely confident in neonatal screening. This situation predisposes to delayed diagnosis, primarily of patients who are symptomatic soon after birth or are screened late.

Among the children analyzed here, there was a predominance of females (1.2:1), but this was less accentuated than reports that are described in the literature (2:1). It is known that CH resulting from synthesis defects is transmitted by autosomal recessive inheritance and, therefore, has similar incidence in both sexes. In contrast, dysgenesis, which is described as being responsible for around 80% of cases,[14] is more common among females. This finding leads us to question whether there may be a greater incidence of CH caused by dyshormonogenesis in the state of Minas Gerais, but studies need to be conducted to test this hypothesis.

Transitory changes to the thyroid function of neonates can take place and are attributed to transplacental transport of maternal antibodies, to antithyroid drugs taken by the mother, to iodine deficiencies or excesses, or are related to prematurity. It is known that initial TSH values cannot be used as a parameter for differentiation between permanent and transitory CH[15] and that children with athyreosis tend to exhibit more significant thyroid function abnormalities than do children with ectopia, hypoplasia or synthesis defects.[16] Furthermore, there is a consensus that even transitory CH should be treated until resolution in order to avoid exposing the child's brain to low thyroxin levels.[15,17] Within the PETN-MG, the etiology of CH and its permanent or transitory nature are only investigated when the child reaches 3 years of age, since at this stage the hormone therapy can safely be interrupted temporarily to carry out etiologic tests. It is therefore possible that there are children with the transitory form of the disease among the cases studied here.

A study carried out in 2004 in Mexico with the objective of describing the epidemiological characteristics of CH in that country showed that the most often identified signs of hypothyroidism among the children screened were umbilical hernia (43.7%) and jaundice (41.5%).[3] In the study described here, the clinical signs most often found were umbilical hernia (51%) and enlarged anterior fontanel (50.3%). The size of the anterior fontanel can be evaluated from the mean of the anteroposterior and transversal diameters. The range of normality is wide, varying from 0.6 to 3.6 cm, with a mean of 2.1 cm on the first day of life.[18] An enlarged anterior fontanel combined with an open posterior fontanel can be an early sign of hypothyroidism in the newborn. When sutures are overly separated at birth, a third fontanel can be observed (between the anterior and posterior fontanels), which has also been described in Down syndrome.[19]

The signs and symptoms most related to CH severity were hypotonia, macroglossia and feeding difficulties, which suggests that these symptoms offer greater specificity for diagnosis of the disease. Tsai et al., in 1993, comparing children with CH with false-positive cases (controls), found a significant difference with relation to the following clinical findings: feeding difficulties, constipation, dry skin, umbilical hernia and posterior fontanel larger than 0.5 cm.[20]

In the analysis described here, a direct relationship was found between biochemical severity of the disease, evaluated in terms of FT4 levels, and frequency of abnormal findings on clinical examination. On the other hand, it was observed that the most symptomatic children were the youngest (presenting for first consultation with less than 30 days of life), possibly because they were referred directly to the CH consultation since they had very high TSH at screening and did not need a second sample to be tested, as happens with children with borderline thyroid function. Therefore, the children with the most severe hypothyroidism were diagnosed and treated earliest.

At the first consultation, bone age was retarded for a full term newborn in 32.1% of the children analyzed. In 2003,Wasniewska et al. found a higher incidence than this (44.3%), with 48.2% of these children exhibiting athyreosis. Those authors considered that bone age was retarded when the diameter of the nucleus of the distal femoral epiphysis was less than 3 mm, increasing the sensitivity of the test. Retarded bone age reflects thyroid function that is already severely compromised at birth and is related to abnormal neuropsychomotor development during the first year of life, irrespective of other variables related to treatment.[21]

Currently, the recommendation is that treatment for CH be initiated as soon as possible, ideally by the second week of life, since from this age onwards the most severe cases (athyreosis and severe forms of dyshormonogenesis) will exhibit some degree of sequelae.[22-24] Notwithstanding, it cannot be stated that early treatments guarantees an absence of sequelae, since intrauterine hormone deficiency can cause minor neurological deficits. Children diagnosed by screening and treated early still exhibit reduced IQ when compared with their own siblings who do not have the disease.[25]

Neonatal screening is a race against time. All of the stages involved in taking blood samples, sending off specimens, analyzing the results, referring suspected cases, confirming diagnosis and initiating treatment must be error-free and take as short a time as possible. False negative results are still a constant concern.[26,27]

A recent study evaluated neonatal screening for CH in another Brazilian state, Sergipe, and found that the age at

start of treatment was 51±12 days of life.[28] In the state of Santa Catarina, also in Brazil, an evaluation of the program carried out between 1994 and 1998 demonstrated a mean age at start of treatment of 40.2 days. During the period analyzed the percentage of children seen before 28 days rose form 24 to 46.7%, demonstrating that the program was improving, although not reaching the recommended level.[29]

In the PETN-MG for CH, during the period studied, 53% of the children started treatment within the first month of life, but the majority, after 15 days of life. The median age of starting treatment, which was 28 days, was still high, but the program demonstrated improvements over time.[1] Late institution of treatment was related to cases in which the family were slow to present at the health center for screening or to the need to collect a second sample on filter paper where thyroid function was borderline.

New strategies are being adopted to improve the performance of the PETN-MG, aimed at treating children with CH earlier. Since 2007, children with TSH over 20 mUI/L (rather than 25 mUI/L as before) are being referred directly for their first CH consultation, but the impact of that intervention has not yet been evaluated. In addition to this, campaigns need to be run to sensitize the public and health professionals to the importance of carrying out neonatal screening by the fifth day of the child's life at latest.

This study demonstrates the low sensitivity and specificity of the signs and symptoms of CH, emphasizes the importance of neonatal screening to early diagnosis of the disease and also constitutes a wake-up call to pediatric physicians, who should maintain a high level of suspicion with relation to symptomatic children. Unfortunately, neonatal screening for CH is not universal and false-negative cases can occur. For these reasons, when presented with a child with clinical signs and symptoms suggestive of hypothyroidism, TSH and FT4 should be assayed to confirm or rule out a diagnosis of CH, irrespective of previous screening results.

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