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Congenital hypothyroidism as a risk factor for hearing and parents' knowledge about its impact on hearing

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ABSTRACT

Aim: To evaluate the hearing of children with congenital hypothyroidism (CH) and to analyze the knowledge that parents' have on the possible auditory impacts of the disease.
Methods: A total of 263 parents/guardians were interviewed about aspects of CH and hearing. Audiological evaluation was performed on 80 participants, divided into two groups: with CH (n= 50) and without CH (n=30). Clinical and laboratory CH data were obtained from medical records, pure tone auditory thresholds and acoustic reflexes were analyzed. The auditory data was compared between groups. Student's t-test and Chi-square were used for statistical analysis at a significance level of 5% ($p \leq 0.05$).
Results: The majority (78%), of the parents were unaware that CH when not treated early is a potential risk to hearing. There was no correlation between socioeconomic class and level of information about CH and hearing ($p>0,05$; $p=0.026$). There was a statistically significant difference between the auditory tone thresholds of the groups and between the levels of intensity necessary for the triggering of the acoustic reflex. The group with CH presented the worst results ($p \leq 0.05$) and absence of acoustic reflex in a normal tympanometric condition.
Conclusions: Children with CH are more likely to develop damage to the auditory system involving retrocochlear structures when compared to healthy children, and that the disease may have been a risk factor for functional deficits without deteriorating hearing sensitivity. The possible impacts of CH on hearing, when not treated early, should be more publicized among the parents/guardians of this population.

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1. Introduction

Congenital hypothyroidism (CH) is characterized as a clinical syndrome resulting from the insufficient/absent synthesis or secretion of thyroid hormones (TH) (Grüters and Krude, 2011). Currently, it's one of the most prevalent endocrine diseases in childhood with an incidence rate between 1:2000 and 1:3000 individuals worldwide (Prezioso et al., 2018). In addition, is considered the most important cause of preventable mental retardation if early diagnosis and levothyroxine replacement ($L\text{-}T_4$) (Léger et al., 2014; American Academy of Pediatrics AAP, 2006). Hormonal dysfunction, is the result of an abnormality in the development of the thyroid gland or an error in the synthesis of THs (American Academy of Pediatrics AAP, 2006).

Guidelines recommend that neonatal screening should be performed no later than the 7th day of life, by obtaining blood

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collected on filter paper, to quantify the thyroid-stimulating hormone (TSH). The diagnosis is confirmed when there is an elevated serum TSH (>10mU/L L), accompanied or not by low levels of thyroxine or T_4 (<6 mcg/dL) (Brasil, 2001; Maciel et al., 2013). Immediately after confirming the diagnosis, treatment with L- T_4 begins and this, when started within the first two weeks of life, can normalize the levels of T_4 and TSH, preventing developmental deficits resulting from the late diagnosis (Léger et al., 2014). Studies demonstrate that good adherence and precocity at the beginning of treatment favors a good prognosis of CH (Rovet, 2014), inversely to what occurs with late start, in which the sequels are often more severe (Agrawal et al., 2015).

The triiodothyronine hormone (T_3) is essential for the maturation of complex brain function and for somatic growth (Ng et al., 2013; Krude et al., 2015). Thyroid hormones influence the process of metabolism development, growth, homeostasis and the morphophysiological maturation of central auditory pathways (Debruyne et al., 1983; Sohmer and Freeman, 1996). Therefore, CH is considered as a potential risk factor for hearing disorders (Wasniewska et al., 2002; Knipper et al., 2000). The incidence of hearing impairment in individuals with CH is uncertain, however, it can affect up to 20% of this population (Debruyne et al., 1983; Rovet et al., 1996; Hashemipour et al., 2012). Studies have demonstrated that 25% of patients with CH at the mean age of 15.4 years had mild and subclinical hearing loss even when submitted to early hormone replacement treatment (Rocco et al., 2015). They also observed a greater risk of hearing loss in young patients with CH when compared to individuals in a matched control group and without the disease.

The impacts of TH deprivation on hearing function depend on the time of onset, intensity, time of hormonal deprivation and, mainly, on the normalization of serum levels over the years, as a result of clinical monitoring and the level of adherence to treatment by parents/guardians (Bagattoli et al., 2000; Lichtenberger-Geslin et al., 2013). Parental adherence is associated with successful therapy (Bagattoli et al., 2000). Therefore, it is important to know the level of information of family members about the possible damage that CH, when not treated early, can cause in the auditory system, for efficient strategies for the prevention and promotion of hearing health, intervention and monitoring.

The hypothesis of the study was that children with CH, even if they have hearing thresholds within normal limits, may have possible subclinical hearing disorders secondary to the CH, either by intrinsic damage related to the pathophysiology, or by damage related to clinical aspects and/or hormonal follow-up. Thus, this study aimed to evaluate the hearing of children with CH compared to children without the disease, and to analyze the knowledge profile that parents and caregivers have on the possible auditory impacts of the disease, since changes in THs on metabolism can generate damage to hearing health.

2. Methods

2.1. Study design

Cross-sectional, descriptive, analytical study performed at the Neonatal Screening Reference Service (NSRS) at the state of Bahia, in Brazil, with approval by the Committee of Ethics in Research of the Federal University of Bahia (statement number 534.704) in which all participants agreed to participate by signing the Term of Free and Informed Consent Form.

2.2. Clinical data

Clinical and biochemical data were extracted from medical records. Age, time of treatment, severity of CH (total $T_4 \geq$ or <2.50 μg/dL in the neonatal screening test) and the etiology of the disease (dysgenesis or dyshormonogenesis). Regarding adherence to treatment, children were classified as "overtreated" (TSH <0.5μUI/mL) and "undertreated" (TSH > 15 μUI/mL) when they had three or more episodes of hormonal dosages in the first five years of treatment (Lichtenberger-Geslin et al., 2013), a period considered important for auditory maturation (Marti et al., 2006). This information was used to establish an association between hormonal control and the knowledge level of their caregivers. The THs measurement (TSH and Free T4) was performed on the day of the audiological evaluation and they were classified as positive for hyperthyrotropinemia when there was a slight increase in TSH levels (between 5.6 and 10 μUI/mL) under conditions of normal free T_4 (Brasil, 2012).

The eligibility criteria was: age ≥5 years; confirmed diagnosis of CH according with the practical clinical guidelines for the management of hypothyroidism (Brenta et al., 2013); positive LT_4 deprivation test after three years of age; not having other metabolic, neurological or psychiatric diseases; as well as any other form of hypothyroidism that is not congenital and is not syndromic; absence of clinical history and risk indicators for auditory deficiency, current or past infectious diseases involving the central nervous system (CNS), auditory thresholds, for pure tone, of air conduction ≤ 25dBHL and vocal within the normality standards confirmed by pure tonal audiometry (PTA) and speech thresholds; tympanometric curve of type A in the imitanciometry. The same inclusion criteria for the control, except not having a diagnosis of CH.

2.3. Characterizing the sample

The study sample consisted of 80 participants divided into two groups: (i) Patients: formed by 50 normal hearing patients, with an average age of 8,1 (±3,9) years, all with confirmed diagnosis of CH previously characterized by a larger project entitled "Screening of mutations in genes implicated in thyroid ontogenesis in patients with congenital hypothyroidism". (ii) Control group: composed of 30 individuals, relatives and/or acquaintances with an average age of 8,1 (±3,0) years, without diagnosis of CH or any other metabolic condition, confirmed by laboratory tests, normo-hearing and paired by age group. The sampling selection was non-probabilistic.

The knowledge of 263 parents/guardians of the children with CH about the possible impacts of this disease on hearing health was analyzed. Participants were parents who regularly attended medical appointments for the treatment of their children and answered a validated questionnaire (Pagnossin and Oliveira, 1998).

2.4. Hearing assessment

Prior to the audiological evaluation all the children underwent the study on evoked otoacoustic emissions which was normal.

All children with normal meatoscopy underwent tympanometry and stapedial acoustic reflex (AR) evaluation (Interacoustics®, Drejervaenget, Denmark), ANSI S3.39-1987 calibration, TDH-29 handset, with a 226 Hz probe tone to 85 dBSPL. All individuals with tympanogram type "A" were included. In the occurrence of other types of tympanometric curves, which did not demonstrate the integrity of this system, referral to the otorhinolaryngologist was performed.

Contralateral acoustic reflex thresholds were evaluated at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz separately for each ear. The evaluation was initiated at an intensity of 80 dB, and the intensity was gradually increased in steps of 5 dB to evoke and confirm the responses. The acoustic reflex (AR) threshold was defined as the

lowest stimulus intensity level of HL in dB, at which a reproducible acoustic reflex deflection (representing a minimum of 0.03-mm change in immittance) from a baseline recording could be detected in two consecutive trials. For evaluating acoustic reflex thresholds ≤100 dB HL were considered normal, whereas thresholds >100 dB HL were considered increased (Jerger et al., 1987). An acoustic reflex threshold was considered absent if reflexes were observed at a level one step above the highest level tested (i.e. if the highest level tested was 110 dB HL and absent reflex was detected at that level, a reflex was recorded at 115 dB HL).

As indicated by pure tonal audiometry (PTA) was performed to evaluate the hearing thresholds using an AD 229 clinical audiometer (Interacoustic®, Middlefart, Denmark) in a soundproof cabin and TDH-39 supraural headphones (ANSI S3.6/96: ANSI S343/92; ISSO 389/91 calibration). The frequencies of 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz were investigated, at a presumably audible intensity, around 25dBHL.They considered thresholds within the normality patterns of audiograms with air conduction values ≤ 25dBHL and bone conduction ≤15dBHL (World Heatlh Organization - WHO, 2014). In the possibility of a probable hearing loss, they classifed the audiometric alteration according to type and degree (WHO, 2014), but they only considered the cases within normality standards in this study.

2.5. Evaluation of parents/guardians knowledge

Three research protocols were applied: (i) a preliminary investigation for the presence of risk factors for hearing loss, history of other diseases and family history of hearing problems (Joint Committee of Infant Hearing, 2014); (ii) objective questions about the knowledge of hearing tests, neonatal hearing screening, the importance of early audiological diagnosis, CH and the relation between early treatment and hearing (Pagnossin and Oliveira, 1998); and (iii) evaluation of the economic classification of parents/guardians (ABEP, 2016). A “face to face” technique, in which the researcher/interviewer read the questionnaire items to the interviewee, but after necessary instructions, did not interfere in the process, was applied.

In order to observe the degree of difficulty of the subject when answering the questions, a previous study before the beginning of data collection, verified the applicability of the instrument of this study. After reviewing the inconsistencies, other study was applied, showing the absence of errors in the questionnaire, composing the sample of this research.

A total of 263 parents/guardians were interviewed and their responses to the questionnaire were scored according to their correctness and the established score range classified the knowledge level of the parents/guardians. For a score obtained between 10 and 8 points, the participant was classified as a high level of knowledge, 7 and 5 points - moderate level of knowledge, 4 and 2 points - low level of knowledge and 1 point or no score - reduced/absent degree.

The protocol to catalog the economic classification of parents/guardians was the Criteria for the Economic Classification of Brazil - CCEB (ABEP, 2016). A score is given for possession of some goods and educational level and the sum defines each class in A, B1, B2, C1, C2 and D-E.

2.6. Statistical analysis

Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS, version 21.0). The results were submitted to descriptive statistical analysis through mean, standard deviation, maximum value, minimum value, logistic regression and Spearman correlation, the latter being used to verify the existence of an association between auditory variables and clinical aspects. To verify the association between the degrees of knowledge of family members and the clinical, laboratory and treatment adherence variables, the Chi-square test was used, with a significance level of 5% ($p \leq 0.05$) in order to reject the null hypothesis, with confidence intervals built with 95% statistical confidence. Student's t-test and Chi-square were used for statistical analysis at a significance level of 5% ($p \leq 0.05$).

3. Results

The clinical and laboratory data of the group of children with CH are shown in Table 1. The female gender was predominant, and age at the neonatal screening test was above the recommended age, with an average of 85 (±39) days of life, and CH disease time of 8,1 (±3,9) years. As for the etiological diagnosis of CH, dyshormonogenesis (71%) constituted the most prevalent phenotypic form.

3.1. Children's audiological evaluation

The study sample consisted of 80 children (160 ears). The analysis of the auditory thresholds and the thresholds of the acoustic reflex of the stapedius muscle were performed considering both ears, since there was no statistically significant difference between them. The results were shown in Table 2 and Table 3.

Table 2 shows the comparison of the means of the pure tonal auditory thresholds obtained by PTA in both ears, for frequencies from 0.25 kHz to 8 kHz, between the average the groups of children with and without CH. There was a statistically significant difference between the groups for all frequencies evaluated, with the group with CH having higher thresholds. Correlations with the mean serum levels (TSH and T_4L) on the day of the hearing assessment, etiology and treatment time did not show significant statistical association strength.

The evaluation performed by immitanciometry, demonstrated in tympanometry the integrity of the tympanic-ossicular system, since all children had type A tympanometric curves. There was no statistically significant difference between the means of static compliance of the group with CH 0.64 ml (±0.32) and the group without CH 0.56 ml (±0.12); $p > 0.05$, $p = 0.274$.

Fig. 1 shows the relative frequencies (%) referring to the acoustic reflex (AR) classifications of the group with CH per ear ($n = 100$), in the frequencies of 0.5 kHz, 1 kHz, 2 kHz and 4 kHz. The data demonstrate absence of bilateral AR at 0.5 kHz ($n = 9$), 2 kHz ($n = 7$) and 4 kHz ($n = 13$). The group without CH showed no AR in one ear only in the frequencies of 2 kHz, out of the total of 60 ears assessed. As for laboratory data on the day of the audiological evaluation, the absence of acoustics reflex demonstrated an association with the 95% probability with the factor hyperthyrotropinemia (p: 0.024; PR = 0.22, CI = 0.03−1.51).

Table 3 shows the comparison between the groups regarding the levels of intensity necessary to trigger the acoustic reflex of the stapedius muscle obtained in the frequencies of 0.5 kHz−4 kHz, with contralateral stimulation. There was a statistically significant difference ($p \leq 0.05$) between the groups for frequencies of 1 kHz, 2 kHz and 4 kHz, and the group of normal-hearing children with CH required greater intensity to trigger AR.

3.2. Evaluation of parents/guardians knowledge

Two hundred sixty-three individuals with a mean age of 32 (±8.2) years, with a predominance of females (92%; $n = 242$), most of whom were mothers of the children (86, 6%; $n = 228$) were evaluated. The results regarding the questionnaire applied to parents/guardians about their knowledge about the influence of CH on

Table 1
Distribution of the absolute and relative frequency of the main clinical and laboratory data of children diagnosed with CH (n = 263).

Clinical and laboratory data	Absolute Frequency	Relative Frequency (%)
Gender		
Female	164	62,3
Male	99	37,6
Age at Neonatal Screening Test		
≤7 days	51	37,5
>7 days	85	62,5
Age at beginning of CH treatment		
≤28 days	83	58
>28 days	60	41,9
TSH- On the day of the hearing assessment**		
Adequate	56	59,5
Inappropriate	38	40,4
Treatment status		
Regular (TSH: 0,5–15 μUI/ml)	20	18,7
Hypertreated (TSH: < 0,5 μUI/ml)	40	36,3
Hipotreated (TSH: > 15 μUI/ml)	50	45
Etiology of CH		
Dysgenesis	20	28,9
Dyshormonogenesis	49	71
Time of illness/treatment CH		
≤7years	193	73,3
>7 years	70	26,4

Legend: (CH) congenital hypothyroidism; (TSH) thyroid stimulating hormone; (n) number of children's.

Table 2
Comparative analysis of the mean pure-tone auditory thresholds between groups of children with and without congenital hypothyroidism (n = 160).

Auditory Thresholds[1]	0.25 kHz	0.5 kHz	1 kHz	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz
Children with CH (n = 100)								
Minimum	5	5	0	5	0	0	0	0
Maximum	20	15	15	20	20	20	20	20
Mean	13	10.9	8.9	9.3	9.3	10.7	11.1	10.9
SD	4.84	3.45	3.68	3.91	4.40	5.05	3.95	4.0
Children without CH (n = 60)								
Minimum	5	0	−5	−5	−5	0	0	0
Maximum	15	10	10	10	10	10	10	10
Mean	7.50	6.17	4.0	4.17	4.50	5.67	6.33	4.33
SD	3.15	3.13	3.32	3.24	4.22	3.14	2.60	3.14
*p[a] value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Legend: [1]dB HL - Decibel hearing level; kHz-frequencies in kilohertz; n - number of ears; CH - children with congenital hypothyroidism; SD – Standard deviation; p, statistically significant difference for all frequencies between groups; *, Student's t-test applied (p ≤ 0.05).

Table 3
Comparison between the groups regarding the levels of intensity necessary to trigger the contralateral acoustic reflex.

	The levels of intensity acoustic reflex				
Frequency	Groups (n)	Min/Max	Mean[1]	SD	*p-values
0.5 kHz	CH (91)	70/105	82,00	14,46	0,37
	CG (60)	70/85	78,83	17,05	
1 kHz	CH (100)	70/95	81,70	11,96	0,00*
	CG (60)	70/85	78.83	17,05	
2 kHz	CH (93)	70/110	86,40	8,75	0,03*
	CG (58)	70/100	81,67	10,02	
4 kHz	CH (87)	70/105	85,50	14,99	0,05*
	CG (60)	70/85	78,33	17,43	

Note: * Student t-test applied (statistically significant p ≤ 0,05). Legend: CH – children with congenital hypothyroidism; CG – group control/children without congenital hypothyroidism, Hz-Hertz; n - number of ears; SD - standard deviation; Min - Minimum; Máx – Maximum; [1]- Decibel values of hearing level.

the development of hearing function are described in Table 4.

Regarding the degree of knowledge about CH and hearing, most interviewees (n = 206) reported not knowing that the disease, when untreated, can affect the development of auditory function and according to the score, eighty-nine (33%) participants presented minimal knowledge. Of the total of 263 parents interviewed, one hundred sixty-four (62%) reported knowledge about an exam that can assess hearing and, of these, one hundred seventeen (54%) were able to specify it.

Regarding the social class the educational level of the guardian and his/her access to public services, most of the sample (60.08%; n = 158) belonged to classes C1 and C2. Therefore, when exposed to the "CCEB" factor, the association with a 95% probability (p = 0.026; PR = 1.06; CI = 0.51–6.05) demonstrated the existence of parents/

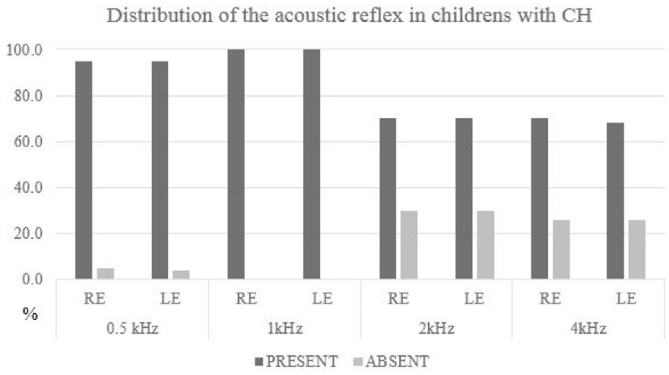

Fig. 1. Distribution of the acoustic reflex, per ear, at frequencies of 0.5 kHz, 1 kHz, 2 kHz and 4 kHz for the group with congenital hypothyroidism (CH) (n = 100).

Table 4
Distribution of responses from parents and guardians interviewed about congenital hypothyroidism and hearing.

INTERVIEW	AF	RF (%)
Do you know any exam\test that can evaluate the hearing?		
Yes	164	62,3%
No	99	37,6%
If you answer YES, check below the one or more options:*		
None	158	55,5%
OAE test	96	36,5%
Audiometry	17	6,4%
ABR	1	0,3%
OAE, ABR, Audiometry	3	1.1%
Do you know the hearing screening test?		
Yes	96	36,5%
No	167	63,5%
If you answer YES, check below the one or more options:*		
None	156	59,3%
Pediatrician	66	25,1%
Endocrinologist	3	1,1%
Nurse	24	9,1%
Speech-Language Pathologist	7	2,6%
Clínical	5	1,9%
Health Center/information stand	2	0,7%
Do you know the importance of early audiological (diagnostic) examination for language development?		
Yes	145	55,1%
No	118	44,8%
Have you received guidance and explanations about Congenital Hypothyroidism?		
Yes	34	12,9%
No	229	87,0%
If you answer YES, check below the one or more options:*		
None	38	14,4%
Endocrinologist	123	46,7%
Pediatrician and/or Social Worker	84	31,9%
Nurse	4	1,5%
Friends/Family/Others	14	5,3%
For you, Congenital Hypothyroidism, when untreated, can affect the development of hearing?		
Yes	57	21,6%
No	206	78,3%
For you, Congenital Hypothyroidism, when untreated, can affect the development of language, oral and written communication?		
Yes	35	13,3%
No	228	86,6%
Responsible' knowledge level		
High	9	3,4%
Moderate	55	20,9%
Low	110	41,8%
Reduced/Null	89	33,8%

Note: *A responsible may have said one or more answers in this regard. Legend: OAE- Otoacoustic emissions, ABR- Evoked auditory brainstem response.

guardians of all economic classes with minimal information about the CH interface and listening. Class - C2 was the only class present in all degrees of knowledge.

The correlation between the degree of knowledge of family members in the CH scope and hearing health with the variable "TSH serum level classification: adequate or inadequate", on the day of the audiological evaluation demonstrated a higher prevalence of guardians with a lower degree of knowledge for the group of children with inadequate serum levels (PR = 1.20; p = 0.39), when compared to children with adequate TSH.

Fig. 2 illustrates the linear regression analysis on the degree of knowledge of the guardians versus the TSH values (μUI/mL) confirming the hypothesis that the higher their level of knowledge, the lower the serum TSH levels in children with CH undergoing Levothyroxine replacement therapy.

Table 5 shows the analysis of the degree of knowledge of parents/guardians and the prevalence ratio with the clinical, phenotypic and laboratory characteristics of children with CH. One found that the established degrees of knowledge were associated with a probability of 95%, with the variable "age of beginning of treatment" (p = 0.0002; PR = 0.71; CI = 0.48–3.00) and with the variable "treatment time" for CH (p = 0.049; PR = 1.43; CI = 0.92–6.49).

4. Discussion

The hypothesis raised in the present study was that individuals affected by CH, even in hormone replacement treatment and in the presence of tonal auditory thresholds within normal standards, may present subclinical auditory disorders, which can be evidenced by the symptomatologic picture, as well as through audiological exams. Thus, the primary goal of this study was to investigate evidence of subclinical hearing disorders in individuals affected by CH.

The audiological data of children with CH were compared to the findings of children without the disease, and it was possible to notice a statistically significant difference between the tonal auditory thresholds of the groups, even when both presented values within the normal range, not showing hearing loss. Regarding this difference, the group with CH presented higher values of tonal thresholds, and this finding may assuming a possible association with thyroid hormone deficits over the years, which possibly had repercussions on the neurophysiology of the auditory pathways of these children, due to the limited quality and adherence to the CH treatment, with 46% of these children having hypotreatment, that is, three or more episodes of TSH >15μUI/mL, in the first five years of treatment with levothyroxine replacement. Recent studies suggest that CH, when untreated or undertreated, can lead to serious behavioral problems and that hypertreatment of CH seems to be more associated with attention problems (Bongers-Schokking et al., 2018).

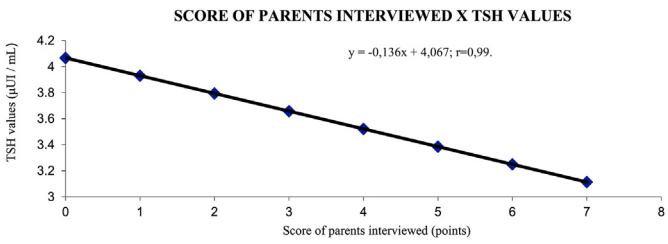

Fig. 2. Linear regression graph of the score of the interviewed parents versus TSH values (μUI/mL) of children with congenital hypothyroidism collected on the day of the questionnaire application (n = 263).

Table 5
Description of the clinical-laboratory variables of the children with congenital hypothyroidism, prevalence ratios (PR) and respective confidence intervals (95% CI) for the parents' knowledge levels (n = 263).

	DEGREE OF KNOWLEDGE OF PARENTS'											
Clinical and laboratory data	Reduced			Low			Moderate			High		
	%	PR	(95% CI)	%	PR	(95% CI)	%	PR	(95% CI)	%	PR	(95% CI)
Relationship												
Mother	30,8	1,00		35,36	1,00		17,11	1,00		3,42	1,00	
Father	1,1	0,44 (0,16-4,47)		3,80	1,29 (0,82-5,72)		2,28	1,60 (0,79-10,09)		0,00		
Brother/Sister	0,0			1,14	2,45 (2,10−13,57)		0,00			0,00		
Grandfather/Grandmother	1,52	1,13 (0,52-6,72)		0,76	0,49 (0,14-5,70)		1,52	2,03 (0,91-16,94)		0,00		
Uncle/Aunt	0,38	0,94 (0,19-12,78)		0,76	1,63 (0,72-11,59)		0,00			0,00		
p-value	*0,312*			*0,095*			*0,259*			*0,838*		
CEEB												
A1	0,38	4,10 (2,82−87,10)		0,00			0,00			0,00		
A2	1,14	4,10 (2,82−87,10)		0,00			0,00			0,00		
B1	1,90	1,28 (0,57-8,13)		2,66	1,02 (0,55-5,07)		1,52	0,86 (0,35-5,87)		0,00		
B2	9,13	1,69 (1,05−8,81)		9,13	0,96 (0,65-3,87)		3,04	0,47 (0,23-3,31)		0,76	0,99 (0,17-15,59)	
C1	10,65	1,59 (0,99-7,88)		11,79	1,00 (0,70-3,90)		3,80	0,48 (0,25-3,13)		1,14	1,19 (0,25-15,86)	
C2	7,98	1,00		14,07	1,00		9,51	1,00		1,14	1,00	
D/E	2,66	1,06 (0,51-6,05)		4,18	0,95 (0,57-4,32)		3,04	1,02 (0,52-5,41)		0,38	1,06 (0,12−26,66)	
p-value	*0,026***			*0,807*			*0,131*			*0,991*		
Neo screening age												
>7 days*	3,80	1,00		9,89	1,00		4,56	1,00		1,14	1,00	
≤7 days	9,89	1,56 (0,82-9,04)		13,69	0,83 (0,58-3,31)		7,22	0,95 (0,50-4,87)		1,52	0,80 (0,19-9,55)	
p-value	*0,159*			*0,328*			*0,874*			*0,763*		
Age - Beginning of CH treatment												
>28 days*	8,37%	1,00		16,35	1,00		5,70	1,00		1,14	1,00	
≤28 days	6,84%	1,13 (0,67-5,24)		8,37	0,71 (0,48-3,00)		6,46	1,57 (0,85-8,82)		1,14	1,38 (0,29-19,08)	
p-value	*0,645*			*0,00002***			*0,146*			*0,683*		
Time of illness/treatment CH												
>7 years	4,84	1,00		11,41	1,00		9,22	1,00		1,14	1,00	
≤7 years	30,00	1,43 (0,92-6,49)		29,42	0,97 (0,70-3,62)		14,69	0,69 (0,42-3,23)		2,28	0,73 (0,19-8,04)	
p-value	*0,049***				*0,838*		*0,134*			*0,642*		
Treatment condition												
Regular	5,70	1,00		8,37	1,00		3,80	1,00		1,14	1,00	
Hypertreated	1,52	0,67 (0,25-5,16)		4,18	1,25 (0,75-5,78)		1,52	1,00 (0,35-7,67)		0,38	0,83 (0,09−20,83)	
Hypotrated	5,32	0,35 (0,19-2,58)		5,70	0,38 (0,23-2,42)		3,42	0,23 (0,10-2,78)		0,76	0,05 (0,01−5,99)	
p-value	*0,489*			*0,434*			*0,953*			*0,973*		
Etiology												
Non-Dysgenesis	3,80	1,00		9,13	1,00		4,94	1,00		0,76%	1,00	
Dysgenesis	3,04	1,96 (0,91-15,34)		2,66	0,71 (0,37-3,96)		1,90	0,94 (0,39-6,25)		0,00%		
p-value	*0,092*			*0,289*			*0,895*			*0,359*		

Note: *Age limit recommended by the Ministry of Health, by the Unique Health System, as appropriate for the beginning of the treatment of congenital hypothyroidism. **p ≤ 0,05 Chi-square test applied. Legend: CCEB: Brazil-ABEP Economic Classification Criteria; Neo = Neonatal, PR = Prevalence ratio; CI = confidence interval; CH- congenital hypothyroidism.

Although it was not possible to associate hearing disorders with the etiology of the CH some studies correlate this variable with the increased risk for hearing problems. Authors report that patients with agenesis and *in situ* gland are associated with a higher frequency of hearing loss than those with ectopic gland (Lichtenberger-Geslin et al., 2013). However, dyshormonogenesis is associated with greater risk and severity of hearing loss (Hashemipour et al., 2012). Recent studies also relate hearing impairment to certain genetic mutations, such as *TPO* and *DUOX2* among patients with CH. Mutations in the gene encoding pendrin (*SLC26A4*), have been associated with Pendred syndrome an autosomal recessive disease characterized by sensorineural hearing loss, goiter and iodide organification defects. Hearing loss is associated with abnormalities of the inner ear, from isolated dilation of the vestibular aqueduct to typical cochlear dysplasia (Johnson et al., 2007). However, there were no such cases in this study.

Regarding the auditory thresholds of the sample, although within normal standards, the group with CH presented higher values when compared to the group without CH. One knows that THs act in the body in a systemic way, influencing the production of myelin and determining the level of lipid in the central nervous system, whereas T4 acts as a neurotransmitter (Sohmer and Freeman, 1996; Ng et al., 2013). Thus, the physiology of the disease could answer about the related findings due to a possible influence of these factors in the central auditory pathways of the group with CH, since all children had integrity of the cochlear amplifier through the presence of otoemissions and the threshold tonal audiometry is a test that evaluates the peripheral portion and central auditory system, suggesting possible hypotheses of neurological dysfunction in the auditory pathways. Thus, children with CH could be more susceptible to the development of subclinical hearing disorders when compared to healthy children.

Although results of hearing in patients with CH undergoing levothyroxine treatment are divergent (Hébert et al., 1986; Heyerdahl, and Oerbeck, 2003), it appears that individuals screened and treated early may have subclinical abnormalities or even mild hearing loss (Lichtenberger-Geslin et al., 2013; Agrawal et al., 2015), and that the risk of hearing loss would be higher in young patients with CH when compared to healthy young people, partially agreeing with the findings of the present study, in which there was no hearing loss at this time, but children with CH seem to be more susceptible to a dysfunction when compared to healthy children (Rocco et al., 2015). How the disease has long-term or even permanent treatment, in the course of time, the likelihood of not following medical guidelines increases. For this reason, professionals who monitor the global and audiological development of these children have an important role in the process of guiding and monitoring the knowledge of their parents/guardians, as well as in the auditory signs and symptoms.

Acoustic reflex that is, the contraction of the stapedius muscle when stimulated by high intensity sounds (Camboim et al., 2012) as a protection mechanism against strong intensity acoustic stimuli, has been considered as an important diagnostic tool in the clinical evaluation of auditory pathways at the level of the peripheral and central nervous system (Northern et al., 1989; Carvallo, 1996). The structures involved in this reflex arc, also play important roles in auditory skills related to auditory processing. In recent studies, one found a close relation between auditory processing disorder and changes in acoustic reflex (whether due to absent reflexes and/or thresholds present, but with levels of sensation outside normal limits) in ears that do not show signs of tympanic-ossicular impairment (Marotta et al., 2002; Saxena et al., 2017).

The findings of this research show that the average level of intensity to trigger the acoustic reflex of the stapedius muscle was within the normality standards adopted. However, in the evaluation between the sample groups, the data demonstrate that some children exposed to CH significantly presented – in the frequencies from 1 kHz to 4 kHz, – intensity levels higher than 100dBHL, not expected for individuals with hearing thresholds within the normal range. Besides that children in the group exposed to CH presented absence of acoustic reflex at the maximum level of presentation of the stimulus. Therefore, these children could present failures in certain auditory abilities that are recruited by the same structures participating in the reflex arch of the stapedius muscle, such as the cochlear nucleus and the superior olivary complex (Carvallo, 1996; Saxena et al., 2017). The explanation for these findings may be related to the condition of CH – a systemic disease – that consequently have influenced neurogenesis in the neonatal period and the maturation of the auditory nervous system in the first five years of life, even with levothyroxine replacement over the period.

It is known that both deficiency and excess of thyroid hormone can induce biochemical and morphological changes in the central nervous system, which, due to the greater number of clinical symptoms observed, seems to be more sensitive to disorders that are associated with hormonal deficit (Marti et al., 2006; Bongers-Schokking et al., 2018; Agrawal et al., 2015). Thus, one believed that in CH, hearing impairment might preferentially affect the central auditory nervous system. The reason for the increased acoustic reflex sensation level, or even the absence of this sensation in conditions of intact middle ear and normal tonal hearing thresholds with the presence of otoacoustic emissions, suggest signs of retrocochlear changes. The importance of early treatment of CH is highlighted for benefits not only to hearing acuity, but also to other subclinical hearing disorders (Hébert et al., 1986; Heyerdahl and Oerbeck., 2003; Andrade et al., 2019).

The main path to health and prevention of deleterious risks that congenital hypothyroidism (CH) can cause when not diagnosed early and/or regularized longitudinally is counselling to the guardians of this population. Children with CH need their caregiver to monitor clinical consultations, observe signs and symptoms and an adequate administration of the prescribed drugs (Gauchard et al., 2004; Léger et al., 2014). According to the literature, the prognosis depends on the start of treatment, the degree of hypothyroidism and maintenance of hormonal levels within the normal patterns (Heyerdahl, and Oerbeck, 2003; Maciel et al., 2013; AAP, 2016).

In this study, most children with CH had adequate serum TSH levels, on the day of the audiological evaluation. Administration of levothyroxine was adequate. The correlation between the degree of knowledge about the disease and serum TSH levels during treatment (Fig. 2) shows that the greater the degree of knowledge of their parents/guardians, the lower the serum TSH levels were observed. This data is discussed in the literature by authors who report difficulty in normalizing hormonal levels longitudinally, even with a low-cost drugs of easy administration (Bagattoli et al., 2000; Gauchard et al., 2004) while other researchers report that adherence is more effective when family members have a good understanding of the benefits of proper treatment (Léger et al., 2015; Bongers-Schokking et al., 2018).

Most parents/guardians, 41%, of children with CH had minimal knowledge about the disease, while 78% of the interviewees reported not knowing that the disease, when untreated, may affect the development of hearing. The data corroborates with publications that emphasize the need for longitudinal guidance regarding neonatal screening and early treatment of CH (Maciel et al., 2013; Arduini et al., 2017), which according to authors, still seems to be superficial and would reflect the healthcare team performance.

The analyzes showed a correlation between the lowest level of knowledge of the interviewees and the age of beginning the treatment of CH above the recommended level. These data are observed in similar studies, reflecting challenging findings to public health policies (Krude et al., 2015; Arduini et al., 2017). In CH, the production or action of thyroid hormones has been affected since the neonatal period under generalized slowing of metabolic processes. The delay in early detection of CH requires attention because, in severe cases of the disease, when not diagnosed and treated in time, they present damage to the central nervous system (Rovet, 2014), impairing the auditory nervous system (Sohmer and Freeman, 1996; Knipper et al., 2000; Ng et al., 2013).

The authors exposed data about acoustic reflex in children with CH, which have not yet been clearly discussed in literature and which may be related to the dysfunctions of auditory processing in this population. The findings of this study suggest that damage to the auditory nervous system of children with CH may be present without deteriorating hearing sensitivity. Although there is not enough evidence, the difference between the acoustic reflex thresholds between children with CH and healthy children, may be a precursor finding on the possible signs of retrocochlear involvement.

Authors (Andrade et al., 2019) have ratified the existence of subclinical auditory findings in individuals with HC, and that these are fundamental in the early targeting of linguistic and behavioral assessments of children. Therefore, the triad is necessary: early diagnosis of CH, regular monitoring of clinical conditions and health promotion strategies to improve not only treatment adherence but the prognosis of long-term hearing disorders (Léger et al., 2014, 2015).

We expect that this study will be valuable in the discussion of inclusion of CH as a risk indicator for hearing loss in neonatal hearing screening programs, as well as the audiological monitoring of this population as part of their clinical routine, according to the guidelines of Joint Committee of Infant Hearing (2019), in order to

assess the longitudinal repercussions of this disease on hearing skills. However, the authors' objective was to contribute by using audiological tests accessible to professionals in public hearing health services.

A future study should propose a research on acoustic reflex and auditory processing in children with CH, in order to truly confirm these connections and discover relevant evidences to the clinical contribution related to thyroid ontogeny, to better corroborate the data found here and reduce the impacts of hormonal deficiency on the development of subclinical findings.

5. Conclusions

The findings presented in this study suggest that children with CH are more likely to develop damage to the auditory system involving retrocochlear structures when compared to healthy children, and that the disease may have been a risk factor for functional deficits without deteriorating hearing sensitivity. The possible impacts of CH on hearing, when not treated early, should be more publicized among the parents/guardians of this population.

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Contribution of each author

The corresponding author, Hélida Braga, was responsible for the elaboration of the initial idea and the collection of data participated in the writing of the text and data analysis. The other co-authors carried out the standardization and the final corrections of the article.

Legend: n- number of ears; RE- right ear; LE - left ear; kHz - kilohertz; % - percentual; CH - children with congenital hypothyroidism.

Legend: n- number of parents interviewed and children with congenital hypothyroidism, TSH - thyroid stimulating hormone.

Declaration of competing interest

We also declare that we have no conflict of interest with the topic addressed.

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