Incidence of congenital hypothyroidism in the city of Uberaba/Minas Gerais and etiological evaluation of the affected subjects

Incidência do hipotireoidismo congênito no município de Uberaba/Minas Gerais e avaliação etiológica dos afetados

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ABSTRACT

Objective: The objective of this study was to determine the incidence and etiology of congenital hypothyroidism (CH) in Uberaba, MG. **Subjects and methods:** From 2001 to 2010, by reviewing patient files from a public reference outpatient unit. The screening program covered 88% of live-born children. **Results:** CH was diagnosed in 16 children, representing an incidence of 1:2,017 live-born children screened. The etiological evaluation was done in 15 children and revealed seven cases of thyroid dysgenesis, seven of dyshormonogenesis, and one case of transient hypothyroidism. One child moved away from the state before etiological investigation was carried out. **Conclusion:** We concluded that both the incidence of CH and of dyshormonogenesis as the main causes of CH were increased in the investigated region, but molecular studies are necessary for a better definition of etiology. Arq Bras Endocrinol Metab. 2012;56(5):305-12

Keywords
Congenital hypothyroidism; newborn screening; epidemiology

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RESUMO

Objetivo: O objetivo deste estudo foi determinar a incidência e etiologia do hipotireoidismo congênito (HC) em Uberaba, MG. **Pacientes e métodos:** Mediante revisão dos prontuários de pacientes atendidos no ambulatório de referência do serviço público, no período de 2001 a 2010. **Resultados:** A cobertura do programa foi de 88%, sendo diagnosticadas 16 crianças com HC, com incidência de 1:2.017 nascidos vivos investigados. A avaliação etiológica foi realizada em 15 crianças, sendo diagnosticados sete casos de disgenesia tireoidiana, sete casos de disormonogênese e um caso de hipotireoidismo transitório. Uma criança não foi investigada devido à mudança de residência para outro estado. **Conclusões:** Concluímos que a incidência do HC é maior nesta região, assim como a disormonogênese como principal causa, sendo necessários estudos moleculares para melhor definição etiológica. Arq Bras Endocrinol Metab. 2012;56(5):305-12

Descritores
Hipotireoidismo congênito; triagem neonatal; epidemiologia

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Received on Mar/14/2012
Accepted on Jul/6/2012

INTRODUCTION

Congenital hypothyroidism (CH) is a clinical syndrome caused by thyroid hormone (TH) deficiency, resulting in reduction of metabolic processes and impaired neurodevelopment. The disorder is classified as primary when the origin of the defect is in the gland itself, or secondary, when the hypothalamic-pituitary axis is affected (1-5).

Thyroid organogenesis and hormonogenesis and the structuring of the hypothalamic-pituitary-thyroid axis are essential early steps of embryonic life (3,4,6). As the amount of TH that crosses the placenta is not sufficient to meet the needs of the fetus, fetal synthesis and secretion are important during the course of the gestation. Any interference that results in inadequate production of fetal TH represents a severe obstacle to the development of the synapses and neuronal myelination, which is clinically expressed by mental retardation and learning difficulties when the disorder is not diagnosed early and properly treated (4).

Based on newborn screening programs, the prevalence of primary CH is approximately 1:3,000 to 1:4,000. Some studies suggest an ethnic variation, with a higher prevalence among Hispanics and Native Americans (1:2,000) and a lower prevalence among Blacks (1:10,000), besides preponderance of female over the male gender (2:1) (3,5,7,8). The main causes of the disorder are: thyroid agenesis; ectopia due to a failure in embryonic migration of the gland; dyshormonogenesis caused by an inborn error of one of the many steps of thyroxin synthesis; and, finally, suppression of the fetal thyroid gland by medication used by the mother (5,8).

The greatest challenge to control CH is neonatal detection by screening programs. The first programs of this kind were developed in Quebec (Canada) and Pittsburgh (USA) in 1974, using radioimmunoassay to measure TH in capillary blood samples obtained by heel puncture (3,9). In Brazil, the Newborn Screening Program started in 1976 with a project to detect phenylketonuria (PKU), coordinated by Prof. Dr. Benjamin J. Schmidt and carried out at the São Paulo Association of Parents and Friends of the Mentally Handicapped (10). In 1983, the screening for PKU and CH by heel puncture became mandatory in the State of São Paulo for children born in public hospitals (*State Law no. 3914*, of November 14th, 1983), and in 1990 it was extended to children born in the whole country, both in public and in private healthcare facilities (*Federal Law no. 8069*, of July 13th, 1990) (11,12).

Despite the existence of the Federal Law, the National Newborn Screening Program was only established in 2001 by the Ministry of Health (13), thereby starting the systematic screening of live-born Brazilian children, and ensuring the performance of all steps, from blood collection to treatment and follow-up of the detected cases, with funding provided by the Federal HealthCare System. In the State of Minas Gerais, the program is coordinated by the Nucleus of Actions and Research in Diagnostic Support, headquartered in the State capital Belo Horizonte, in collaboration with the Municipal Health Offices of the State of Minas Gerais.

According to the program protocol, blood for the neonatal screening test is ideally collected on the 5th day of life, in order to ensure early diagnosis and onset of treatment. Once detected, the affected child is referred to a trained physician for follow-up. In Minas Gerais, this screening program was set up in 1993, and until 2008 a total of 3,574,476 children had been screened (14).

The objective of the present study was to determine the incidence of CH in Uberaba, a medium-sized city of Minas Gerais, and to outline the screening, treatment and etiology of CH cases detected from 2001 to 2010.

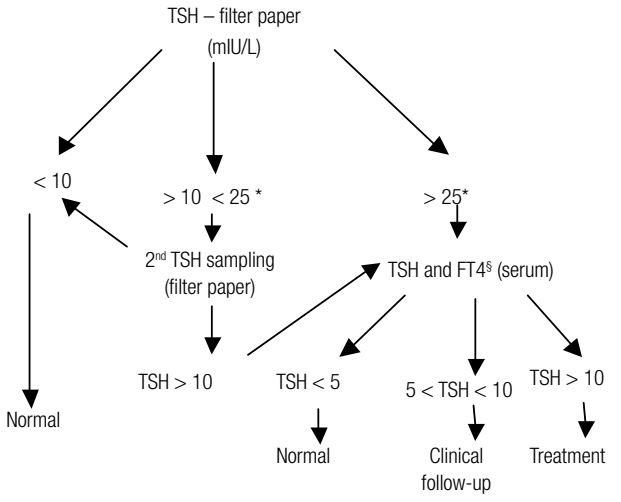
MATERIAL AND METHODS

Study protocol

This is a descriptive, retrospective study, performed by reviewing patient records from a public reference outpatient unit for the treatment and follow-up of children with CH diagnosed by the State Newborn Screening Program. The study was approved by the Ethics Committee of the institution.

Neonatal screening has been systematically performed in all newborns in public healthcare facilities, and was analyzed since 2001. The healthcare units are directed to collect blood samples between the 3rd and 5th day of life by heel puncture and impregnation of filter paper. The material is then sent to a reference laboratory, where it is processed and TSH levels are determined. Whenever TSH concentration is higher than 25 mIU/L, parents are officially referred to the pediatric endocrinology outpatient clinic of the Hospital de Clínicas of the Federal University of Minas Gerais in Belo Horizonte, where the patient goes to a medical appointment and venous blood samples are drawn for TSH, free T4, anti-thyroperoxidase antibody, and thyroglobulin measurements.

Once CH is confirmed, *i.e,*. by serum TSH concentrations higher than 10 mIU/L and low free T4 (FT4), treatment is started with levothyroxine, 10-12 µg/kg/day. The child is referred to a local physician, trained to provide proper care. Borderline TSH values in the screening test (10-25 mIU/L) indicate the need to repeat blood collection on filter paper and, if confirmed (TSH > 10 mIU/L), serum measurement and medical evaluation are also required (Figure 1).



§ FT4: free T4.
* Since 2007, TSH test level was changed to < 20 mIU/L.

Figure 1. Protocol proposed by the Nucleus of Actions and Research in Diagnostic Support for newborn screening test analysis (Modified from Pezzuti IL, 2009).

Thereafter, the child is followed up by means of periodic medical examinations and L-thyroxine doses are adjusted according to clinical progress and periodic TSH and FT4 measurements.

After reaching three years of age, children have their medication suspended to determine CH etiology, and they undergo the following exams: thyroid scintigraphy with ^{123}I, ultrasound, and perchlorate test, besides anti-thyroperoxidase antibodies and thyroglobulin measurements.

In the studied population, TSH analysis on filter paper was performed using ELISA (enzyme-linked immunosorbent assay; reference value < 10 mIU/L), and serum TSH and FT4, anti-thyroperoxidase antibodies and thyroglobulin measurements were carried out by chemoluminescence (reference values: 0.3 to 5.0 µIU/mL; 0.75 to 1.8 ng/dL; and < 15 IU/mL and < 30 ng/mL, respectively).

Clinical and laboratory data and the information obtained by the protocol (baby's age upon the first medical appointment, gender, clinical signs, and symptoms suggestive of CH, age at screening, value of the first serum TSH and FT4 measurements, age at the beginning of treatment and etiology of the CH) were analyzed.

Statistics

All observations were recorded in a database, using Excel 7.0 (Microsoft®) and GraphPad 5.0 (Graph Pad Prism®). Descriptive analysis based on absolute frequencies and percentages was used for the categorical variables, and measures of centrality (mean and median) and dispersion (standard deviation, coefficient of variation, minimum and maximum) were used for numerical variables. Data are presented in tables.

To calculate coverage, the following formula was used:

$$\text{Coverage} = \frac{\text{number of local live-born babies screened during the year in the city}}{\text{total number of live-born babies during the year in the city}} \times 100$$

The formula used to calculate the incidence coefficient per year was:

$$\text{Incidence coefficient} = \frac{\text{number of tests performed during the year in the city}}{\text{number of live-born babies screened during the year in the city}} \times 1000$$

Taking into account that the incidence of a disease is defined as the number of new cases that occur within a certain period of time in a population exposed to the risk of getting sick (15), we considered for the incidence calculation of each time period the number of confirmed cases screened by means of the newborn test, and the total number of newborn tests performed by the public healthare system from 2001 to 2010.

RESULTS

From 2001 through 2010, a total of 36,666 babies were born in Uberaba/MG, and 32,278 of them underwent the newborn screening test provided by the public healthcare system. Thus, 88% of the babies were screened for CH, and 16 cases were detected, indicating a CH incidence of 1: 2,017 screened newborns during this period (2001-2010).

The percent coverage of the screening test varied from 84% to 92% and CH incidence coefficient varied from 0.00 to 1.25 cases/1,000 live-born children/year.

Of the 16 babies diagnosed with CH, 11 (68.8%) were female, representing a Female/Male ratio of 2.2:1.

Gestations of most of the babies with CH (n = 15; 93.8%) were normal; in one case, pre-eclampsia and gestational diabetes occurred. Half of the deliveries were normal and at term; one was normal but post-term (42 weeks), five babies were delivered by cesarean section, and two by pre-term cesarean section (34 and 36 weeks). Eight babies (50%) presented prolonged neonatal jaundice. One baby, small for gestational age at birth, had trisomy 21. In seven babies (43.8%), the screening test was positive, but signs did not suggest hypothyroidism. In the baby with trisomy 21, the characteristics of the syndrome were predominant. The other eight babies (50%) showed manifest hypothyroidism, with pale, dry, and rough skin or *cutis marmorata*, macroglossia, open anterior and posterior fontanels, umbilical hernia, and infiltrated appearance.

The newborn screening test was performed on the 5th day of life in five of the babies diagnosed with CH, and between the 5th and 10th day in eight babies (mean of 7 ± 2 days). Three babies had their tests delayed (performed at 17, 20, and 30 days of life, respectively) due to intercurrences at birth.

Once the diagnosis was confirmed, therapy was started between day 14 and 59 after birth (median: 32 days; Table 1). Excluding the cases of late blood collection and/or recall, mean time of treatment onset was at 24.2 ± 10.2 days (14 to 48 days).

Of the 16 babies diagnosed with CH, 6 (37.5%) presented TSH < 25 mIU/L upon the first screening test, so a second blood sample was collected on filter paper, which delayed the diagnosis.

The babies' first medical visit occurred at 14 to 59 days of age (median: 32 days), when they presented the anthropometric characteristics listed in table 1.

TSH concentrations obtained in the newborn screening test, TSH and free T4 measurements performed later on, and anti-thyroperoxidase and thyroglobulin values are presented in table 2. Anti-thyroid antibodies at low concentrations do not support the existence of intrauterine autoimmune thyroiditis. There was one case with a rather low thyroglobulin level, and CH etiology in this patient is still being investigated (ultrasound showed normal topic thyroid).

An etiologic investigation was carried out in 15 children, between 3 and 4 years of age; one patient moved away from the State before the etiologic investigation was carried out. Cervical ultrasound (n = 15) showed a topic thyroid in 12 cases (80%), thyroid ectopia in one case (6.7%), and in two cases the gland was not visualized. Among the topic thyroids,

Table 1. Clinical data on the children with CH at birth and at the onset of treatment (Uberaba/MG, 2001-2010)

Case	Gender	At birth		Age at 1st ST* (days)	Age at 2nd ST* (days)	Onset of treatment		
		Weight (g)	Length (cm)			Age (days)	Weight (g)	Length (cm)
1	F	3,200	51	17.0	43	52.0	4,900	56.5
2	F	3,400	49	10.0	-	32.0	4,600	55.5
3	M	3,310	47	30.0	42	55.0	4,400	53.0
4	F	3,250	51	5.0	-	48.0	4,700	56.0
5	F	1,280	37	20.0	-	59.0	2,450	44.5
6	F	3,000	49	5.0	20	33.0	3,700	49.0
7	F	2,550	47	5.0	-	24.0	3,100	49.0
8	F	3,150	51	9.0	-	23.0	3,700	51.0
9	M	3,300	49	5.0	26	39.0	4,700	56.0
10	F	2,645	46	9.0	28	37.0	4,200	51.3
11	M	3,165	45	10.0	33	45.0	3,800	50.5
12	M	3,650	52	5.0	-	20.0	3,600	53.0
13	F	3,980	53	9.0	-	19.0	4,600	54.0
14	M	3,360	48	7.0	-	18.0	3,700	49.5
15	F	3,100	49	7.0	-	20.0	3,200	52.0
16	F	2,750	47	7.0	-	14.0	2,900	48.0
Median	-	3,182	49	8.0	30	32.0	4,000	52.0
Minimum	-	1,280	37	5.0	20	14.0	2,450	44.5
Maximum	-	3,980	53	30.0	43	59.0	4,900	57.5

* ST: screening test.

four were hypoplastic, six had normal volume, and two were enlarged. Scintigraphy was performed in 11 (68.8%) children. In three of them (27.2%), the thyroid was ectopic (sublingual), in the other cases (72.7%) it was topic. The perchlorate test, performed in eight children with topic thyroid, was positive in one case (12.5%), indicating a defect in iodine organification (Table 3).

Table 2. Results of the screening test and hormone dosages confirming CH (Uberaba/MG, 2001-2010)

Case	Filter paper		Serum			
	1st ST* TSHmIU/L	2nd ST* TSHmIU/L	TSH µIU/mL	FT4 ng/dL	Anti-TPO IU/mL	TG** ng/mL
1	11.8	249.2	129.1	0.62	1.0	1,176.0
2	33.9	-	371.0	0.34	1.0	300.7
3	13.8	10.8	13.8	1.35	3.0	94.3
4	77.4	-	48.0	1.04	1.0	102.8
5	134.0	-	138.2	0.78	NT	NT
6	23.0	24.9	24.5	1.11	13.0	66.0
7	27.2	-	11.5	1.08	1.0	21.1
8	38.6	-	61.9	0.66	73.0	281.1
9	10.8	33.1	15.7	1.02	1.0	483.0
10	24.2	49.3	75.6	0.77	1.0	180.0
11	22.6	13.7	32.4	0.91	1.0	61.2
12	119.3	-	317.4	0.50	NT	NT
13	164.7	-	397.4	0.40	1.0	0.1
14	30.0	-	166.5	0.53	3.0	66.4
15	150.0	-	500.0	0.01	3.0	66.1
16	34.2	-	108.0	0.21	2.0	737.3
Median	34.0	29.0	91.8	0.71	1.0	98.6
Minimum	10.8	10.8	11.5	0.01	1.0	0.1
Maximum	164.7	249.2	500.0	1.35	73.0	1176.0

TSH: 0.3 to 5.0 µIU/mL; FT4: 0.75 to 1.8 ng/dL; ANTI-TPO: < 15 IU/mL; TG: up to 30 ng/mL.
* ST: screening test; ** TG: thyroglobulin; NT: not tested.

Table 3. Results of etiologic and diagnostic tests of children with CH (Uberaba/MG, 2001-2010)

Case	TSH µIU/mL	FT4 ng/dL	Thyroid characteristics at ultrasound	Scintigraphy	Perchlorate test	Diagnosis
1	11.0	1.38	Topic; normal volume	Topic	Positive	Defect in iodine organificaion
2	10.5	1.08	Topic; left lobe hypoplastic	Topic	Negative	Left lobe hypoplastic
3	10.0	1.33	Topic; enlarged	Topic	Negative	Dyshormonogenesis
4	65.6	0.96	Topic; normal volume	Topic	Negative	Dyshormonogenesis
5	20.4	1.28	Topic; hypoplastic	Topic	Negative	Hypoplasia
6	72.9	1.36	Ectopic	Ectopic	Not done	Ectopia
7	11.3	0.81	Topic; normal volume	Topic	Negative	Dyshormonogenesis
8	320.1	0.05	Topic; hypoplastic	Topic	Negative	Hypoplasia
9	6.5	0.87	Topic; normal volume	Topic	Negative	Transient hypothyroidism
10	NT	NT	Topic; hypoplastic	Not done	Not done	Probable hypoplasia
11	NT	NT	Topic; normal volume	Not done	Not done	Probable dyshormonogenesis
12	476.1	0.25	Not visualized	Ectopic	Not done	Ectopia
13	NT	NT	Topic; normal volume	Not done	Not done	Probable dyshormonogenesis
14	377.1	0.25	Not visualized	Ectopic	Not done	Ectopia
15	NT	NT	Not done	Not done	Not done	Moved away from the State
16	NT	NT	Topic; enlarged	Not done	Not done	Probable dyshormonogenesis

TSH: 0.3 to 5.0 µIU/mL; FT4: 0.75 to 1.8 ng/dL.
NT: not tested.

Of the children investigated thoroughly, only one case had transient hypothyroidism, so the medication was discontinued. This child was nevertheless followed up for other 2 years and, as he remained euthyroid, he was discharged from the program. Ten of the remaining children were diagnosed with permanent hypothyroidism and resumed the treatment with sodium levothyroxine. Currently, four children are waiting for a complementation of their etiologic investigation (scintigraphy and perchlorate test) while under treatment.

Neuropsychomotor development has been considered adequate for age in 12 children, except for one who presented neonatal seizures and the patient with trisomy 21. Six children are already at school age and six are at preschool age.

DISCUSSION

Access to the newborn screening test is still highly variable in Brazil, ranging from virtually 100% in the southern states to less than 60% in the northern states of the country, where geographic, political, economic, social, cultural, and educational barriers still persist (16).

In the State of Minas Gerais, the coverage of the newborn screening program is 94.6% (17) and comprises almost 100% of the 853 cities of the state. In Uberaba, this coverage has been maintained over the years at around 88%, and we believe that the remaining babies are screened by the private healthcare system, since the socioeconomic conditions of part of the population allows them to afford private healthcare. This assumption is corroborated by 2003 data showing that almost one fourth of the Brazilian population (24.6%) was covered by private health insurance plans (18). This overall coverage rate is similar to the States of Paraná and Santa Catarina, which in 2007 presented an 88% and 88.5% coverage, respectively (19), and higher than in states of Pernambuco and Piauí, where in 2007 only 51% and 64% of the live-born babies were screened, respectively (20), and Sergipe, where in 2005 the coverage was 76.3% (21).

The incidence of CH in Uberaba is higher (1:2,017) than the reported by most of the newborn screening programs in Brazil. This city is situated in a well-developed region of the State of Minas Gerais that has been considered iodine-deficient in the past. However, there is no recent data on the regional iodine status (22). The greater number of cases may also be due to not yet identified environmental factors. An even higher incidence was observed in the State of Rio de Janeiro from 2005 to 2007 (1:1,030). This finding was attributed to variations in the neonatal TSH cutoff values among the screening models used there (23). According to a Brazilian newborn screening epidemiologic survey, in 2001, the prevalence of CH was 1:3,694, and in 2002, it was 1:3,808 (24).

Ideally, the age for collecting the first blood sample for TSH screening is between the 3rd and the 5th day of life, when the postnatal peak of physiological TSH elevation has already decreased (25-27). In Uberaba, the mean age at the first blood collection of the diagnosed patients was 7 days, except for the three cases with late blood collection due to various reasons. This value is similar to the newborn screening program of the city of Ribeirão Preto, state of São Paulo (8 days) (12), but higher than the limits established as ideal in the Administrative Rule no. 822 (13) of the Brazilian Ministry of Health (2 to 7 days of life). Compared with other Brazilian states, the mean of 7 days is higher than the one found in the states of Paraná (3 days) and Santa Catarina (5 days), but lower than in Rio Grande do Sul (11 days) (19) and in Paraíba (29.8 days) (28). In a study published in 2006 on CH screening in Scotland (29), the median age at blood collection for the test was 6 days, and 93.8% of the samples were collected before eight days of life.

Treatment was started on average at 24.6 days of life and, in the last 4 years, it was observed that, even if the screening test was not carried out exactly on the 5th day, but between the 5th and the 10th day, treatment was started before 20 days of age. This observation proves how fast samples are sent to the reference laboratory, results are provided, and the children officially called in for medical examination, confirmation of the diagnosis, and onset of treatment. In a further effort to start treatment as early as possible, ideally by the second week of life, the Newborn Screening Program of the State of Minas Gerais has called in children with TSH test results higher than 20 mIU/L (rather than 25) for a medical examination since 2007 (30). In the long run, this intervention will certainly show an impact on achieving the desired results.

Comparing the data of the present study with those of other Brazilian newborn screening programs, we observed a similarity in treatment onset with the program performed at the Ribeirão Preto School of Medicine University Hospital, equal to 25.9 ± 14.2 days (12), and in the State of Rio Grande do Sul, where it was 24

days (19). It is, however, still longer than in the States of Paraná (15 days) and Santa Catarina (16 days) (data for 2007) (19). National data obtained by the Brazilian Society of Newborn Screening for the years 2001 and 2002 showed that the mean age at start of CH treatment was 34 ± 17 days (19). In the Scottish study (29), the median age at treatment start was 11 days, but 12% of the evaluated children started treatment at over 16 days of life, which was considered late.

In order to be able to start treatment as early as possible, campaigns directed to healthcare professionals have been conducted in Uberaba, so that they would instruct parents regarding the importance of early testing (up to the 5th day of life), and alert the basic healthcare unit professionals about the importance of collecting blood samples properly, and quickly sending them to the reference laboratory.

So far, the analysis of CH etiology confirmed six cases of thyroid dysgenesis and four cases of dyshormonogenesis. Four cases are still under investigation (probable dysgenesis in one case and dyshormonogenesis in three). Compared with the literature, where thyroid dysgenesis is predominant (9,31-34), in the CH patients of Uberaba, dyshormonogenesis was observed to have a higher frequency. One case of iodine organification defect and three cases with a normal perchlorate test were also found. In three children with a topic thyroid on ultrasound, scintigraphy and perchlorate test are still to be performed, and molecular studies will be necessary in the future for a better etiologic definition. We raised the possibility of parental consanguinity (35) as the factor responsible for this finding, but information obtained from the parents did not confirm this hypothesis. The results found in Uberaba are consistent with a study carried out on 243 patients with CH from the Newborn Screening Program of the State of Minas Gerais from 1996 to 2003, which also observed a higher frequency of hormone synthesis defects (52%) than thyroid dysgenesis (47%) (36).

CH is one of the most common causes of preventable mental retardation, and its natural course can be dramatically modified depending on how early it is diagnosed and how quickly proper treatment is started. Thus, every effort should be made to carry out newborn screening programs, in order to ensure early diagnosis and treatment. To reach this goal, it is important to set time patterns for each step of the screening process, because delays in one or more steps will lead to unacceptable delays in the treatment of the affected children. The Newborn Screening Program of the State of Minas Gerais is actively attempting, together with the municipal health offices, to overcome the difficulties and, consequently, reach the desired goals. Specifically in Uberaba, it is still necessary to optimize the extent of program coverage, and to reduce the age at sample collection. However, promising results are already being obtained, offering a better perspective to the patients.

Acknowledgments: the authors are grateful to the Health Office of Uberaba/MG and to the Nucleus of Actions and Research in Diagnostic Support of the Federal University of Minas Gerais for giving them access to all the records, and to Ms. Silvana Silva, social worker of the Newborn Screening Program of the City of Uberaba, for her invaluable help.

Disclosure: no potential conflict of interest relevant to this article was reported.

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