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Neurodevelopmental Disorders, Cognitive Function, and Quality of Life in Children with Congenital Hypothyroidism in a Portuguese Population

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What is already known on this topic?

Neonatal screening programs have largely eliminated severe intellectual disability in congenital hypothyroidism (CH). Subtle neurodevelopmental deficits and a higher prevalence of attention deficit hyperactivity disorder and learning disabilities remain, even with early intervention.

What this study adds?

Delayed treatment initiation more than 15 days after birth negatively impacts cognitive outcomes, particularly in non-verbal domains, and lowers emotional and social QoL. This study highlights the importance of continuous monitoring and targeted interventions to address neurodevelopmental and QoL challenges in children with CH.

Abstract

Objective: Although neonatal screening programs have reduced severe intellectual disability, children with congenital hypothyroidism (CH) are still at risk for neurodevelopmental deficits and a lower quality of life (QoL). The aim of this study was to evaluate cognitive profiles, prevalence of neurodevelopmental disorders, and QoL in children with CH.

Methods: A longitudinal study was conducted at the northern reference endocrinology unit for CH in Portugal. Cognitive assessments were performed at four time points using standardized intelligence scales. Diagnoses of attention deficit hyperactivity disorder (ADHD), learning disorders, and intellectual disability were based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-DSM-V criteria. QoL was measured using the Pediatric Quality of Life Inventory-PedsQL™.

Results: Forty-six children (mean age 9.1 years, 58.7% female) were included. While overall intelligence quotients (IQ) scores were normal, later treatment was associated with significantly lower performance IQ ($r = -0.50$, $p = 0.028$) and perceptual organization index ($r = -0.57$, $p = 0.022$). ADHD was present in 26%, and affected children showed lower verbal IQ (90.2 vs. 106.8, $p = 0.022$), perceptual organization index (79.9 vs. 95.2, $p = 0.041$), and school-related QoL (63.3 vs. 81.6, $p = 0.002$). QoL scores were comparable to the Portuguese pediatric population, but treatment delays were linked to lower total QoL ($r = -0.45$, $p = 0.002$), particularly in emotional and social domains.

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Conclusion: Early thyroid hormone therapy is essential to mitigate neurocognitive deficits and improve QoL in CH. While severe intellectual disabilities are rare, non-verbal deficits persist, emphasizing the need for timely treatment and continuous monitoring.
Keywords: Adolescent development, attention deficit disorder with hyperactivity, child development, congenital hypothyroidism, learning disabilities, neurodevelopmental disorders, quality of life

Introduction

Congenital hypothyroidism (CH), affecting nearly 1 in 2000 newborns, is a chronic disease characterized by a congenital deficiency in thyroid hormone production. Primary CH arises from either thyroid gland dysgenesis or dyshormonogenesis. While thyroid gland dysgenesis has historically been the most common cause of primary CH, the widespread implementation of neonatal screening programs and lower thyroid-stimulating hormone (TSH) cut-off values have increased the detection of mild cases and cases of dyshormonogenesis, leading to a shift in etiological distribution (1,2,3).

Thyroid hormone is crucial for normal brain development, both pre- and post-natally. Untreated CH may result in irreversible intellectual and motor disabilities (4). Early diagnosis and intervention have dramatically improved outcomes. In developed countries, universal newborn screening conducted within the first days of life has virtually eradicated severe intellectual disabilities related to untreated CH (1,2).

Despite the success of these screening programs, emerging evidence indicates that even with early treatment, children with CH remain at risk for subtle neurodevelopmental deficits. Research exploring the long-term cognitive and developmental outcomes in children with CH has highlighted the importance of treatment timing, as delays are associated with more pronounced cognitive challenges (2,5). Furthermore, neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and learning disabilities (LD) are more prevalent among children with CH compared to the general population, particularly in cases of severe neonatal hypothyroidism or maternal thyroid dysfunction during pregnancy (6,7,8,9,10,11,12). These deficits can significantly affect academic performance and overall well-being. However, findings on the impact of CH on quality of life (QoL) remain inconsistent, with some studies reporting similar or even better QoL compared to healthy peers (13,14,15,16,17) while others suggest poorer outcomes (18).

While early detection and treatment have greatly reduced the risk of severe intellectual disability, ongoing monitoring and interventions may be necessary to address the subtler but significant neurodevelopmental challenges that can persist into childhood and adolescence. Previous studies suggest that neuropsychological impairment may continue despite early treatment, yet few studies have comprehensively assessed both neurodevelopmental outcomes and QoL, particularly with long-term follow-up.

The aim of this study was to address these gaps by evaluating cognitive profiles, the prevalence of neurodevelopmental disorders, and QoL in children with CH, providing a more comprehensive understanding of the long-term challenges faced by this population.

Methods

A longitudinal study was carried out in the pediatric endocrinology unit of a tertiary hospital, the northern reference center for CH in Portugal.

Participants

Patients diagnosed with permanent primary CH between 2006 and 2023 were included. All diagnoses were established through the national newborn screening program within the first days of life. Exclusion criteria included refusal to participate, inability to respond to the questionnaire, and syndromic CH. Delayed treatment was defined as initiation of levothyroxine therapy more than 15 days after birth. Four patients were excluded due to missed appointments or unsuccessful contact.

The study was approved by the Unidade Local de Saúde de São João Ethical Committee (approval no: 202-2023, date: 23/10/2023). All eligible participants and their parents provided informed consent.

Patient Diagnosis and Follow-up

In Portugal, CH was included in the Newborn Screening Program in 1981. It primarily uses TSH as a marker, analyzing dried blood samples collected ideally between the 3rd and 6th day of life. Initially, the program employed a high TSH cut-off level of 90 µU/L, which meant that only severe cases of CH were identified. In 1996, the cut-off level was lowered to 20 µU/L, and in 2006, it was further reduced to 10 µU/L. Since our study includes patients diagnosed from 2006 onwards, this last cut-off was applied, enabling the detection of milder cases. Elevated TSH levels (above 40 µU/mL) prompt immediate referral to a reference center.

TSH values falling within the range of 20 to 40 µU/mL are considered suspicious, prompting ongoing observation of newborns until values normalize. For cases where TSH values range from 10 to 20 µU/mL, total T4 levels are assessed; if higher than 9.5 µg/dL, continued observation is the chosen strategy; if less than 9.5 µg/dL, values are considered within the normal range. In confirmed cases of CH, early referral to a reference center is implemented to initiate therapy with levothyroxine as early as possible (19). All cases are initiated on the same weight-adjusted levothyroxine dose (10-15 µg/kg/day), adjusted subsequently to maintain serum T4 concentrations at the upper limit of normal and TSH levels below 3.8 µU/L.

All patients diagnosed with CH at our center were followed by a multidisciplinary team, including a pediatric endocrinologist, a psychologist, and a specialized nurse. Routine assessments occurred every 4-6 months, with increased frequency during the initial treatment phase. Levothyroxine dosages were adjusted to maintain target thyroid hormone levels. Growth parameters, medication-related symptoms, and associated malformations were routinely monitored. Psychomotor development was assessed regularly by the same psychologist affiliated with the pediatric endocrinology unit.

Study Assessments

Psychomotor Development

Standardized assessments were conducted at specific time points. Results were expressed as intelligence quotients (IQ) with a normal distribution [mean 100, standard deviation (SD) 15]. Four formal psychometric assessments were performed: the first (IQ1) at 24 months of age, and the second (IQ2) at 4 years of age, both using the Griffiths Mental Development Scales. The third assessment (IQ3) was performed before school entry (5 to 6 years of age), using the Wechsler Preschool and Primary Scale of Intelligence. A fourth assessment (IQ4) was conducted during primary school, using the Wechsler Intelligence Scale for Children (WISC-III). This evaluation generated scores for Verbal, Performance, and Full-Scale IQ, along with index scores for the verbal comprehension index, perceptual organization index, and Processing Speed Index (the Freedom from Distractibility Index is not available in the Portuguese version) (20).

Neurodevelopmental Disorders

If neurodevelopmental disorders were suspected, children were referred to our neurodevelopment unit for clinical evaluation. Diagnoses of intellectual disability, LD, and ADHD were made based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-DSM-V criteria. School support, therapy (occupational, speech, and psychotherapy), and medications were provided as indicated.

Quality of Life

The Portuguese version of the Pediatric Quality of Life Inventory (PedsQL™ 4.0) was used for parent-reported QoL assessments. The questionnaire was administered during a school-age medical visit. The instrument, validated for Portuguese children, consists of 23 items across four domains: Physical, Emotional, Social, and School Functioning. Scores range from 0 to 100, with higher values indicating better QoL (21,22). Healthy individuals from the instrument's validation studies served as the control group (22).The control group was derived from a sample of 381 Portuguese children aged 8 to 12 years, recruited from schools in northern Portugal, as part of the PedsQL™ validation study. This sample provided normative QoL data for comparison and was not specifically age- and sex-matched to the study population. However, it is broadly representative of the general pediatric population within the specified age range (22).

Statistical Analysis

Statistical analysis was performed using SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, while continuous variables are presented as means and SDs. Normality of continuous variables was assessed using the Shapiro-Wilk test. One-sample t-test was used to compare QoL scores of our study group with the Portuguese pediatric population (22). Pearson's correlation coefficients were used to assess associations between continuous variables. The strength of the relationship was interpreted based on the following r values: very weak (<0.25), weak (0.26 to 0.49), medium (0.50 to 0.69), high (0.70 to 0.89), and very high (0.90 to 1.0). A p value <0.05 was considered statistically significant.

Results

Characterization of the Population

The population analyzed is described in Table 1. Forty-six children were included in the study, 58.7% of whom were female. The mean age was 9.1 ± 0.6 years. The diagnosis was established at a mean of 12.9 ± 2.2 days of age, and treatment initiation at 14.5 ± 2.1 days. Treatment was initiated within the first 15 days of life in 37 out of 47 (78.7%) patients, between 15 and 45 days in eight (17.0%) patients, and at three months in one (2.1%). The mean venous TSH level at diagnosis was 177 ± 28.3 IU/mL. Thyroid dysgenesis was the predominant condition (82.6%) (18).

Neurodevelopment Assessments

Cognitive function was assessed longitudinally at four time points, at a mean age of: 2.4 years (mean IQ = 100.1 ± 10.4); 4.8 years (mean IQ = 100.1 ± 8.9); 5.6 years (mean IQ = 100.2 ± 15.9); and 9.1 years (mean IQ = 93.6 ± 19.5). At the final assessment, five children scored below average (IQ < 80), including two (4.3%) with scores more than two SDs below the average (IQ < 70).

Throughout the longitudinal follow-up, 26.1% of the children were diagnosed with ADHD, and 19.6% with LD. One child (2.2%) met criteria for intellectual disability.

QoL Assessments

Table 1. Demographic, clinical characteristics, and cognitive assessment of the study population

Characteristics	(n = 46)
Age, years	9.1 ± 0.6
Female sex	27 (58.7%)
Age at diagnosis, days	12.9 ± 2.2
Age at initiation of treatment, days	14.5 ± 2.1
TSH level at diagnosis, IU/mL	177.2 ± 28.3
Etiology of congenital hypothyroidism	
• Dysgenesis	38 (82.6%)
• Dyshormonogenesis	8 (17.4%)
Gestational risk	
• Gestational diabetes	7 (15.2%)
• Maternal thyroid pathology	3 (6.5%)
• In vitro fertilization	1 (2.2%)
Gestational age, weeks	39.0 ± 0.3
Birth anthropometry	
• Weight, grams	3088.3 ± 67.9
• Height, centimeters	47.8 ± 0.3
• Head circumference, centimeters	34.6 ± 0.3
Cognitive assessments, n/mean age (years)	
• First evaluation	43/2.4 ± 0.6
• Second evaluation	35/4.8 ± 0.2
• Third evaluation	13/5.6 ± 0.2
• Fourth evaluation	20/9.1 ± 0.4
Intelligence quotient scores	
• First evaluation (Griffiths)	100.1 ± 10.4
• Second evaluation (Griffiths)	100.1 ± 8.9
• Third evaluation (WPPSI)	100.2 ± 15.9
• Fourth evaluation (WISC)	93.6 ± 19.5
- Verbal IQ	99.7 ± 18.9
- Performance IQ	91.8 ± 19.3
- Perceptual organization index	88.5 ± 16.9
- Verbal comprehension index	100.4 ± 18.9
- Processing speed index	97.5 ± 17.9
Neurodevelopment disorders	
• ADHD	12 (26.1%)
• Learning disorder	9 (19.6%)
• Intellectual disability	1 (2.2%)

Data are expressed as n (%) or mean ± standard deviation.
ADHD: attention deficit hyperactivity disorder, IQ: intelligence quotient, IU: international units, TSH: thyroid stimulating hormone, WISC: Wechsler intelligence scale for children, WPPSI: Wechsler preschool and primary scale of intelligence

The QoL results are shown in Table 2. Overall, children with CH demonstrated QoL scores similar to the normative data for the Portuguese pediatric population, with a mean total QoL score of 83.0 ± 13.8. Statistically significant higher emotional QoL scores were reported for children with CH (80.6 vs. 73.3, p = 0.007). No significant differences were observed in the other domains.

Correlations Between Diagnosis, Treatment Timing, TSH, and Cognitive/QoL Scores

Table 3 presents the correlations between age at diagnosis, age at treatment initiation, TSH levels at diagnosis, and cognitive and QoL measures in our population.

Age at treatment initiation showed significant negative correlations with performance IQ (r = -0.50, p = 0.028) and perceptual organization index (r = -0.57, p = 0.022).

When assessing the impact on QoL in children with CH, significant negative correlations were found between the age at treatment initiation and multiple QoL domains. Specifically, later treatment initiation was associated with lower scores in total QoL (r = -0.45, p = 0.002), emotional QoL (r = -0.46, p = 0.001), and social QoL (r = -0.39, p = 0.007).

Neurodevelopment and QoL

The relationship between IQ and QoL is shown in Table 4. A positive correlation was observed between early psychomotor development (IQ1) and QoL outcomes, specifically in the social (r = 0.36, p = 0.017) and school (r = 0.33, p = 0.029) domains when assessed at school age. In the second preschool assessment (IQ2), a significant positive correlation was observed between IQ and total QoL (r = 0.34, p = 0.046) and physical QoL (r = 0.40, p = 0.029). By school age (IQ4), these associations strengthened: IQ showed strong positive correlations with total QoL (r = 0.78, p < 0.001), physical QoL (r = 0.66, p = 0.002), school-related QoL (r = 0.72, p < 0.001), and social QoL (r = 0.64, p = 0.002). However, emotional QoL did not demonstrate a significant correlation with IQ at any stage of development.

Table 2. Quality of Life scores of children with congenital hypothyroidism and comparison to the Portuguese pediatric population

	CH patient	Portuguese population (22)	p
Total QoL	83.0 ± 13.8	79.8 ± 12.1	0.120
Physical	87.0 ± 15.5	83.5 ± 14.8	0.138
Emotional	80.6 ± 17.6	73.3 ± 16.7	**0.007**
Social	87.6 ± 18.1	84.6 ± 15.1	0.263
Scholar	76.8 ± 18.8	78.2 ± 15.9	0.616

The data are presented as mean ± standard deviation.
CH: congenital hypothyroidism, QoL: quality of life

Cognitive and QoL Scores in Children with and without ADHD

To analyze the most common neurodevelopmental disorder diagnosed in this CH cohort, we compared the IQ and QoL scores of children with ADHD to those without this diagnosis (Table 5). Children with ADHD had lower total IQ scores (85.6 vs. 100.2, p = 0.051), with significantly lower results in verbal IQ (90.2 vs. 106.8, p = 0.022) and perceptual organization index (79.9 vs. 95.2, p = 0.041). Regarding QoL, children with ADHD demonstrated significantly lower scores in the school domain (63.3 vs. 81.6, p = 0.002), but no significant differences were found in total QoL, or in other domains.

Cognitive and QoL Scores in Children with and without LD

Similarly to the previous analysis, we compared the IQ and QoL scores of children with LD to those without this diagnosis (Table 6). Children with LD had significantly lower total IQ scores (77.5 vs. 104.3, p = 0.001), with significant differences observed in both verbal (83.9 vs. 109.5, p = 0.002) and performance IQ (78.1 vs. 100.9, p = 0.010). In addition, children with LD demonstrated lower scores in the verbal comprehension index (84.0 vs. 108.6, p = 0.010) and the perceptual organization index (79.9 vs. 97.0, p = 0.002).

Regarding QoL, children with LD had a significantly lower total QoL score (70.3 vs. 86.1, p = 0.005). Differences in specific QoL domains showed that children with LD scored lower in the school-related QoL (56.0 vs. 81.9, p < 0.001). However, no significant differences were observed in the others QoL domains.

Discussion

In this study, we assessed the prevalence of neurodevelopmental disorders and QoL in children with CH.

Table 3. Correlations between age at diagnosis, age at treatment initiation, TSH levels at diagnosis, and cognitive and quality of life scores in children with congenital hypothyroidism

	Diagnosis age (days)		Treatment initiation age (days)		TSH levels at diagnosis (IU/mL)	
	r	p	r	p	r	p
Total IQ	-0.43	0.098	-0.42	0.063	0.36	0.301
- Verbal IQ	-0.23	0.383	-0.22	0.338	0.39	0.234
- Performance IQ	-0.50	0.050	-0.50	**0.028**	0.237	0.510
Perceptual organization index	-0.54	**0.040**	-0.57	**0.022**	0.32	0.373
Verbal comprehension index	-0.14	0.597	-0.17	0.495	0.38	0.246
Processing speed index	-0.42	0.119	-0.44	0.920	0.32	0.373
Total QoL	0.41	**0.008**	-0.45	**0.002**	0.18	0.306
- Physical	-0.18	0.249	-0.27	0.075	0.17	0.333
- Emotional	-0.39	0.013	-0.46	0.001	0.30	0.087
- Social	-0.41	**0.008**	-0.39	0.007	0.07	0.713
- Scholar	-0.28	0.072	-0.29	0.053	0.07	0.707

r: Pearson correlation coefficient
TSH: thyroid-stimulating hormone, IQ: intelligence quotient, QoL: quality of life,

Table 4. Correlation between intelligence quotient scores and quality of life in children with congenital hypothyroidism

	Total QoL		Physical QoL		Emotional QoL		Social QoL		School QoL	
	r	p	r	p	r	p	r	p	r	p
IQ1 Griffiths	0.28	0.065	0.14	0.356	0.04	0.814	0.36	**0.017**	0.33	**0.029**
IQ2 Griffiths	0.34	**0.046**	0.40	0.029	0.57	**< 0.001**	0.59	**< 0.001**	0.50	**0.030**
IQ3 WPPSI	0.46	0.118	0.31	0.310	0.17	0.585	0.50	0.081	0.46	0.118
IQ4 WISC	0.78	**< 0.001**	0.66	**0.002**	0.40	0.078	0.64	**0.002**	0.72	**< 0.001**
IQ4 VIQ	0.69	**< 0.001**	0.62	**0.003**	0.32	0.160	0.52	**0.016**	0.71	**< 0.001**
IQ4 PIQ	0.74	**< 0.001**	0.66	**0.002**	0.37	0.105	0.66	**0.002**	0.61	**0.005**
IQ4 VCI	0.67	**0.002**	0.62	**0.007**	0.40	0.096	0.47	0.050	0.71	**< 0.001**
IQ4 POI	0.82	**< 0.001**	0.75	**< 0.001**	0.50	0.050	0.73	**< 0.001**	0.68	**0.004**
IQ4 PSI	0.51	**0.042**	0.47	0.070	0.29	0.285	0.52	**0.038**	0.38	0.148

r: Pearson correlation coefficient.
IQ: intelligence quotient, QoL: quality of life, WPPSI: Wechsler preschool and primary scale of intelligence; WISC: Wechsler intelligence scale for children, VIQ: verbal IQ, PIQ: performance IQ, VCI: verbal comprehension index, POI: perceptual organization index, PSI: processing speed index

ADHD and LD were prevalent, affecting 26% and 20% of the cohort, respectively. Although overall IQ scores in the cohort were within the normal range, a slight decline was observed over time, with mean IQ dropping from 100.1 in early assessments to 93.6 at school age. Notably, children treated later had lower cognitive scores, specifically in performance IQ and perceptual organization index. In addition, later diagnosis and treatment initiation was associated with lower QoL, particularly in emotional and social domains. No significant correlations were observed between TSH levels at diagnosis and IQ or QoL. ADHD and LD were linked to lower IQ and school-related QoL scores. Despite these challenges, QoL in the cohort was similar to the Portuguese pediatric population. There was a strong positive correlation between IQ and total QoL, emphasizing the relationship between cognitive function and QoL in this population.

Table 5. Comparison of intelligence quotients and quality of life scores between children with and without attention deficit hyperactivity disorder in congenital hypothyroidism

	ADHD n = 12	Non-ADHD n = 34	p
Total IQ 4	85.6 (19.9)	100.2 (17.1)	0.051
- Verbal IQ	90.2 (17.3)	106.8 (17.4)	**0.022**
- Performance IQ	85.2 (21.8)	97.2 (15.9)	0.095
Verbal comprehension index	95.6 (18.1)	104.2 (19.5)	0.175
Perceptual organization index	79.9 (17.5)	95.2 (13.8)	**0.041**
Processing speed index	92.9 (19.8)	101.1 (16.6)	0.196
Total QoL	78.0 (15.6)	84.8 (12.8)	0.096
Physical	85.8 (16.0)	87.4 (15.6)	0.387
Emotional	80.1 (18.2)	80.8 (17.7)	0.456
Social	82.7 (22.7)	89.4 (16.3)	0.180
School	63.3 (12.8)	81.6 (16.4)	**0.002**

The data is presented as mean (standard deviation).
ADHD: attention deficit hyperactivity disorder, IQ: intelligence quotient, QoL: quality of life

Table 6. Comparison of intelligence quotients and quality of life scores between children with and without learning disorders in congenital hypothyroidism

	LD n = 9	Non-LD n = 37	p
Total IQ 4	77.5 (15.0)	104.3 (14.0)	**0.001**
- Verbal IQ	83.9 (12.4)	109.5 (15.3)	**0.002**
- Performance IQ	78.1 (17.8)	100.9 (14.6)	**0.010**
Verbal comprehension index	84.0 (12.9)	108.6 (16.0)	**0.010**
Perceptual organization index	79.9 (17.5)	97.0 (11.3)	**0.002**
Processing speed index	89.8 (18.9)	102.1 (16.6)	0.163
Total QoL	70.3 (16.3)	86.1 (11.3)	**0.005**
Physical	80.4 (19.2)	88.6 (14.3)	0.197
Emotional	73.0 (25.3)	82.4 (15.1)	0.397
Social	71.9 (27.5)	91.5 (12.9)	0.063
Scholar	56.0 (13.5)	81.9 (16.4)	**< 0.001**

The data is presented as mean (standard deviation).
IQ: intelligence quotient, QoL: quality of life, LD: learning disorders

Thyroid hormone insufficiency has been linked to structural abnormalities in the brain, particularly in the corpus callosum, which connects the cerebral hemispheres and is crucial for integrated brain function (23). Abnormalities in these neural connections have been observed not only in hypothyroidism but also in autism spectrum disorders (ASD) and ADHD (24). This suggests that structural defects in the brain in CH may contribute to the neurodevelopmental issues observed in these children. The high prevalence of ADHD observed in our cohort is consistent with literature that reports elevated attention-related disorders in children with thyroid dysfunction (6,7,8,9,10), including a large Australian cohort where mildly elevated neonatal TSH levels were linked to a higher risk of ADHD and school performance issues (25). Maternal thyroid dysfunction during pregnancy has also been associated with neurodevelopmental problems, including ADHD (6,11,12). Recent studies have also reported a higher prevalence of ASD among patients with CH (9,10). Notably, one study linked the occurrence of ASD to undertreated CH, contrasting with the association of ADHD with overtreatment (9). However, no cases of ASD were observed in our cohort, indicating potential variability in neurodevelopmental outcomes associated with different treatment practices in this population.

Children with ADHD in our cohort exhibited lower total IQ, with significantly lower verbal and perceptual organization scores. Previous studies have consistently shown that, in addition to symptoms of inattention and hyperactivity-impulsivity, children with ADHD often experience distinct cognitive impairments (26,27,28). Interestingly, the pattern of subscores in our cohort differs from the typical cognitive profile seen in ADHD, where lower scores are generally observed in the processing speed index and freedom from distractibility index (not included in the Portuguese WISC-III), rather than in the verbal comprehension or perceptual organization index (27,29). The lower perceptual organization index in our cohort may be associated with and influenced by CH, as it was the lowest score in the WISC evaluation for this population and showed a decline when CH treatment was initiated later.

The lower school-related QoL scores in children with ADHD in our cohort are consistent with studies highlighting the negative impact of ADHD on academic and social functioning (30,31). These children often face difficulties with attention and executive functioning, which likely contributes to their diminished QoL in different settings (30,31). Together, these

findings highlight the need for comprehensive management of ADHD in children with CH, as both conditions appear to have a significant impact on cognitive function and QoL, particularly in academic and social settings. Early detection and tailored interventions for ADHD in this population may play a role in improving long-term neurodevelopmental outcomes.

In our cohort, 37 of 47 patients began treatment before 15 days of life, aligning with current best practices (2). However, eight patients started treatment between 15 and 45 days, and one outlier, due to an administrative error, initiated treatment at three months. This case is the only instance of an intellectual disability diagnosis in our study. This underscores the critical importance of efficient communication within screening programs to prevent delays in treatment, which can significantly impact neurocognitive development throughout life.

Numerous studies have demonstrated the importance of early treatment of CH to prevent developmental defects (5,32). Despite neonatal screening programs significantly reducing the rates of severe intellectual disability in children with CH, neurocognitive impairment, including difficulties in cognitive function, language development, motor skills, and learning achievements, remain evident into school-age and adolescence (1,33). In our cohort, the proportion of children with cognitive levels below the norm and intellectual disability aligned with expectations for the general population (20). However, the high prevalence of LD in our cohort highlights the significant academic challenges faced by children with CH. Moreover, the poorer general and school-related QoL observed in children with LD reflects its profound impact on academic functioning and daily life. The observed decline in IQ scores over time, particularly in those diagnosed and treated later, further illustrates the impact of late treatment in cognitive functions. Our results are in line with the study of Pulungan et al. (5) that also reports a negative correlation between later treatment initiation and performance IQ, with no association with verbal IQ. This suggests that non-verbal cognitive domains may be more vulnerable to treatment delays, a vulnerability that may only manifest at later developmental stages. However, some studies have found correlations between treatment timing and other IQ components, highlighting variability in how delays may affect different cognitive domains (32).

Our study found that children with CH generally had a QoL comparable to the normative Portuguese pediatric population, with significant associations between later treatment initiation and lower QoL scores in the emotional, social, and total QoL domains. Interestingly, QoL was associated only with the age of treatment initiation, not the age of diagnosis, emphasizing the critical importance of timely treatment. The literature on QoL in CH patients presents mixed findings. Some studies report similar QoL scores to those of healthy individuals (13,14,15), while others report either better (16,17), or lower QoL (18). In terms of the relationship between QoL and the timing of treatment initiation, other recent studies have also found significant negative correlations, consistent with our findings (16,17). These studies, like ours, reported no significant association between QoL and TSH levels at diagnosis, reinforcing the relevance of treatment timing over biochemical markers at diagnosis in predicting long-term outcomes. However, not all research supports these conclusions, with some studies reporting no correlation between age at treatment initiation and QoL (5,34). A recent critical review suggested that no single physiological, genetic, clinical, demographic, or behavioral factor can be definitively linked to either poor or good QoL in CH patients (35). Nevertheless, factors such as weight gain, the presence of anti-thyroid peroxidase antibodies, physical activity, and lifestyle choices may all play a role in shaping QoL (35). This range of potential influencing factors highlights the complexity of the interactions between hormone levels, hypothyroidism symptoms, and QoL.

Moreover, the clear link between IQ and QoL observed in our cohort emphasizes the broader implications of cognitive function for overall well-being. This association between cognitive function and QoL has been noted in a previous study (34), where lower IQ was linked to worse QoL, though with no clear association to later therapy initiation. In our study, parents of children with higher IQ reported better QoL, particularly in school-related domains, which underscores the importance of cognitive support for this population. These findings highlight the need for targeted interventions to improve cognitive outcomes, whether through early treatment, educational support, or ADHD management. Routine neurodevelopmental evaluations and tailored interventions should be a priority in the long-term care of children with CH, as preventing cognitive damage and addressing neuropsychological impairments must remain central goals in CH screening and treatment programs.

Study Limitations

Despite the valuable insights provided by our study, certain limitations should be acknowledged. The relatively small sample size, especially in the later cognitive assessments, may limit the generalizability of our findings. In addition, questionnaire-based assessments of QoL can be influenced by biased recall and variable interpretation. However, they

still serve as a useful tool for a general assessment of QoL in CH. While the study's longitudinal design allows for the observation of changes over time, the assessments conducted at specific intervals may not fully capture the nuances of long-term cognitive trajectories. Furthermore, the tests administered to the subjects may be influenced by various sociodemographic factors, such as family characteristics and parental education level, which were not available for analysis in this study. To confirm our results and explore the mechanisms underlying cognitive decline in children with delayed treatment initiation, future studies with larger sample sizes, and longer and more frequent follow-up periods are needed. Investigating specific interventions, such as cognitive training or behavioral therapy for ADHD, will also be important to improve outcomes for children with CH.

Conclusion

Our study reinforces the critical importance of early thyroid hormone replacement therapy, in mitigating neurocognitive deficits and improving future QoL in children with CH. Despite advances in neonatal screening that have reduced severe intellectual disability, subtle cognitive impairments, particularly in non-verbal domains, persist. Early diagnosis, timely treatment before 15 days after birth in our study, and continuous monitoring are crucial for optimizing long-term cognitive and QoL outcomes. Furthermore, addressing comorbid ADHD and LD is essential for improving both neurodevelopmental and academic outcomes in this population.

Ethics

Ethics Committee Approval: The study was approved by the Unidade Local de Saúde de São João Ethical Committee (approval no: 202-2023, date: 23/10/2023).

Informed Consent: All eligible participants and their parents provided informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Sofia Ferreira, Rita Santos Silva, Micaela Guardiano, Paulo Almeida, Cíntia Castro-Correia, Concept: Laura Leite-Almeida, Rita Curval, Paulo Almeida, Cíntia Castro-Correia, Design: Laura Leite-Almeida, Rita Curval, Paulo Almeida, Cíntia Castro-Correia, Data Collection or Processing: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Analysis or Interpretation: Laura Leite-Almeida, Rita Curval, Inês Pais-Cunha, Bárbara Pereira-Neto, Sofia Ferreira, Rita Santos Silva, Micaela Guardiano, Paulo Almeida, Cíntia Castro-Correia, Literature Search: Laura Leite-Almeida, Rita Curval, Writing: Laura Leite-Almeida, Rita Curval.

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