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Performance in motor, communicative and cognitive skills of girls with congenital hypothyroidism treated from the neonatal period

Desempenho em habilidades motoras, comunicativas e cognitivas de crianças com hipotireoidismo congênito tratadas desde o período neonatal

Keywords

Congenital Hypothyroidism
Child Language
Child Development
Motor Development
Cognitive Development

ABSTRACT

Objective: To compare the performance in gross motor, fine motor-adaptive, language, cognitive and personal-social development skills of girls with a mean age of 36 to 71 months with Congenital Hypothyroidism treated from the neonatal period with that of their peers without thyroid alterations. **Methods:** The participants included in the study were 30 children aged between 36 and 70 months divided into two groups paired for chronological age and socioeconomic status: 15 girls diagnosed with Congenital Hypothyroidism – Experimental Group (EG) and 15 girls without thyroid changes – Control Group (CG). The following assessment instruments were used: Interview with parents, Peabody Picture Vocabulary Test - Revised (PPVT-R), and Denver Developmental Screening Test - 2nd edition (DDST-II). Psychological testing of intellectual functioning was conducted with application of the Stanford-Binet Intelligence Scale (SBIS). The descriptive statistical analysis was performed using Student's t-test and the Mann-Whitney test at a significance level of 5% ($p<0.05$). **Results:** Comparison of the PPVT-R and SBIS results showed a statistically significant difference between the EG and CG. Comparison of the DDST-II results showed a statistically significant difference between the groups for the fine motor-adaptive, language and gross motor areas. **Conclusion:** The present study confirms that Congenital Hypothyroidism affects child development, even when children are diagnosed and treated early, leading to alterations that can impair their motor, cognitive and language development.

Descritores

Hipotireoidismo Congênito
Linguagem Infantil
Desenvolvimento Infantil
Desenvolvimento Motor
Desenvolvimento Cognitivo

RESUMO

Objetivo: Comparar o desempenho das habilidades motora grossa, motora fina-adaptativa, linguagem, cognitiva e pessoal-social de meninas entre 36 e 70 meses com hipotireoidismo congênito tratado no período pós-natal com seus pares sem alterações tireoidianas. **Método:** Participaram 15 meninas com diagnóstico de hipotireoidismo congênito, com idade cronológica variando de 36 a 70 meses no Grupo Experimental (GE); e 15 meninas sem alterações tireoidianas no Grupo Comparativo (GC), pareadas por idade cronológica e nível socioeconômico. Os instrumentos de avaliação utilizados foram: Entrevista com os pais; Teste de Vocabulário por Imagem *Peabody (TVIP-R)*; *e* Teste de Triagem do Desenvolvimento de Denver II *(TTDD-II)*. Foi realizada a avaliação psicológica, quanto ao nível intelectual, com a aplicação da *Stanford-Binet Intelligence Scale (SBIS)*. A estatística foi realizada por meio de análise descritiva, teste "t" de Student e Teste de Mann-Whitney, nível de significância de $p <5\%$. **Resultados:** Na comparação do TVIP-R e *SBIS*, houve diferença estatisticamente significante entre o GE e o GC. Na comparação entre as áreas do TTDD-II, houve diferença estatisticamente significante entre os grupos para as áreas de Linguagem, Motora Grossa e Motora Fina-Adaptativa. **Conclusão:** O presente estudo confirmou a interferência do Hipotireoidismo Congênito no desenvolvimento infantil, mesmo quando diagnosticado e tratado precocemente, levando a mudanças no desenvolvimento que podem trazer prejuízos nas áreas motora, cognitiva e linguística.

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INTRODUCTION

Congenital hypothyroidism (CH) is a pediatric endocrine disorder characterized by insufficient thyroid hormone production caused by thyroid dysgenesis or dysormonogenesis[1-3]. Its incidence is of approximately 1 in 3000-4000 newborns, with a two to three-fold higher prevalence in females[4-6]. It is the leading cause of preventable intellectual disability when diagnosed and treated early[4,7-11].

The severity of neurodevelopmental impairment in individuals with CH is associated with age at diagnosis, initiation of treatment and hormone replacement dose[4-6]. A study[9] suggested that screening programs should consider thyroid hormone replacement based on the etiology of CH and early initiation of treatment. However, changes in neurodevelopmental abilities have also been observed in children with CH even in cases of early diagnosis followed by appropriate treatment[12-15].

Due to the important role of thyroid hormones in brain development, which involves the processes of central nervous system vascularization, myelination, dendritic arborization, cell differentiation and gene expression, the longer the hormone insufficiency period, the greater the severity and extent of brain damage, and the earlier hormone replacement begins, the less affected the child will be[9,12,16,17].

Cognitive deficits have been observed in children, adolescents and adults with CH, especially in cases of late initiation of treatment and/or more severe hormonal alterations[12,18-20]. Hormone deficiency in brain regions responsible for cognitive activities leads to perceptual changes[12], which can interfere with information processing and impair language development. Delays in the beginning of oral language production, comprehension difficulties, reduced vocabulary and morphosyntactic changes have been reported in children with CH[1,8,13,21,22], as well as changes in behavior such as hyperactivity, impulsivity, sleep disorders, agitation, among others[1,10,14,19,23,24], which may contribute to deficits in school learning and social integration of children. Motor impairment has also been reported with regards to delayed inhibition of primitive reflexes, alterations in static and dynamic balance and, especially, gross and fine motor coordination[14,15,17,18,25].

The consensus in this field is that early treatment is a protective factor for intellectual disability[4,7-11], although there are gaps in understanding the effects of CH on child development, even in children who underwent early hormone replacement therapy.

In this context, the present study aimed to compare the performance in gross motor, fine motor-adaptive, language, cognitive and personal-social development skills of girls with CH aged between 36 and 71 months who received treatment from the neonatal period with that of their peers without thyroid alterations.

METHODS

This study was conducted at Faculdade de Odontologia de Bauru, Universidade de São Paulo (USP), and approved by the Human Research Ethics Committee of the institution under protocol no. CAAE 22823913.9.0000.5417. All parents and/or legal guardians of the participants signed an Informed Consent Form (ICF) prior to data collection.

Participants were divided into two groups: Experimental Group (EG), composed of children diagnosed with congenital hypothyroidism (CH), and Control Group (CG), composed of children without thyroid changes.

Inclusion criteria

For inclusion in the EG, participants were required to: have undergone neonatal screening (NS) for metabolic changes between the second and seventh day of life; be female with chronological age between 36 and 70 months; be attending public school; have received treatment and follow-up for CH according to the guidelines of Ministério da Saúde (MS) [Brazilian Ministry of Health][26]; have obtained normal results on hearing and visual assessments; present normal thyroid hormone levels at the pre-study evaluation (TSH = 0.2-6.0 mUI/L; free T4 > 6.1 µg/dL). In addition, participants were required not to: present other congenital or acquired impairments or proven genetic and/or neurological syndromes that are not part of the specific context of CH; have been born prematurely or with very low weight; present intellectual disability (IQ>70); have shown neurodevelopmental delay.

According to the MS protocol, hormone levels are to be monitored every four to six weeks during the first six months of life, every two months between the age of six and eighteen months, and every three to six months thereafter[26].

In order to be included in the CG, participants were required to: have undergone NS including all metabolic tests, presenting normal results; be female and paired with the EG for chronological age, educational level and socioeconomic status as per the Brazilian Socioeconomic Classification Criteria[27]; have obtained normal results on hearing and visual assessments; have no history of neuropsychomotor developmental delay. They were also required not to have been born prematurely or with very low weight nor to present intellectual disability (IQ>70).

The variable "female" was considered to minimize the effects of differences in language development.

The legal guardians of the children included in the EG answered a questionnaire containing information about pregnancy, neuropsychomotor development, and history of diagnosis and treatment of CH. The parents of children with CH were asked to bring information on school life and the levels of TSH, total blood T4 and free T4, especially the first and last exams performed prior to evaluation.

Assessment was conducted through application of the following instruments: anamnesis, Brazilian Socioeconomic Classification Criteria (CCSB)[27], Stanford-Binet Intelligence Scale (SBIS) adapted by Terman and Merrill[28], Denver Developmental Screening Test - 2nd edition (DDST-II), and Peabody Picture Vocabulary Test - Revised (PPVT-R).

The CCSB[27] includes levels of income, material goods and parental schooling. The Stanford-Binet Intelligence Scale (SBIS) adapted by Terman and Merrill[28] was used to evaluate the intellectual level of the participants. Individuals with an Intelligence Quotient higher than 70 (IQ>70) were rescheduled

for the next study phase. The DDST-II[29] is a developmental screening scale that verifies performance on the following skills: personal-social (PS), fine motor-adaptive (FMA), language (LG), and gross motor (GM). The PPVT-R[30] aims to verify lexical development in the auditory-receptive vocabulary sphere in a wide variety of semantic categories. Individual results were classified as follows: 1= Extremely low; 2= Low; 3= Moderately low; 4= Average; 5= Moderately high; 6= High; 7= Extremely high.

The laboratorial neonatal screening (NS) identified 96 children (29 boys and 67 girls) with CH. Among the girls, seven did not undergo NS until the seventh day of age and initiation of treatment was postponed; 18 did not adhere adequately to treatment; seven refused to participate in the study; 11 presented other genetic and neurological disorders such as Down syndrome, cerebral palsy, intellectual disability, hydrocephalus etc.; two did not attend school; two failed the auditory and/or visual assessment; three had been born prematurely or with very low weight; and two did not show normal levels of thyroid hormones at the pre-study evaluation. Thus, only 15 girls met all inclusion criteria of the study.

Study sample

Study participants were 30 girls with chronological age between 38 and 70 months (mean=54.8) who attended public school at three levels of education: Pre-kindergarten I (26.67%), Pre-kindergarten II (46.66%) and Kindergarten (26.67%). The 30 participants were divided into two groups: 15 girls in the Control Group (CG) and 15 girls in the Experimental Group (EG), with participants in the latter group presenting high TSH levels (>10 mUI/ml) at NS. The NS was performed between the second and seventh days of life (mean=5.9), and initiation of treatment ranged from 15 to 58 days of age (mean=35.2). L-thyroxine at a dose of 25-88 µg/day was used for hormone replacement.

As for the socioeconomic status in each group[27], 26.66% were middle class, 53.34%, lower-middle class and 20%, low class.

Regarding anamnesis, participants in the EG presented weight at birth ranging from 2580 to 3280 g (mean=3105) and height at birth between 46.5 and 49.5 cm (mean=48.4); 26.67% were born by caesarean section and 73.33%, by normal delivery. Participants in the CG presented weight at birth ranging from 3185 to 4075 g (mean=3322) and height at birth between 48 and 51 cm (mean=49.37); 40% were born by caesarean section and 60%, by vaginal delivery.

Parents in the GE reported that 100% of their children showed inattention and 67% presented agitation or hyperactivity; 80% of the parents reported sleep disorders. All study participants (EG and CG) presented typical neuropsychomotor development for their age.

Statistical analysis

Data were processed using the SPSS 17 software. The assessment results were analyzed as mean, minimum and maximum values, and standard deviation for the quantitative variables, in addition to frequency of results in the PPVT-R. The Shapiro-Wilk test was initially applied, thereby two statistical tests were used: the Mann-Whitney test for the variables with non-normal distribution (comparison between groups in the PPVT-R) and Student's t-test for the variables with normal distribution (comparison between groups in the SBIS and DDST-II). A significance level of 5% ($p<0.05$) was adopted for all statistical analyses.

RESULTS

Table 1 shows the compared results for the two groups (EG and CG) obtained from the Peabody Picture Vocabulary Test – Revised (PPVT-R) and the Stanford-Binet Intelligence Scale (SBIS) using mean, standard deviation, and minimum and maximum values.

A statistically significant difference was observed between EG and CG. It is worth noting that the EG did not behave homogeneously, as the minimum, maximum and standard deviation values show. A comparison of the Intelligence Quotient (IQ) scores obtained from application of the SBIS showed statistically significant difference between EG and CG, although all participants in both groups presented scores within the normality standards.

Table 2 shows the comparative qualitative results of the PPVT-R for the two groups (EG and CG).

Table 1. Compared results of the two groups (EG and GC) for the Peabody Picture Vocabulary Test - Revised (PPVT-R) and Stanford-Binet Intelligence Scale (SBIS)

	EG		CG		*p*-value
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
PPVT-R	92.46 ± 18.35	65-135	118.66 ± 10.56	97-135	<0.000*
SBIS	98.06 ± 6.55	97-109	104.86 ± 2.06	100-108	<0.000*

*Statistically significant; Significance level $p<0.05$

Captions: PPVT-R: Peabody Picture Vocabulary Test - Revised; SBIS: Stanford-Binet Intelligence Scale; EG: Experimental Group; CG: Control Group; SD: Standard Deviation; Min: minimum; Max: maximum; Mann-Whitney test (comparison between groups for the PPVT-R); Student's *t*-test (comparison between groups for the SBIS)

Table 2. Compared qualitative results of the two groups (EG and CG) for the Peabody Picture Vocabulary Test - Revised (PPVT-R)

Group	Classification						
	1	2	3	4	5	6	7
EG	6.67%	20%	20%	40%	6.67%	6.67%	0%
CG	0%	0%	0%	13.33%	80%	6.67%	0%

Captions: EG: Experimental Group; CG: Control Group; 1= Extremely low; 2= Low; 3= Moderately low; 4= Average; 5= Moderately high; 6= High; 7= Extremely high

Table 3. Compared results of the two groups (EG and CG) for the Denver Developmental Screening Test - 2nd edition (DDST-II)

DDST-II	EG		CG		*p*-value
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
PS	61.00 ± 10.81	36-71	64.13 ± 5.30	50-71	0.322
FMA	64.86 ± 10.21	49-72	70.80 ± 3.36	60-72	0.041*
LG	58.66 ± 5.85	50-68	69.40 ± 5.99	52-72	<0.000*
GM	61.26 ± 11.89	39-71	70.26 ± 2.34	62-71	<0.007*

*Statistically significant by Student's t-test; Significance level p<0.05
Captions: DDST-II: Denver Developmental Screening Test - 2nd edition; EG: Experimental Group; CG: Control Group; PS: personal-social; FMA: fine motor-adaptive; LG: language; GM: gross motor; SD: standard deviation; Min: minimum; Max: maximum

Table 3 presents the compared mean, standard deviation, minimum and maximum values obtained from the DDST-II for the two groups (EG and CG) in all areas tested (personal-social, fine motor-adaptive, language, and gross motor).

A statistically significant difference was verified between the groups for the fine motor-adaptive, language and gross motor areas.

DISCUSSION

In the present study, evaluation using the Peabody Picture Vocabulary Test – Revised (PPVT-R) (Table 1) showed delayed lexical development regarding the auditory-receptive vocabulary of children with Congenital Hypothyroidism (CH) compared with that of individuals without metabolic changes. Heterogeneous performance was verified in the Experimental Group (EG) (Table 2), in which approximately 46.67% of the children presented below-average results compared with the participants in the Control Group (CG).

Research has shown differences in the language skills of children with CH[9,13-15,18,25], although there are controversial results regarding the language of this population[16,17]. Bulus and Tiftik[17] found no statistically significant differences in language in a comparison between individuals with and without CH.

The PPVT-R can be used as a non-verbal Intelligence Quotient (IQ) measure[30]. Nevertheless, this skill (receptive vocabulary) involves other dimensions that should be observed, i.e. vocabulary acquisition is also related to children's experiences in their different social environments and in the opportunities they are offered in their exchange with different interlocutors, in addition to the anatomo-functional conditions of the central nervous system.

The literature also shows that the socioeconomic status and educational level of mothers influence development of children and their performance in tasks involving language and communication skills, such as vocabulary development. Thus, low socioeconomic status also increases the risk of delayed language acquisition and development[7,13,15]. The present study was careful to control this variable, having paired the groups by socioeconomic status. Furthermore, maternal schooling was also observed as part of the socioeconomic criteria used[27].

Analysis of the participants' IQ levels demonstrated that even individuals with CH (EG) with IQ scores within normality (according to the inclusion criteria) presented lower scores compared with those of children in the CG. The literature points to this issue, stating that early diagnosis and treatment of CH are extremely important to prevent intellectual disability[7-9,15,20]. However, it also states that children with CH may present lower cognitive test results compared with their peers[7,12,18]. A study showed that children with CH, despite not presenting intellectual disabilities, had lower scores compared with siblings without metabolic disorders[12].

Early diagnosis and treatment of children with CH bring enormous benefits to the family and community, as they avoid social, emotional and financial costs through prevention of intellectual disability[4]. However, although early screening programs for CH have proven effective in reducing intellectual disability, the key issue is identifying neurocognitive sequelae, even the subtlest ones, which may persist despite early treatment[2,4-6,9,11,19]. Studies have reported that individuals with CH may present attention, memory, visuocognitive, visuospatial and psychomotor disorders[1,10,12,14,18-20,24]. Yang et al.[24] demonstrated that children with CH are more likely to present symptoms of attention-deficit hyperactivity disorder (ADHD). In this study, the parents of the individuals in the EG reported that their children presented inattention as well as agitation and/or hyperactivity. Because of the relationship between attention disorders and performance in learning activities, it is worth considering the potential deficit of this cognitive process in children with CH.

Compared results between the groups (EG and CG) on the DDST-II showed statistically significant differences in the gross motor, fine motor-adaptive and language areas (Table 3).

Several authors have reported that children with CH may present motor impairment[13-15,18,19,21-23,25]. The DDST-II assesses gross motor skills in terms of static and dynamic balance—for example, holding a foot, jumping etc. Two studies that applied the DDST-II reported statistically significant differences in the gross motor area[14,18].

Núnez et al.[18] stated that the severity of CH is a risk factor for impaired motor skills. Kempers et al.[20] conducted a study with three subgroups of individuals with CH, where classification was defined according to the concentration of free T4 at pre-treatment. The groups were divided as to mild, moderate and severe CH. Motor problems were verified in the three subgroups, but the severe CH group presented more substantive deficits. Motor deficits are commonly observed in children with CH with alterations in gross and fine motor skills, motor coordination, and balance[18].

The fine motor-adaptive area of the DDST-II evaluates the ability of children to organize stimuli, handle objects in daily tasks, among others. Exploration of the environment, manipulation of objects, repetition of actions, control of body image and

relationships established in the situations experienced enable knowledge acquisition, showing that cognitive and linguistic processes are integrated with motor activity[14]. Conflicting results have been reported on the occurrence of fine motor impairment in individuals with CH. Some studies have found significant differences in comparing groups of individuals with and without CH[14,25], whereas others have not observed this difference[15,18].

A study conducted by Frezzato and collaborators[25] detected alterations in the language domain associated with motor deficits and reported that children with CH presented worse performance in fine motor skills. They observed an association between fine motor and language skills, demonstrating that these skills were interrelated, where the group with CH was twice as likely to show expressive language impairment when fine motor skills were compromised.

As to the language area of the DDST-II, statistically significant differences were found, which corroborates the findings of other studies[9,13-15,18,19,26].

Oerbeck et al.[19] reported that schoolchildren and adolescents with CH may present lower scores in receptive and expressive language and fine and gross motor skills compared to healthy children. From the sample of the aforementioned research, it can be inferred that the participants' adherence to treatment may have prevented intellectual disability but not the deleterious effects of CH, such as the difficulties found in the present study. It was observed that some children did not initiate treatment before the first month of life, according to the regulations of the Brazilian Ministry of Health[26]. Initiation of hormone replacement in this sample ranged from 15 to 58 days of age (mean=35.2). A study[17] reported that the number of patients with atypical developmental skills was larger when treatment was initiated after 15 days of life. The neonatal period is undoubtedly the ideal time for CH diagnosis, as it is known that from the second week of life, thyroid hormone deficiency may cause damage leading to alterations in child development.

Komur et al.[15] reported that there is a significant correlation between the effects of neurodevelopment and the age at initiation of treatment, drug dose at initiation of treatment, severity of CH, thyroid stimulating hormone normalization time, and socioeconomic status.

It is worth highlighting that none of the children in this study underwent follow-up or intervention procedures in the developmental areas. A limitation to this study regards the lack of access to all medical treatment follow-up exams, and with the transfer of the assistance service to another city, many families reported difficulties in monitoring their daughters' hormone doses over time. Maintaining normative levels of thyroid hormones is essential; thus, thyroid function should be assessed and the replacement dose, regularly adjusted, in order to restore and maintain consistent euthyroidism[4,5,26]. Another limitation concerns the study sample size.

It can be inferred that the clinical heterogeneity found in individuals with CH could be explained by epigenetic mechanisms and environmental factors that would lead to variability in phenotype expression in CH[3]. Thus, it is important to consider the age at diagnosis and initiation of treatment, CH etiology and severity, effectiveness of hormone replacement dose, follow-up overtime regarding the maintenance of normative metabolic indices and follow-up of the trajectory of the child's development in stimulation programs. These are some of the variables that could explain the clinical variability in child development impairment.

Longitudinal follow-up of the development of children with CH in the gross motor, fine motor-adaptive, cognitive and language areas is considered extremely important. It aims to help prevent the deleterious effects of CH in different areas of development, which certainly brings benefits to the learning processes and quality of life of these children and their families.

Children with CH are considered at risk of developmental alterations. Early diagnosis and follow-up of the child's development are key to prevent the deleterious effects of CH. It is worth noting that the National Neonatal Screening Program [Programa Nacional de Triagem Neonatal] does not include speech-language pathologists as members of the specialized multidisciplinary follow-up team[26].

These findings corroborate several studies addressing the impact of CH on child development, noting that individuals with CH, even when early diagnosed and treated, may present developmental alterations, which can affect them and interfere with their relationships with family, school and the society.

CONCLUSION

The present study confirms the impact of Congenital Hypothyroidism on child development with regard to impairments of gross motor, fine motor-adaptive, language and cognitive functions.

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Author contributions

DACL: Study design, analysis and interpretation of data, and writing, critical review of intellectual content and approval of the final version of the manuscript; FLAP: Study design, collection, analysis and interpretation of data, and approval of the final version of the manuscript; PMDPF: Study design and writing, critical review of intellectual content and approval of the final version of the manuscript; CCR: Study design, interpretation of data, and writing, critical review of intellectual content and approval of the final version of the manuscript.