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Artigo Original

Phonological acquisition in children with early-treated congenital hypothyroidism: association with clinical and laboratory parameters

Aquisição fonológica em crianças com hipotireoidismo congênito precocemente tratado: associação com dados clínicos e laboratoriais

Ana Paula Dassie-Leite[1,2]
Mara Behlau[3,4]
Suzana Nesi-França[2,5]
Monica Nunes Lima[2]
Luiz de Lacerda[2,5]

Keywords

Hypothyroidism
Congenital Hypothyroidism
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ABSTRACT

Purpose: To evaluate the phonological characteristics of children with congenital hypothyroidism (CH). **Methods:** Observational, analytical, cross-sectional, ambispective study including prepubertal children with CH (*n*=100; study group, SG) and controls without CH (*n*=100; control group, CG). Assessments included a speech language pathology interview, the phonological evaluation of the ABFW Child Language Test, medical data, and neuropsychological tests in the first three years of life. **Results:** On treatment onset of the SG, the median chronological age of the participants was 18.0 days and 48.4% had total T4 <2.5 µg/dL (31.75 nmol/L). At the age of 7 years, children in the SG had higher rates of consonant cluster simplification and lower rates of complete phonological system compared to those in the CG. On analysis of combined age groups (4+5 and 6+7 years), the CG had a higher frequency of complete acquisition versus the SG. On multivariate analysis, thyroid agenesis, abnormal scores on the Clinical Linguistic and Auditory Milestone Scale and developmental quotient tests were associated with the occurrence of phonological disorders. **Conclusion**: Children with CH present delay in phonological acquisition, despite early diagnosis and adequate treatment, especially between the ages of 6–7 years. The etiology of CH and the results of neuropsychological tests in the first years of life seem to be related to this delay.

Descritores

Hipotireoidismo
Hipotireoidismo Congênito
Criança
Fala
Distúrbios da Fala

RESUMO

Objetivo: Avaliar as características fonológicas de crianças com hipotireoidismo congênito (HC). **Método:** Estudo observacional, analítico, transversal e ambispectivo que incluiu crianças pré-púberes com HC (n = 100, Grupo de Estudo, GE) e um grupo controle de crianças pré-púberes sem HC (n = 100, Grupo Controle, GC). As avaliações incluíram uma entrevista fonoaudiológica, avaliação fonológica por meio do teste de linguagem infantil ABFW, e coleta de dados nos prontuários referentes às avaliações médicas e testes neuropsicológicos realizados nos três primeiros anos de vida. **Resultados:** Quanto ao início do tratamento no GE, a idade cronológica mediana dos participantes foi de 18,0 dias e 48,4% apresentaram T4 total <2,5 µg / dL (31,75 nmol / L). Na comparação da avaliação fonológica por idade, aos 7 anos as crianças no GE tiveram maior ocorrência de simplificação de encontros consonantais e menor ocorrência de sistema fonológico completo quando comparadas às crianças do GC. Na análise de grupos etários combinados (4 + 5 e 6 + 7 anos), observou-se que o GC teve aquisição completa do sistema fonológico mais precocemente. Na análise multivariada, agenesia da tireoide, resultados alterados nos testes Clinical Linguistic and Auditory Milestone Scale (CLAMS) e Developmental Quotient Tests (CDC) foram associados à ocorrência de desvios fonológicos. **Conclusão:** Crianças com HC apresentam atraso na aquisição fonológica, mesmo com diagnóstico precoce e tratamento adequado, especialmente entre as idades de 6-7 anos. A etiologia do HC, bem como os resultados obtidos nos testes neuropsicológicos nos primeiros anos de vida, parecem ter relação com este atraso.

Correspondence address:
Ana Paula Dassie-Leite
Departamento de Fonoaudiologia, Universidade Estadual do Centro-Oeste – UNICENTRO
Rodovia PR 156, Km 07, Riozinho, Irati (PR), Brasil, CEP: 84500-000.
E-mail: pauladassie@hotmail.com

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Study conducted at Universidade Federal do Paraná – UFPR – Curitiba (PR), Brasil.

[1] Departamento de Fonoaudiologia, Universidade Estadual do Centro-Oeste – UNICENTRO - Irati (PR), Brasil.

[2] Programa de Pós-graduação em Saúde da Criança e do Adolescente, Universidade Federal do Paraná – UFPR - Curitiba (PR), Brasil.

[3] Programa de Pós-graduação em Distúrbios da Comunicação, Universidade Federal de São Paulo – UNIFESP - São Paulo (SP), Brasil.

[4] Centro de Estudos da Voz – CEV - São Paulo (SP), Brasil.

[5] Unidade de Endocrinologia Pediátrica, Departamento de Pediatria, Universidade Federal do Paraná – UFPR - Curitiba (PR), Brasil.

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INTRODUCTION

Congenital hypothyroidism (CH) is the second most common chronic endocrine disease in children[1], affecting an estimated one out of 2,000 to 4,000 live births[2]. With the advancement of programs of neonatal screening (PNS), diagnosis of CH is established earlier and its treatment is initiated during the first few days of life, minimizing physical and mental damage to the child[3]. However, during intrauterine life children still undergo a phase of hormonal deprivation. Considering that thyroid hormones are fundamental for brain development (neuronal migration, formation of axons and dendrites, and myelination), the child, despite early treatment, may present small deficits associated with impaired neuropsychomotor development[4-7]. These problems include, among others, language and motor skills disabilities, reduced intelligence and learning problems[8-10]. As for the phonological development, impairments have been reported at ages 3, 5 and 7 years[11]. However, the occurrence of these impairments has not yet been compared in children with and without CH.

Early diagnosis of phonological impairment in children is fundamental to prevent disabilities that may interfere with social and academic activities, and ultimately with their quality of life as adults[12]. Therefore, the objective of this study was to evaluate the phonological acquisition in children with early-treated congenital hypothyroidism, comparing them with those without the disease, and to associate phonological findings with clinical and laboratory parameters related to the disease.

METHODS

The study was approved by the Research Ethics Committee of the *Hospital das Clínicas* of the Federal University of Paraná, under the number 2179.073/2010-03. This was an observational, analytical, cross-sectional, ambispective study that included 200 prepubertal children (according to Tanner stage), aged between 3 and 12 years: 100 children with CH (study group, SG), recruited from the outpatient clinic of home institution, and 100 children without the disease (control group, CG), recruited from the dermatology, childcare and general pediatric endocrinology clinics, as well as daycare, all associated with the home institution. Participation in this study was voluntary and confidential after signing of an informed consent by parents/guardians.

We adopted the following parameters as exclusion criteria in both groups: lack of cooperation during the evaluation; diagnosis or suspicion of mental disability of any degree, history of impairment in neurological and psychological development; neurological diseases or genetic syndromes; history of pre-, peri-, or post-natal complications; facial features or family information suggestive of oral breathing or myofunctional impairment; anterior or short lingual frenulum; hearing complaints and history of speech and hearing monitoring for speech disorder. We also excluded from the CG those children with any other diseases or suspected endocrinological abnormalities, and from the SG those that the diagnosis of CH was not established during neonatal screening or who did not appropriately adhere to treatment. For the purpose of convenience, data were collected on the day of the child's appointment at the Clinical Hospital.

In addition to the data identifying each child, we asked the parents/guardians about possible phonological complaints. Following that, we administered the phonological assessment part of the ABFW Child Language Test[13]. This part of the test can be administered to children between the ages 3 to 12 years to assess the phonetic inventory and to identify and categorize the phonological processes presented by the child. It uses phonetically balanced naming and repetition tests. After checking all the criteria proposed by the instrument, the productive processes were identified and tabulated. Children without productive phonological process were characterized as presenting full acquisition of the phonological system, whereas those who presented one or more abnormal productive processes in any of the tests were characterized as having phonological deviation.

We collected medical information about:

- The age (in days) at onset of CH treatment;
- Etiology of CH: thyroid agenesis (absence of thyroid gland), thyroid hypoplasia (defects in thyroid gland development), ectopy (thyroid gland located in other place than the normal position anterior to the laryngeal cartilages) or dyshormonogenesis (defects in the proteins involved in thyroid hormone synthesis)[14];
- Severity of the disease at diagnosis (total T_4 > or < 2.5 µg/dL [31.75 nmol/L]) – lower level of total T_4 can cause higher severity of fetal hypothyroidism and, consequently, higher risks to development[14].
- Quality of the treatment during the first three years of life (percentage of abnormal total T4, free T4 and TSH), using the normality values established by consensus in pediatric area[15].
- Thyroid function tests on the day of the phonological assessment, using the normality values established by the laboratory of *Hospital das Clínicas* - Federal University of Paraná (UFPR)[16].

Finally, we collected data about neuropsychological tests which were performed at the unit[17] and collected by a psychologist. At the ages of 12, 24 and 36 months, patients are evaluated with the Cognitive Adaptive Test (CAT) / Clinical Linguistic and Auditory Milestone Scale (CLAMS, CAT/CLAMS), which together generate a development quotient (DQ)[17]. In this study, CAT, CLAMS and DQ were considered normal when the evaluations at all time points yielded results equal to or greater than 80 points, and abnormal when the scores were lower than 80 points in one or more evaluations. We included in this analysis only children who succeeded on at least two of the three evaluations. We sought to observe whether children with one or more abnormal results would present more impairments related to phonological development.

For specific analysis concerning the acquisition of the phonological system (complete or incomplete), the groups were matched by gender and age, which generated a total of 64 pairs, i.e., 128 children.

The data were tabulated and analyzed statistically. The differences between continuous variables of normal distribution were estimated by the parametric tests Student's t and ANOVA. For variables with asymmetric distribution, we used the nonparametric tests of Mann-Whitney and Kruskal-Wallis ANOVA. To analyze categorical variables, we used Fisher's exact test and Pearson's chi-square test with Yates's correction when necessary. A multivariate logistic regression model was applied to estimate independent variables for the outcome of phonological deviation. For all analysis, we adopted a significance level of 0.05 or 95%.

RESULTS

CG was composed by 100 children (36 of female gender and 64 of male gender) and the SG also was composed by 100 children (65 of female gender and 35 of male gender). Therefore, there were more girls in the SG (n = 64) and boys in the CG (n = 65), with a significant difference between the groups ($p < 0.001$). Regarding age, there was no difference in the average results between the groups (CG = 7.3 ± 2.3 years; SG = 7.3 years ± 2.2 years; $p = 0.91$). As for education level, there was a difference between the groups, with the SG presenting a larger number of preschool children who were still not attending school (SG, n = 8; CG, n = 1).

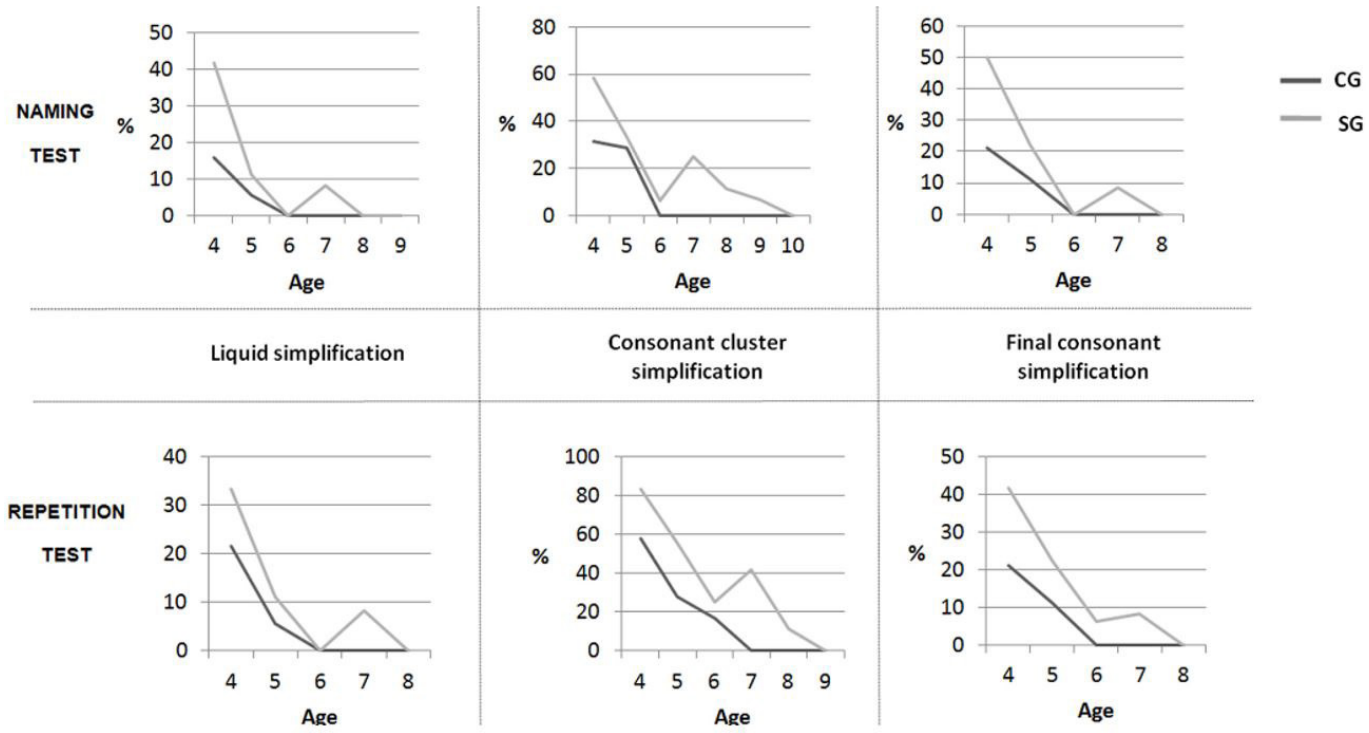
At the time of the phonological evaluation, only one child in the SG (1.0%) showed abnormal total T4, none presented abnormal free T4, and 18 (18.0%) had abnormal TSH values: 10 with values between 6.3 µU/mL [6.3 mU/L] and 12.0 µU/mL [12.0 mU/L]; five between 12.0 µU/mL [12.0 mU/L] and 30.0 µU/mL [30 mU/L]; and three above 30.0 µU/mL [30.0 mU/L].

In their medical history, 10 (10.0%) parents/guardians in the CG and 21 (21.0%) in the SG reported phonological complaints, with a significant difference between the groups ($p = 0.05$). The occurrence of phonological deviation was similar between genders, considering all studied participants (n = 200). Overall, 16.6% of the boys (16/99) and 18.8% of the girls (18/101) presented phonological deviation ($p = 0.90$).

We also analyzed the occurrence of productive phonological processes according to the child's age, comparing the CG and the SG. During the naming test, there was no difference between the groups when each of the ages were compared individually ($p > 0.05$) (Figure 1), though, at the age of 7 years, there was a trend towards a difference ($p = 0.06$). On the repetition test, there was a difference between the groups in the comparison of the process "consonant cluster simplification" at the age of 7 years ($p = 0.006$), with the SG presenting a larger number of occurrences (Figure 1).

The analysis of the variables "complete or incomplete phonological system", conducted with the groups matched for gender and age (n = 128), indicated that children in the CG had a higher frequency of complete systems at the age of 7 years. When the ages 4 + 5 years and 6 + 7 years were compared between the groups, there was also a difference indicating that the acquisition in the CG occurred earlier (Table 1).

The age at treatment start was related to the presence or absence of phonological deviation and there was no statistically significant difference ($p = 0.21$ and $p = 0.73$, respectively).



Note: Fisher's exact test for comparison of groups by age: $p > 0.05$ for all comparisons. Number of children per age group: 4 years (n = 31), 5 years (n = 27), 6 years (n = 22), 7 years (n = 29), 8 years (n = 26)

Figure 1. Occurrence of productive phonological processes according to the child's age, comparing the CG and the SG

Regarding the etiology, children with thyroid agenesis (n = 9) had a higher occurrence of deviation when compared with children with other etiologies (hypoplasia n = 12; ectopy n = 12; dyshormonogenesis n = 37) – p = 0.00; the same occurred with children with abnormalities in the CLAMS and DQ tests (Table 2).

As for the association between the severity of the hypothyroidism at the moment of diagnosis (pretreatment), children with total T4 values < 2.5 µg/dL (31.75 nmol/L, n = 44) and > 2.5 µg/dL (31.75 nmol/L, n = 47) showed comparable phonological deviations (6.59% and 13.19%, respectively; p = 0.19). Regarding the severity of the hypothyroidism at the moment of diagnosis, collected from 90 children in the SG, 46 (48.4%) had T4 < 2.5µg/Dl and 49 (51.6%) had T4 < 2.5µg/Dl.

There was no association between the variable percentage of abnormal values of total T4, free T4 and TSH for the first three years of life and the occurrence of phonological deviation (p > 0.05). A speech complaint reported by parents/guardians was associated with the presence or absence of phonological deviation in the SG (p < 0.01).

The presence or absence of phonological deviation was selected as a dependent variable for multivariate analysis and compared with data related to medical and therapeutic evaluation, according to the relevance for the analysis. The model applied was logistic regression. First, the variable referring to the presence or absence of phonological disorders was associated with age at the beginning of treatment, etiology of CH, initial levels of total T4, free T4 and TSH, and percentages of abnormal total T4, free T4 and TSH during the first three years of life. We observed that none of the variables was independently predictive of phonological deviation. Phonological deviation as a dependent variable was also associated with results of the neuropsychological tests performed at the ages of 12, 24 and 36 months, with speech problems reported by guardians/parents and with the beginning of the child's oral period. We observed that children who presented abnormal CLAMS during the first three years of life and those whose parents/guardians reported speech complaints had a greater chance of presenting phonological deviation (odds ratio 13.4 and 10.8, respectively) (Table 3).

Table 1. Comparison between the CG and SG regarding complete or incomplete phonological system acquisition according to age*

Age	CG				SG				p
	Complete		Incomplete		Complete		Incomplete		
	N	%	N	%	n	%	n	%	
4.0 to 4.11	1	14.3	6	85.7	1	14.3	6	85.7	1
5.0 to 5.11	4	44.4	5	55.6	4	44.4	5	55.6	1
6.0 to 6.11	6	100	0	0	3	50	3	50	0.18
7.0 to 7.11	10	100	0	0	7	63.3	4	36.4	0.09
8.0 to 8.11	8	100	0	0	7	87.5	1	12.5	1
9.0 to 9.11	9	90	1	11.1	10	100	0	0	1
10.0 to 10.11	7	100	0	0	7	100	0	0	

*Fisher's exact test; 4 years (n = 14), 5 years (n = 18), 6 years (n = 12), 7 years (n = 22), 8 years (n = 16), 9 years (n = 20), 10 years (n = 14)
P = 0.02 for the comparison between ages 4 and 5 years versus 6 and 7 years in the CG and SG

Table 2. Association between the presence of phonological deviation and the variables of CH etiology and results of neuropsychological tests

Etiology of CH	Phonological Deviation			
	No		Yes	
	n	%	n	%
Agenesis (n=9)	4	44.4	5	55.6
Hypoplasia (n=12)	11	91.7	1	8.3
Ectopy (n=32)	30	93.7	2	6.3
Dyshormonogenesis (n=37)	27	73	10	27
p*	0.004			
Neuropsychological Test	**Phonological Deviation**			
	No		Yes	
	n	%	n	%
Normal CAT	51	82.3	11	17.7
Abnormal CAT	6	60	4	40
p**	0.2			
Normal CLAMS	52	85.2	9	14.7
Abnormal CLAMS	5	45.4	6	54.5
p**	0.007			
Normal DQ	54	84.4	10	15.6
Abnormal DQ	3	37.5	5	62.5
p**	0.008			

*Pearson's chi-square test n = 100
**Fisher's exact test; n = 72
Caption: Abbreviations: CAT = Cognitive Adaptive Test; CLAMS = Clinical Linguistic and Auditory Milestone Scale; DQ = Development Quotient (CAT + CLAMS)

Table 3. Logistic regression considering as a dependent variable the occurrence of phonological deviation and as independent variables the results from neuropsychological tests and information from parents/guardians

Variables	OR	CI	p
CAT	0.64	0.1-7.3	0.72
CLAMS	13.40	2.5-71.3	0.002
DQ	3.18	0.3-31.9	0.32
Speech complaint	10.81	2.4-48.8	0.002
Beginning of the oral period	0.85	0.1-5.5	0.87
% of cases correctly classified	81.94		<0.001

Caption: Note: OR = odds ratio; CI = confidence interval. Abbreviations: CAT = Cognitive Adaptive Test; CLAMS = Clinical Linguistic and Auditory Milestone Scale; DQ = Development Quotient; OR = odds ratio; CI = confidence interval

DISCUSSION

During the anamnesis, speech impairments were reported more frequently in the SG, and this complaint was subsequently confirmed by the phonological assessment. There is still a general controversy about the association of language development with CH. Some studies report an appropriate development when children with CH are compared with a control group[18,19]. In contrast, other studies report evidence of phonological deficits or significant delays in language development[7,8,10,11]. Such differences are believed to be related to the large methodological diversity observed in the studies, such as selection of variables, sample size, type of tests applied and type of analysis of the data.

Regarding the presence of phonological deviation in this study, there was no statistically significant difference between the groups. This information was based on the criteria of normality of the phonological assessment of the ABFW Child Language Test[13], which accounts for complete phonological acquisition by the age of 7 years (7.0 years). Although the prevalence of phonological deviation in the general pediatric population is quite variable according to the literature (considering that there are many forms of evaluation), more robust epidemiological studies from a methodological point of view indicate values close to 15%[20,21]. Therefore, we may infer that the frequency of phonological deviation in the SG was higher than that observed in the general population.

We decided to analyze the productivity of each one of the processes described by the ABFW according to age. At the age of 7 years, there was no difference between the CG and SG in the repetition test and a tendency to a difference in the naming test. Children in the SG had a higher frequency of consonant cluster simplification than those in the CG. In this age group, according to the parameters of the instrument, all children should already have a complete phonological system[13].

A study of the analysis of phonological processes in children with normal phonological development concluded that between the ages of 7.0 and 7.11 years, consonant cluster simplification has an occurrence rate of less than 0.5%, which is in line with the results found in the CG in this study[22]. Another study compared the neuropsychological development of a child with CH and her identical twin who was not affected by the disease[9]. One of the evaluations performed corresponded to the phonological and expressive language development. It was noted that, at the age of four years, the child with CH presented delayed phonological acquisition compared with the sister who did not have the disease. However, at the age of 8 years, the child with CH, as well as her twin, showed a complete phonological system.

The results of the research mentioned above draw attention to the present study in which CH children between the ages of 8 and 9 years also had completed systems and were comparable with children in the CG in regard to phonological acquisition. However, is unknown to what extent this mild delay presented by children in the SG until that age could impose a negative influence on academic skills, since at this age range children are already in the process of alphabetization.

When the CG and the SG were matched in gender and age, they were comparable regarding the variable concerning complete or incomplete acquisition of the phonological system. When we considered the age groups with 4 + 5 years and 6 + 7 years, the CG presented a higher frequency of complete acquisition when compared with the SG ($p = 0.02$). We observed that up to the age of 6 years and 11 months, 100% of the children in the CG already had a complete phonological system, compared with 50% in the SG. At the age of 7 years and 11 months, this frequency increased to 63.3% in the SG; however, it only reached 100% at the age of 9 years and 11 months.

At the age of 7 years (7.0 years), all children should have a complete phonological system according to the ABFW. However, as mentioned earlier, due to the variables involved during the validation process, this instrument has more permissive criteria when compared with those of other authors. At the age of 6 years, children with normal phonological development no longer present speech processes, according to the literature. Therefore, only children in the SG presented phonological problems[22].

The variables related to the phonological assessment were also compared with the clinical data in children with CH. The presence of phonological deviation was not associated with age at treatment onset (median 18 days). In a study evaluating intelligence, motor skills and behavior in 51 children with CH and the association of these variables with age at onset of treatment, no association was observed[18].

As for the severity of the disease before treatment, there was also no association with the variable phonological deviation. This contrasts with several studies in this area, which have concluded that the larger the initial hormonal deficit, the worse the development of the child with CH in areas such as intelligence scores[8], mathematics, motor development, behavior[23] and language[10,11,24]. It is important to highlight that these studies have a wide methodological variation in relation to the definition of severity, with different cut-off values which can explain the discrepancy with the data of this study.

Children with thyroid agenesis presented a higher frequency of phonological deviation compared with those with other CH etiologies. A study conducted with 108 children with CH, aged between 1 and 5 years and 71 siblings without the disease, concluded that children with thyroid agenesis had a higher risk of neurodevelopmental problems[7]. Following the same line of investigation, another study concluded that children with thyroid agenesis present greater impairments related to

verbal fluency when compared to children with CH secondary to other etiologies[8].

The results also showed an association between the presence of phonological deviation and the results of neuropsychological tests performed in children with CH at the ages of 12, 24 and 36 months. Children who had at least one abnormal result in the CLAMS test, related to speech and language, had a higher frequency of deviation when compared with those in whom all evaluations were normal. The same occurred to the DQ. This information is of extreme importance to the health team and allows us to infer that children who fail the CLAMS test are more susceptible to present delays in phonological acquisition and, therefore, must be accompanied more rigorously.

The multivariate analysis with phonological deviation as a dependent variable indicated that children whose parents/guardians complained about speech problems were approximately 10 times more likely to present this problem. When the child fails in at least one of the assessments of the CLAMS test, the chances of delays in phonological acquisition increase 13 times. Such data should be analyzed with caution and taken into consideration by the health team, since even with multivariate analysis, none of the other variables of medical follow-up (etiology, age at onset of treatment, disease severity before treatment and quality of treatment) were independently predictive of phonological deviation. Results from this study allow us to conclude that there is a delay in phonological development in the SG compared with the CG, which is worsened when taking into consideration the etiology of the disease, complaints reported by parents/guardians and results of neuropsychological tests carried out in the early years of life. The relationship between the delay in phonological acquisition and school difficulties deserves to be explored in more depth in a new longitudinal study following up on children with CH.

Based on the results of this study, we expect the creation of preventive and therapeutic proposals in the area of speech therapy to allow appropriate health development of children with CH. With these proposals for intervention, it will be possible to perform new studies that clarify issues such as: What would be the results of working early on the development of phonological skills in children with CH who fail in neuropsychological tests in the first three years of life? Would such results allow the phonological system of these children to be complete in the same age range as in children without the disease? Would early phonological work, especially in regard to the development of phonological awareness, allow children with CH to have the same academic performance as healthy children? What is the association between the delay in phonological development and school impairments in children with CH?

CONCLUSION

From the analysis of these results, we can conclude that children with CH have a delay in phonological acquisition when compared with children without the disease, especially between the ages of 6 and 7 years. The etiology of CH is associated with phonological development, since children with thyroid agenesis are more susceptible to present deviation. Also, children who fail neuropsychological tests in the first three years of life are 13 times more likely to present phonological deviation in subsequent years.

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Author contributions

APDL participated in the idealization of the study, data collection, analysis and interpretation, and article writing; LL, MB, SNF and MNL participated in the idealization of the study, analysis, data interpretation and article writing, in the condition of guide, mentor and members of the research team, respectively.