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ARTIGO ORIGINAL

Characterization of children with Down syndrome concomitant with congenital hypothyroidism in the state of Mato Grosso, Central Region of Brazil, 2010 - 2021

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Congenital Hypothyroidism, Down syndrome, Neonatal screening, Thyrotropin.

Abstract

Objective: Congenital hypothyroidism is a frequent disease in pediatric endocrinology, with a high prevalence among children with Down syndrome. In Brazil, publications on the coexistence of these two syndromes in children are scarce. The aim of this study was to clinically and laboratory characterize children with Down syndrome concomitant with congenital hypothyroidism. **Methods:** This is a cross-sectional and retrospective study with data from medical records of patients with Down syndrome concomitant with congenital hypothyroidism among live births from January 2010 to December 2021, followed at a neonatal screening service in Mato Grosso, Brazil. **Results:** 318 children with congenital hypothyroidism were analyzed, 11 of them with Down syndrome (prevalence of 1:28.9 among children with congenital hypothyroidism). The most common clinical finding was jaundice (90.0%), followed by macroglossia (80.0%), hypotonia (66.7%) and livedo reticularis (62.5%). Congenital cardiac anomalies occurred in all children with Down syndrome studied. Interatrial communication and patent ductus arteriosus were the most frequent cardiac anomalies. Serum levels of thyrotropin were between 10 µIU/mL and 20 µIU/mL in 63.6% of the sample and in two patients, these values ??were above 100 µIU/mL. In 81.8% of the children, free thyroxine levels were normal. The absolute majority of children did not show thyroid ultrasonographic alteration. **Conclusions:** A high prevalence of Down syndrome was observed among patients with congenital hypothyroidism, with the subclinical form of hypothyroidism being the most common presentation. Jaundice, macroglossia and congenital heart disease were the most relevant clinical findings in this study.

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INTRODUCTION

Congenital hypothyroidism (CH) is considered a common disease in pediatric endocrinology, present in approximately 1:2,000 to 1:4,000 newborns (NBs), and it is a frequent cause of intellectual disability worldwide, but it can be prevented if neonatal screening, when early diagnoses are performed[1]. This disease is caused by a failure in the synthesis of hormones by the thyroid (primary hypothyroidism) or by a defect in the production of thyrotropin (TSH) due to pituitary or hypothalamic dysfunction (central hypothyroidism)[2]. Thyroid hormones play an important role in the normal development of the central nervous system and, when absent, lead to changes in brain development[3]. Most cases of CH are classified as primary hypothyroidism, with thyroid dysgenesis responsible for approximately 85% of cases and dyshormonogenesis for the remaining 15%.[4] Primary hypothyroidism can present in a subclinical or compensated form[3,5] when the TSH level is high, but the free or total thyroxine (T4) value is normal, or in a classic form when there is high TSH and low T4[3].

Down syndrome (DS) or 21-trisomy is the most common chromosomal anomaly[6,7] in the population and occurs due to the failure of chromosome 21 to separate during gametogenesis, resulting in an extra chromosome in all body cells[8]. This chromosomal disorder is associated with cognitive impairment and learning difficulties[6,7], affecting approximately 14 in 10,000 live births in the United States of America each year[6], a figure well above the national statistic (4 in 10,000 live births)[7]. Thyroid dysfunctions, including all forms of thyroid disease[8], are frequently present in approximately 7 to 40% of individuals with DS[9], with CH being present in 1%[10,11] to 12% of this population[11]. It is estimated that the prevalence of newborns with this chromosomal abnormality is up to 1:50 among those with CH detected by neonatal screening programs[1], with a frequency 28[5,12] to 50 times higher than that expected in the general population[13].

It is relatively common for CH among children with DS to present a slight elevation in TSH levels without, however, altering thyroxine values[1,10,14]. The reasons for the occurrence of CH in children with DS are not clear[5], but dysregulation of the hypothalamic-pituitary-thyroid axis has been considered[15], as well as, in cases of thyroid dysgenesis, the presence of events related to the migration and differentiation of thyroid cells in the embryonic period and delayed growth of the thyroid gland in fetal life[16].

CH has as clinical characteristics the presence of hypotonia, jaundice, livedo reticularis, umbilical hernia, large fontanelles, macroglossia, changes in weight and height growth, delayed neuropsychomotor development with intellectual disability, and other changes. Due to the clinical similarities between the two diseases in question, there is certainly underreporting of hypothyroidism in children with DS, especially when neonatal screening is not performed[6,17]. Therefore, some cases of CH in children with DS are only identified late, in a routine assessment of the first 6 months of life[18]. Based on this, Pierce et al.[8] (2017) recommended that screening for CH be more frequent during the first six months of life in children with DS, although the American Academy of Pediatrics (AAP)[11] considers that there is insufficient evidence to recommend this additional routine screening.

The association of CH with extrathyroidal diseases ranges from 10.5% to 59%, with cardiac malformations being the most frequent[13]. Gu et al.[19] (2009) found cardiac defects in 54 (62.8%) children with DS concomitantly with primary CH, with atrial septal defect (ASD) and patent ductus arteriosus (PDA) being the most prevalent.

The present study aimed to describe the prevalence and characterize children with DS concomitantly with CH in the state of Mato Grosso between 2010 and 2021.

METHODS

This is a cross-sectional study with retrospective analysis of data recorded in physical and electronic medical records of the management application for university hospitals, of children monitored by the Neonatal Screening Reference Service (NSRS) of the teaching hospital of the Federal University of Mato Grosso. This screening service has guaranteed an average coverage of over 75% for the population of live births in the state since 2003[20].

Newborns undergoing neonatal screening by the NSRS were selected from among the live births registered in the Live Birth Information System (SINASC) from January 1, 2010 to December 31, 2021. Of these, only those who had a diagnosis of DS, confirmed by karyotype, concomitant with CH were analyzed. Children diagnosed with acquired hypothyroidism were excluded. Data on the number of live births during the period analyzed and neonatal screening coverage were obtained from the State Health Department of the State of Mato Grosso, from SINASC and the National Neonatal Screening System (SISNEO), respectively.

In Mato Grosso, screening and diagnosis of CH follow the protocol established by the State Neonatal Screening Program (PETN). Initially, neonatal TSH (TSHneo) is measured in blood collected on filter paper using the time-resolved fluoroimmunoassay method (reference value less than or equal to 5 µUI/mL). If the level is between 5 and 10 µUI/mL or if the child was born prematurely, the child is called for a new blood collection for TSHneo measurement. If it is equal to or greater than 10 µUI/mL, the newborn is called for a specialized medical consultation and TSH and thyroid hormone measurements. The diagnosis of CH is confirmed when serum TSH levels are higher than 10 µIU/mL and its classification as classic or subclinical depends on whether serum free T4 levels are low or normal, respectively. Thyroid ultrasound was performed to clarify the etiology of CH, using a Madison Sonoace 9900 device with a linear probe of 5 to 13 mHz. The children were described in relation to the following variables: sex, gestational age, age

at the time of neonatal screening, age at the first follow-up visit, serum concentrations of TSHneo, TSH and postnatal free thyroxine, clinical findings at the first visit, presence of congenital anomalies, thyroid ultrasound result and age at which treatment began. For data analysis, Microsoft® Office Excel 2010 was used and, after data compilation, the median, mean and standard deviation (SD) of the quantitative variables and the frequency distribution of the categorical variables were described. The prevalence of CH was calculated by the ratio of live births that had a confirmed diagnosis in the period among those with screening performed in the same period. For the prevalence of children with DS concomitant with CH, the ratio of those diagnosed with DS among those who had a confirmed diagnosis of CH was calculated.

The study was approved by the Human Research Ethics Committee of the hospital under opinion number 5,775,975 and CAAE registration number 64310422.3.0000.5541.

RESULTS

Between 2010 and 2021, Mato Grosso recorded 660,571 live births, of which 488,580 were screened by the PETN, reaching a population coverage of approximately 74%. Among the children screened during the study period, 318 were diagnosed with CH (prevalence of 1:1,536), and of these, 11 (3.5%) had a concomitant diagnosis of DS, a prevalence of 1:28.9 (Table 1).

The demographic characteristics of the sample and the age at approach, from neonatal screening to CH treatment, are presented in Table 1. Of the 11 individuals analyzed, five (45.4%) were female, with a male to female ratio of 1.2. Regarding gestational age, three (27.3%) were classified as late preterm and the others were full-term. The premature infants underwent the second neonatal screening test, according to the PETN protocol, and all had altered results. Neonatal screening was performed in the first week of life in 63.6% of the children, with a mean life expectancy (SD) of 5.4 (SD=1.6) days. Regarding the first outpatient consultation, five (45.4%) children were under three months old, four (36.4%) attended the consultation in the second trimester of life and the others (18.2%) only in the second semester of life. Treatment began before 3 months for five (45.4%) of them, between 3 and 6 months of life for 27.3%; and after 6 months of life for the others (n=3; 27.3%). The concentrations of the first neonatal TSH, TSH and free T4 in serum, as well as the findings of thyroid ultrasound are presented in Table 2. Seven (63.6%) children presented alterations in the first TSHneo and in two, the alterations occurred only at the screening re-collection. Despite the normal initial screening in the other in both children, CH was confirmed during routine outpatient investigation. The mean (SD) of the first TSHneo was 33.1 (73.0) µUI/mL.

The diagnosis of CH was confirmed in eight children by the first serum TSH. For the others, confirmation was given in subsequent tests. The mean (SD) serum TSH concentrations of the 11 children with concomitant DS and CH was 37.5 (43.8) µUI/mL. Values between 10 µUI/mL and 20 µUI/mL were observed in seven (63.6%) patients. For the remaining four patients, serum TSH was between 20.1 µUI/mL and 100 µUI/mL or even above 100 µUI/mL. Regarding free T4, the mean serum concentration (SD) was 1.1 (0.4) ng/dL, with low levels (<0.7 ng/dL) in only two children (18.2%). Those with low free thyroxine concentrations were the same ones who had serum TSH above 100 µUI/mL, being classified as classic CH.

According to the ultrasound results, only one of the 10 children who underwent the test had thyroid dysgenesis compatible with hypoplasia of the gland.

Due to the lack of complete information in the medical records analyzed, it was not possible to clinically assess 100% of the children in the sample. Table 3 presents the most frequently found findings: jaundice (90.0%), macroglossia (80.0%), hypotonia and livedo reticularis (62.5%). Some clinical signs were recorded in approximately 30.0% to 45.0%, namely: pale skin (44.4%), abdominal distension (44.4%), lethargy (42.9%), cold and dry skin (37.5%), umbilical hernia (30.0%) and intestinal constipation (28.6%). The least frequently found clinical manifestations were inguinal hernia (14.3%) and wide fontanelles (11.1%). All children in the study had congenital cardiac anomalies. ASD alone and PDA associated with ASD or atrioventricular septal defect (AVSD) were the most prevalent anomalies, with a frequency of 18.2% for each. Gastrointestinal anomaly such as Hirschsprung's disease was present in only one patient.

DISCUSSION

This study demonstrated a high prevalence of DS among patients with CH, with the subclinical form being the most common. Congenital cardiac anomalies were present in all children in the study.

The coverage observed here was 73.9%, like that from 2010 to 2012 (approximately 74%)[22] and slightly below that recorded by Costa et al.[20] (2020), which was 75.2% for the same program. Coverage remains stable, but still below the national rate, which is over 80%[4].

The study obtained a CH prevalence of 1:1,536, similar to that observed by Mengreli et al.[23] in 2010 (1:1,749). Although using the same analytical methods and disease detection cutoff point, the current figures are higher than those found in previous years, in the same program (1:2,234)[22].

There is a higher risk of children with DS having thyroid dysfunction[1,10,12] such as CH, being 28[5,13,24] to 35[13,24] and up to 50[13] times more prevalent when compared to the general population. In this study, the prevalence of children with DS among all those who confirmed the endocrine disease was 1:28.9, well above that mentioned by Connelly and LaFranchi[1] (2022) of up to 1:50 newborns. However, Razavi et al.[25] (2012) and Baş et al.[13] (2014) found a frequency of children with DS

Table 1. Data on the performance of the State Neonatal Screening Program, description of the prevalence and characterization of children with Down syndrome concomitant with congenital hypothyroidism (n=11), Mato Grosso, 2010 to 2021.

State Neonatal State Program Performance	**2010 – 2021**
Live births (N)	660,571*
Screened children (n)	488,580**
Screening coverage (%)	73.96
Prevalence of congenital hypothyroidism and Down syndrome	
Congenital Hypothyroidism (n)	318**
Prevalence of the disease	1:1.536
Down Sd with Congenital Hypothyroidism (n)	11**
Prevalence of Down Sd with Congenital Hypothyroidism	1:28,9
Down Sd Frequency in Congenital hypothyroidism (%)	3,5
Demographic characteristics of the sample investigated	
Gender ratio (Female:Male)	1:1.2
Gestational Age	n (%)
Prematures	3 (27.3)
Term	8 (72.7)
Time of visit	
Age of the neonatal screen collection (days)	n (%)
Up to 7	7 (63.6)
8 - 14	2 (18.2)
15 – 30	1 (9.1)
Ignored	1 (9.1)
Age during the first outpatient visit (months)	n (%)
Up to 1	1 (9.1)
1 – 3	4 (36.4)
3 – 6	4 (36.4)
6 – 12	2 (18.2)
Age at treatment onset (months)	n (%)
Up to 1	1 (9.1)
1 – 3	4 (36.4)
3 – 6	3 (27.3)
6 – 12	2 (18.2)
> 12	1 (9.1)

Sources:*http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinasc/cnv/nvmt.def/21; **Data from SRTN/MT in the SISNEO system and the Hospital genetics ward. **Acronym:** Sd=Syndrome.

among those with CH (8% and 6.3%, respectively) higher than those observed here (3.5%).

There is a female preponderance in CH, which is generally not found in patients with CH and DS[24]. Several studies have corroborated this statement, such as this one, where the male/female ratio was 1.2, identical to that found by Pierce et al.[8] (2017) and close to the findings of Laignier et al.[7] (2021) of 1.1.

Table 2. Results from the measurement of the first neonatal TSH, of serum TSH and free T4 and of the thyroid ultrasound findings of children with Down syndrome concomitant with congenital hypothyroidism in Mato Grosso, 2010 to 2021.

TSH measures (n=11)	**Neonatal screening**	**Confirmation tests**	
	TSHneo (µUI/mL)	**TSH no soro (µUI/mL)(1)**	**T4 livre no soro (ng/dL)(2)**
Mean	33.1	37.5	1.1
Median	10.4	16.5	1.2
Standard deviation	73.0	43.8	0.4
Minimum – Maximum	0.77 – 250.0	10.5 – > 150	< 0.4 – 1.63
Thyroid ultrasonography			
Ecographic findings		**N**	**%**
No changes		9	90,0
Reduced volume		1	10,0
Total		**10**	**100,0**

Legenda: (1)For the purpose of data analysis, serum TSH values >100 µIU/mL and >150 µIU/mL were considered as 101 µIU/mL and 151 µIU/mL, respectively; (2)For the same reason, free T4 results reported as <0.40 ng/dL at diagnosis were considered as 0.39 ng/dL.

Laignier et al.[7] (2021) observed that pregnant women with fetuses with DS were 2.4 times more likely to have premature births. In the study, prematurity was present in 27.3% of the sample. Publications on the prematurity rate among children with these associated pathologies are scarce but considering the higher frequency of congenital anomalies among children with DS, the occurrence of newborns with lower gestational ages should be considered.

Neonatal screening and early initiation of treatment improve the outcome in relation to the growth and development of these children. In this study, 63.6% of the children underwent neonatal screening by the 7th day of life, which is in agreement with Fort et al.[5] (1984), who found that the first screening was performed on average 6 days after birth. Although neonatal screening was performed in a timely manner for most of the children studied, a delayed approach was observed in subsequent stages. Of the seven children who presented abnormal results in the first neonatal screening test, in six (54.5%) the TSHneo was above 10 µU/mL, associated with elevated serum TSH, confirming CH; two patients were premature and the laboratory abnormalities were only evidenced in the new TSHneo collection. In the others, the neonatal screening test was normal; however, serum hormonal alterations appeared between the ages of 3 and 5 months, a behavior that corroborates the AAP recommendation on the need for periodic hormonal evaluations in the first year of life[10]. In 0.1 to 1.0% of newborns with CH, hormone concentrations in neonatal screening will be normal due to errors in sample collection and processing[12] or due to late increases in TSH[10,12], or in mild forms of the disease[8,12] that escape detection in early screening[8].

Table 3. Signs and symptoms present at the first consultation and associated congenital malformations in the children in the study, Mato Grosso, 2010 to 2021.

Clinical traits	Sample assessed*	Frequency of findings	%
Jaundice	10	9	90.0
Macroglossia		8	80.0
Umbilical hernia		3	30.0
Hypotonia	9	6	66.7
Paleness		4	44.4
Abdominal distention		4	44.4
Broad Fontanels		1	11.1
Broad sutures		0	0.0
Reticular livedo	8	5	62.5
Dry and cold skin		3	37.5
Face edema		0	0.0
Goiter		0	0.0
Lethargy	7	3	42.9
Intestinal obstipation		2	28.6
Umbilical hernia		1	14.3
Umbilical stump late fall (> 21 days)	6	1	16.7
Hoarse cry		0	0.0
Congenital malformations			
Cardiac			
IAC	11	2	18.2
IAC + PDA		2	18.2
IVC		1	9.1
IVC + PFO		1	9.1
AVSD		1	9.1
AVSD + PDA		2	18.2
PFO		1	9.1
Pulmonary supravalvar stenosis		1	9.1
Gastrointestinal			
Doença de Hirschusprung	11	1	9.1

Acronyms: IAC: Interatrial communication; PDA: Patent Ductus Arteriosus; IVC: Interventricular Communication; AVSD: Atrioventricular Septum Defect; PFO: Patent Foramen Ovale

*Sample according to available information

As for diagnosis, six (54.5%) children had the disease confirmed before2 months of age and five (45.5%) after this period. Of the latter, only one child had persistent hyperthyrotropinemia; the decision to initiate treatment occurred after 2 years of age. According to Myrelid et al.26 (2009), children with hyperthyrotropinemia have an increased risk of developing subclinical CH. Regarding hormone concentrations, Fort et al.[5] (1984) found an average of 27.4 µUI/mL for the first TSHneo among children with DS, close to that observed in the study (33.1 µUI/mL; SD=73.0). Razavi et al.[25] (2012) observed in children with CH concomitant with DS, an average (SD) for serum TSH of 42.7 (41.9) µUI/mL; therefore similar (p=0.774) to that found in this study (37.5 µUI/mL; SD=43.8). In the profile of these children, Cebeci et al.[27] (2013) observed a median of 1.18 ng/dL for free thyroxine, close to that found here (1.2 ng/dL). According to Rodriguez et al.[9] (2022), thyroid hypoplasia is the main cause of CH in DS, while ectopia and agenesis are rare. Cebeci et al.[27] (2013) found a high frequency of thyroid hypoplasia in children with both concomitant diseases. Thyroid ultrasound was normal in 90.0% of the children in the study and only one child had the classic form of CH due to thyroid hypoplasia. In a similar sample, Fort et al.[5] (1984) demonstrated that the position and volume of the thyroid gland were normal in 45.5% of children studied.

Due to the similar clinical findings, it is difficult to consider the diagnosis of hypothyroidism in children with DS on clinical grounds[15]. Hypothyroidism initially presents subtle signs and symptoms and can initially be attributed only to Down syndrome[12]. Among the findings, jaundice and macroglossia were present in 90.0% and 80.0% of cases, respectively. It is possible that macroglossia is attributed to DS, since the subclinical form of CH, which is usually oligosymptomatic, predominated among the children in this study. Cebeci et al.[27] (2013) pointed out prolonged jaundice as the most frequent finding (70%) among children with DS associated with CH.

The occurrence of cardiac malformations among children with CH can reach the figure of 4.67%[25]. Atrioventricular septal and ventricular septal defects are reported as the most common among children with DS[28]. In this study, cardiac malformations had an absolute preponderance (100%), with ASD and PDA being the most prevalent, while Hirschsprung's disease was detected in only one child. Pierce et al.[8] (2017) found some type of congenital heart disease in 52% of children with DS. Gu et al.[19] (2009) observed Hirschsprung's disease only in children with CH, but not when the diseases coexisted.

Some limitations should be considered when interpreting the results of this study. For example, the retrospective approach was accompanied by a failure to record data related to the clinical manifestations of the sample, which may represent a systematic error in the study due to selection bias. In addition, it was not possible to calculate the real prevalence of DS concomitant with CH among all live births with Down syndrome who were screened by the PETN, since the information regarding this entity was not available on the specific form for neonatal screening.

In conclusion, the present study observed a high prevalence of Down syndrome among patients with predominantly subclinical CH. Congenital heart disease, jaundice, and macroglossia were the most relevant clinical findings among children with these two syndromes in conjunction. Considering that the signs and symptoms resemble those related to the natural course of DS, there may be a significant risk to the health of children with DS if CH is not found early on.

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