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CAROLINA LOPES DE ALMEIDA

***NEURODEVELOPMENTAL OUTCOMES IN
CHILDREN WITH
CONGENITAL HYPOTHYROIDISM***

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Neurodevelopmental Outcomes in Children with Congenital Hypothyroidism

Carolina Lopes de Almeida¹, Frederico Duque^{1,2}, Guiomar Oliveira^{1,2}

¹Faculty of Medicine, University of Coimbra, Coimbra, Portugal

²Neurodevelopment and Autism Unit, Child Development Centre, Hospital Pediátrico –
Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

E-mail:
c.almeida1991@gmail.com

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Neurodevelopmental Outcomes in Children with Congenital Hypothyroidism

Abstract

Although prognosis of Congenital Hypothyroidism (CH) has been greatly modified since the introduction of newborn screening programs, persistent cognitive deficits are still reported.

The aim of this study was to evaluate neurodevelopmental outcomes of children with CH and to determine whether severity of CH, age of start of L-thyroxine supplementation and control of CH play an important role.

We analyzed a sample of children with CH (N=44) using neurodevelopmental assessment tests according to child's age and level of functioning: Griffiths Scale of Mental Development (GSMD), Portuguese version of Wechsler Intelligence Scale for Children – Third Edition (WISC-III), and Vineland Adaptive Behaviour Scale (VABS) and early developmental milestones. We further compared this data with screening TSH values and follow-up mean values of TSH, fT4 and L-thyroxine dosage.

Communication Disorders and Attention-Deficit/Hyperactivity Disorder were the most common diagnosis, 25% and 15.9% respectively, found among children with neurodevelopmental problems (59.1%). Average scores in Practical Reasoning Quotient in the Griffiths subscale and Adaptive Behaviour Composite, Daily Living Skills and Socialization (VABS domains) in children with CH were significantly lower than in normal population. A correlation was found between mean L-thyroxine dosage and Full Scale Intelligence Quotient (WISC-III). No correlation was found between screening level of TSH, age of treatment

initiation, follow-up mean TSH, mean fT4 values and results in the three global scales of neurodevelopmental tests.

Even though prognosis of CH has been greatly modified since early detection through screening programs, careful monitoring of these children is crucial to guarantee an early intervention and to assure optimal neuro- and sociodevelopmental outcomes.

Keywords: Congenital Hypothyroidism, Child, Screening program, Neurodevelopmental disorder, Cognition

Abbreviations

ADHD - Attention-Deficit/Hyperactivity Disorder

CH - Congenital Hypothyroidism

FIQ - Full Scale Intelligence Quotient

GDQ - General Developmental Quotient

GSMD - Griffiths Scale of Mental Development

LDQ - Locomotor Developmental Quotient

L-thyroxine - Levothyroxine

PIQ - Performance Intelligence Quotient

PRDQ - Practical Reasoning Developmental Quotient

SD - Standard deviation

ft4 - Free thyroxine

T4 - Thyroxine

TSH - Thyroid Stimulating Hormone

T3 - Triiodothyronine

VABS - Vineland Adaptive Behaviour Scale

VIQ - Verbal Intelligence Quotient

WISC-III - Portuguese version of Wechsler Intelligence Scale for Children – Third

Edition

Introduction

Congenital Hypothyroidism (CH) is the most common congenital endocrine disorder and one of the most preventable causes of intellectual disability. It has an incidence of, approximately, 1/2000 to 1/4000 worldwide. (1-3) In Portugal, it has an incidence of 1/2953 births. (4) CH may be permanent or transient and aetiology of this disorder may be diverse: thyroid dysgenesis (agenesis or hypoplasia/ectopic) – the most common cause, dyshomogenesis, hypopituitarism/Thyroid Stimulating Hormone (TSH) deficiency, resistance to TSH or iodine deficiency. (1,2,5-7) This is relevant because it specifies when the disorder began.

It has been long established the critical role of the thyroid hormone in central nervous system maturation both during pre- and postnatal life, growth, metabolism and cardiovascular function. (8-10) Thyroxine (T4) and triiodothyronine (T3) binding to α , β_1 and β_2 receptors in target tissues, for example pituitary and hypothalamus (β_2), liver (β_1 and β_2) heart (α), and brain (α and β_1), results in an increase in oxygen consumption, altered protein carbohydrate and lipid metabolism and potentiation of catecholamines' action.(8) Nervous system development involves neurogenesis, gliogenesis, neural cell migration, neuronal differentiation, dendritic and axonal growth, synaptogenesis, myelination, and neurotransmitter synthesis. Thyroid hormones have been shown to stimulate a number of developmentally regulated nervous tissue genes, but the role of these factors in the central nervous system developmental program remains undefined. (11) Before introduction of screening programs, most children with CH sustained damage to their developing brain and were left with moderate to severe cognitive impairment. (6,12-13) This was due to difficulties in identifying children with CH, since signs were scarce and unspecific in about 80% of cases. In the first 2 weeks of life, such signs and symptoms may include but are not limited to:

protruding tongue, hoarse cry, floppiness, sleepy/lethargic state, goitre and poor feeding. (1,5) The aim of neonatal screening programs is to prevent cerebral damage through early initiation of levothyroxine (L-thyroxine) supplementation, which shortens the period of postnatal hypothyroidism. With its implementation in developed countries, prognosis of this disease has been greatly modified. (1,5-7,9,14) However, there are still some parts of the world where screening programs are not implemented yet, therefore knowledge of CH clinical features continues to be helpful. (5,15)

In Portugal, CH screening program began in 1981 and, even though participation is voluntary, it currently maintains a near total coverage rate of about 100% of live births. (4) From its beginning until 2014, 1160 children were diagnosed with CH in Portugal (on average 34 cases per year). (4) From 2002 until 2014, our hospital has received a total of 67 children in this time line, with an average of 5 children per year.

The screening method consists in measuring TSH levels in dried heel-prick blood samples from the baby's heel onto filter paper cards between the 3rd and 6th day of age, collected at Primary Care Health Services. Samples are sent to *Unidade de Rastreio Neonatal* in *Instituto Nacional de Saúde Doutor Ricardo Jorge - Porto*. (4) After confirmation of CH, the newborn is referred to a reference treatment centre where he must initiate substitution treatment with L-thyroxine in order to normalize levels of free thyroxine (fT4) within two weeks and TSH within a month. The recommended initial dosage of L-thyroxine is 10-15µg/kg, depending on the severity of CH. (2,15-16) According to *European Society for Paediatric Endocrinology* consensus guidelines, severity of CH can be defined clinically on the basis of symptomatic hypothyroidism; biologically as severe, moderate, or mild on the basis of serum fT4 levels of < 5,5 to < 10, and 10 to 15 pmol/L, respectively; on the basis of delayed epiphyseal maturation on knee x-ray; and in terms of aetiology of CH. (17) Treatment success depends on regular medical follow-up, measuring serum or plasma TSH and either

total T4 or fT4 concentrations in order to maintain TSH concentration in age-specific reference range and total T4 or fT4 concentration should be maintained in the upper half of age-specific reference range. (8,17)

Despite early neonatal treatment and good compliance, many studies describing outcomes of patients during childhood suggest that, although early management is effective in preventing intellectual disability associated with cretinism (severe growth retardation with mental handicap), some individuals may still have some subtle selective cognitive deficits and other neurodevelopmental deficits when compared to control groups. (1,6,9,13,18-22) This can result in subnormal cognitive and motor development, which persists into adulthood. Cognitive deficits in both verbal and performance domains and motor deficits in balance, coordination, fine motor and ball skills are most prominent deficits. (10,13,23-24) It is also referred that delays in expressive language acquisition are also common. (6,10) Attention deficit disorder, impulsiveness and hyperactivity have also been described. (10,25)

The origin of these deficits may be in influences during *in-utero* neurodevelopment because CH is already expressed in fetal life and maternal T4 is not sufficient to fill the gap in fetal T4 production. The importance of *in-utero* thyroid hormone state has been proven by cognitive and motor deficits seen in offspring of women with hypothyroidism during pregnancy. (6,13,26)

Studies have shown that severity of CH, in contrast to timing of treatment initiation, is a major factor determining long-term neurodevelopmental outcomes. In fact, these disabilities are more prevalent in patients with severe CH, being more subtle in patients with mild to moderate CH. (13,20-22)

Therefore, clinically monitoring these children is of paramount importance in order to detect them at preschool age, before learning difficulties may arise, and they can benefit from

early and personalized psychoeducational intervention programs to optimize neurodevelopmental outcomes. (9)

This study aims to examine the effects in neurodevelopment and to determine whether severity of CH, age of start of L-thyroxine supplementation and control of CH play an important role on its outcome in children with CH who have received an early treatment and are followed in our Child Development Centre.

Methods

Participants

From 2002 until 2014, our Endocrinology Unit (regional reference treatment centre) has received a total of 67 children, with an average of 5.2 cases per year. Table 1 shows the distribution of CH cases per year in our hospital.

Table 1- Distribution of CH cases per year in Endocrinology Unit from 2002 until 2014

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of cases	2	3	4	3	8	7	10	4	7	3	10	2	4

In our Child Development Centre, 60 of 67 CH cases, ranging from 2 to 14 years old, were regularly evaluated and followed up between 2010 and 2015, are here analysed. Data was collected from a clinical electronic register - FileMaker-Pro 5 database according to national policy on archival research (*Comissão Nacional de Proteção de Dados*).

All patients were screened through Portugal's National Screening Program. The specimen used for newborn screening tests is blood from a heel-prick collected on special filter paper cards between the 3rd and 6th day of age collected at Primary Care Health Services. The algorithm for screening of CH in Portugal is represented in Figure 1.

In Portugal, the primary marker is TSH level. The TSH cut-off value used is 10mUI/L. Values below 10mUI/L are considered normal and more evaluation is no longer required. If TSH value is above 20mUI/L, there is a high suspicion of CH and the newborn is transferred to our tertiary hospital, regional reference treatment centre. A TSH value between 10-20mUI/L is considered suspect and demands determination of total T4 levels in the same specimen. If T4 is inferior 6,5µg/dL, the suspicion of CH is confirmed and the newborn starts L-thyroxine. Also, diagnosis of CH is made if TSH is above 40mUI/L (Figure 1).

For preterm newborns, protocol dictates, besides the first TSH determination between the 3rd and 6th day of age, a second and a third TSH determination after two and four weeks, respectively. (4)

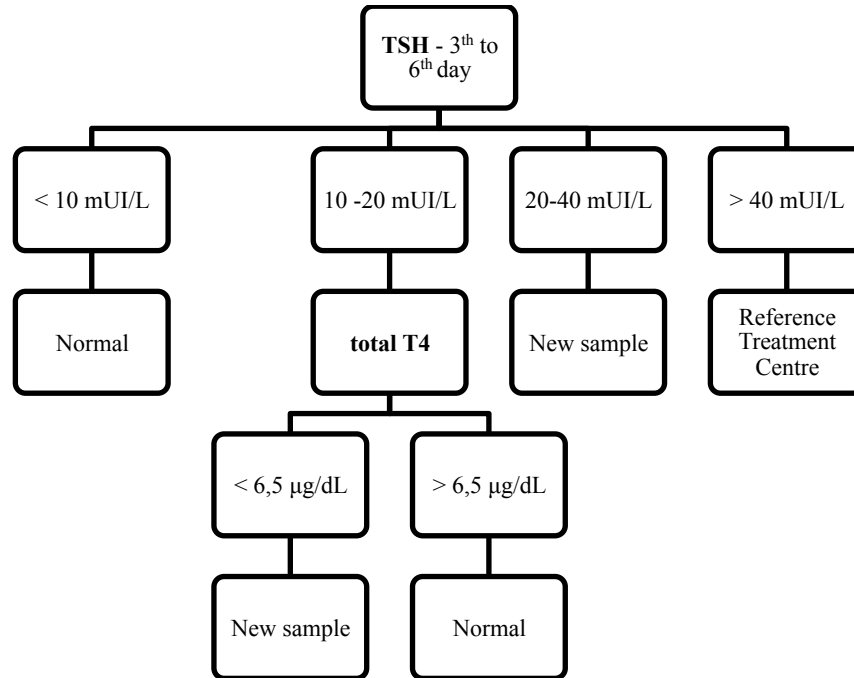


Figure 1 - CH neonatal screening algorithm in Portugal (adapted from Vilarinho *et al.*)

The criteria for participants' eligibility were: (1) having early diagnosis for permanent CH attending periodic Endocrinology follow-up; (2) not presenting other congenital or acquired alterations apart from CH; (3) having been evaluated by Griffiths Scale of Mental Development (GSMD) or Portuguese version of Wechsler Intelligence Scale for Children – Third Edition (WISC-III) and/or Vineland Adaptive Behaviour Scale (VABS) between 2010 and 2015. From the initial 60 participants, after exclusion criteria, we remained with 44 (73.3%) subjects.

Measurements

Age, gender, gestational age, neurodevelopmental diagnosis and early developmental milestones variables like age of gait, first words and first phrases were recorded. Regarding

the evaluation of severity of CH until 2011, we could only consider the screening value of TSH. Nevertheless, since 2012, these children are evaluated first in a consult booked the immediate moment we receive notification of the case, where measurements of TSH and fT4 are made, before initiation of L-thyroxine treatment. Screening TSH values and follow-up mean values of TSH, fT4 and L-thyroxine dosage were collected too.

Cognitive testing was undertaken by a psychologist who is experienced in conducting neurodevelopmental tests and was blinded for neonatal TSH levels of the selected children.

The assessment of cognitive development was performed using different scales as appropriate for the child's chronological age and level of functioning: GSMD and/or WISC – III, and adaptive behaviour assessed with VABS.

All age data is presented in months of age.

Griffiths Scale of Mental Development (2-8 years old)

Griffiths assesses the developmental quotient of children from 2 to 8 years old. It comprises six subscales: locomotor, social/personal, hearing and speech, eye and hand coordination, performance, and practical reasoning. These subscales yield standardized scores for each domain and a composite general developmental quotient (GDQ). For each subscale, a standardized score over 2SD below the mean indicates severe impairment. The evaluation of mental development through appraisal of different developmental areas allows results to demonstrate the relative level of development of each area. Practical reasoning (PRDQ) can only be evaluated after 36 months of age. A normal quotient is 100 ± 15 (mean \pm SD). (27)

Portuguese version of Wechsler Intelligence Scale for Children – Third Edition

The WISC-III is a reference in the assessment of intelligence, identifying a global level of cognitive ability. Its analysis also allows for the verification of performance in a specific

subtest and whether it suggests the presence of a specific cognitive deficit or, on the contrary, is widespread evidence of global cognitive deficit. This test enables the calculation of a Full Scale Intelligence Quotient (FIQ), a Performance Intelligence Quotient (PIQ) and a Verbal Intelligence Quotient (VIQ) in children between ages of six and sixteen years and eleven months.

Each quotient has a mean of 100 and a standard deviation (SD) of 15 representing the average range of functioning and scores more than 2 SDs below the mean (<70) indicates severe impairment. It has been adapted and standardized for the Portuguese population by Simões and colleagues in 2003. (28)

Vineland Adaptive Behaviour Scale

VABS is a standardized, although semi-structured, widely used norm-referenced caregiver interview that measures children adaptive abilities. It comprises three main domains (communication, daily living skills, and socialization) and two optional domains (motor skills for children under 6 years old and maladaptive behaviour for those over 5 years old). Each domain contains several subdomains that enquire a specific developmental area. VABS total score, the Adaptive Behaviour Composite, is calculated as the sum of the raw scores from the domains measured, reflects cognitive and social competences acquired by the child to respond to daily life demands. Similar to IQ, normal scores in, domain areas and the composite are 100 ± 15 (mean \pm SD). (29-30)

Early developmental milestones variables

We also analyze age of acquisition of major early developmental milestones, such as: gait, first words and first phrases.

Gait was defined as age of acquisition of independent walking (an early motor development variable). A normal child should acquire this milestone by the age of 12 months.

For language milestones, first words and phrases variables, parent-reported ages for first single words used meaningfully and phrase speech were taken from medical records. The use of first meaningful words should begin at about 10 months of age. A phrase speech is defined as the spontaneous, flexible use of at least two words in combination, one of which must be a verb, and it should be acquired by 24 months of age. (31)

Neurodevelopmental Disorders diagnosis were made according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria fulfilment (32), presented as *Supplementary Material* (Appendix A), and behaviour questionnaires (Achenbach's and Conner's). (33,34) Specifically, for communication disorder diagnosis all children were also evaluated by our speech and language therapist.

For more detailed description see *Supplementary Material* (Appendix A).

All age data is presented in months of age.

Statistical analysis

Initially, summary measures were sought for each variable: frequencies for qualitative variables and mean, standard deviation, median and the 25th and 75th percentiles for quantitative variables. The normality of each quantitative variable was assessed resorting to Shapiro-Wilk tests. To compare means of quantitative variables with reference values, one sample t-tests were used. The correlation between quantitative variables was evaluated using Spearman's correlation tests. The level of significance adopted was $\alpha=0.05$. All statistical computations were performed resorting to IBM SPSS Statistics version 23.

Ethics Statement

This study and all the procedures were reviewed and was conducted in accordance with the declaration of Helsinki.

Results

A total of 44 children with CH, including 17 boys (38.6%) and 27 girls (61.4%) were enrolled into the study. All children had been detected by newborn screening at chronological age refereed in methods. For gestational age, 21% of the patients were preterm newborns, but all were born with more than 34 weeks of gestational age.

Descriptive analysis

Table 2 shows the neurodevelopmental diagnosis made in children with CH. Communication Disorders and Attention-Deficit/Hyperactivity Disorder (ADHD) were the most common diagnosis found among children with neurodevelopmental disorders, together accounting for 40.9%. On the other hand, 40.9% of patients did not have a neurodevelopmental diagnose.

Table 2 - Neurodevelopment diagnosis in patients with CH

Neurodevelopment diagnosis	n	Percentage
ADHD	7	15.9
Dyslexia	1	2.3
Communication Disorders	11	25.0
- Developmental Language Disorder	5	11.4
- Speech Sound Disorder	6	13.6
Learning disorder	2	4.5
Intellectual Disability	3	6.8
Global Developmental Delay	2	4.5
No Neurodevelopmental Problems	18	40.9
Total	44	100.0

Legend: ADHD - Attention-Deficit/Hyperactivity Disorder, Dyslexia (specific learning disorder), Communication Disorders (Developmental Language Disorder, Speech Sound Disorder), Learning disorder, Intellectual Disability, Global Developmental Delay (adapted from DSM-5). Diagnostic criteria as *Supplementary Material* in Appendix A.

Ages of early neurodevelopmental milestones (gait, first words and first phrases) are presented in Table 3.

Table 3 - Descriptive Statistics for age of early developmental milestones

	n	Mean	Standard Deviation	Median	Percentile 25	Percentile 75
Gait	36	14.1	2.3	14.0	12.0	15.5
First Words	39	13.6	2.7	13.0	12.0	15.0
First Phrases	37	25.1	7.4	24.0	22.0	25.0

Legend: All age data is presented in months of age.

After the normality of each quantitative variable was assessed resorting to Shapiro-Wilk tests, one sample t-tests were used to compare means of quantitative variables with reference values.

Out of 44 cases, 29 (65.9%) children with CH were evaluated using GSMD. The mean age at the time this test was performed was 44.2±19.9 months. Table 4 and Figure 2 present overall scores for the six GSMD subscales and GDQ. Average scores on Practical Reasoning Developmental Quotient (PRDQ) in children with CH were significantly lower than in normal population ($p < 0.05$). LDQ was statistically higher than in normal population. However, no significant alterations in GDQ scores were observed. It should be noted that there was a subject that consistently scored lower across all Griffiths subscales, corresponding to a moderate to severe Intellectual Disability.

Table 4 - Descriptive statistics for Griffiths Scale of Mental Development

	n	Mean	Standard Deviation	Median	Percentile 25	Percentile 75	p-value
GDQ	29	98.6	17.3	100.0	93.0	107.0	0.895
LDQ	29	108.3	22.0	108.0	98.0	125.0	0.016
SPDQ	29	103.1	22.7	103.0	89.0	117.0	0.352
HSDQ	29	94.9	19.8	97.0	88.0	106.0	0.190
HEDQ	29	98.8	17.9	100.0	89.0	109.0	0.909
PDQ	29	95.8	19.3	97.0	85.0	100.0	0.224
PRDQ	23	90.0	19.2	92.0	79.0	105.0	0.025

Legend: The p-values were obtained using one-sample t-tests. No correction for multiple comparisons was performed. GDQ – General Developmental Quotient, LDQ – Locomotor Developmental Quotient, SPDQ – Social-Personal Developmental Quotient, HSDQ – Hearing/Speech Developmental Quotient, HEDQ – Hand/Eye Developmental Quotient, PDQ – Performance Developmental Quotient, PRDQ – Practical Reasoning Developmental Quotient.

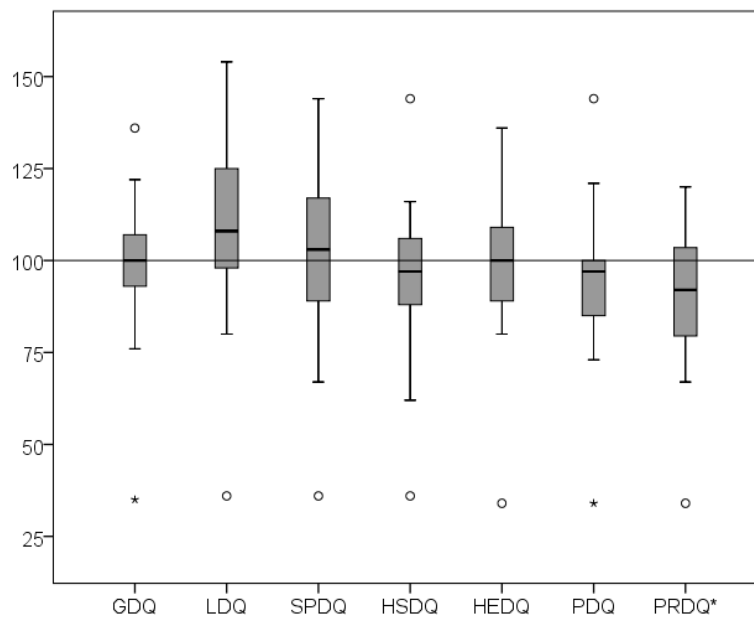


Figure 2 - The box plot shows GDQ, LDQ, SPDQ, HSDQ, HEDQ, PDQ and PRDQ Griffiths scores. Legend: GDQ – General Developmental Quotient, LDQ – Locomotor Developmental Quotient, SPDQ – Social-Personal Developmental Quotient, HSDQ – Hearing/Speech Developmental Quotient, HEDQ – Hand/Eye co-ordination Developmental Quotient, PDQ – Performance Developmental Quotient, PRDQ – Practical Reasoning Developmental Quotient.

WISC – III was performed in 17 (38.6%) cases at 111.9±23.7 months. No significant alterations in FSIQ, VIQ or PIQ scores were observed ($p>0.05$), presented on Table 5 and Figure 3.

Table 5 - Descriptive statistics for Portuguese version of WISC-III

	n	Mean	Standard Deviation	Median	Percentile 25	Percentile 75	p-value
FSIQ	17	99.6	19.8	98.0	82.0	110.0	0.776
VIQ	17	98.8	23.2	101.0	86.0	115.0	0.906
PIQ	17	99.1	17.1	98.0	82.0	111.0	0.653

Legend: The p-values were obtained using one-sample t-tests. No correction for multiple comparisons was performed. FIQ – Full Scale Intelligence Quotient; PIQ – Performance Intelligence Quotient; VIQ – Verbal Intelligence Quotient.

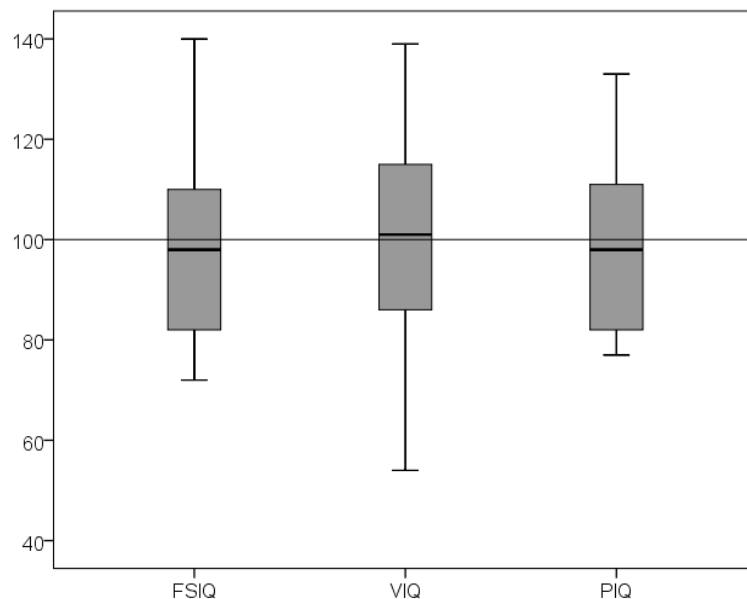


Figure 3 - The box plot shows FSIQ, VIQ, and PIQ scores (WISC - III).

Legend: FIQ – Full Scale Intelligence Quotient; PIQ – Performance Intelligence Quotient; VIQ – Verbal Intelligence Quotient.

VABS was performed in 21 (47.7%) children at 89.9±44.6 months of age. No statistical differences were observed in Communication and Motor Skills domains. On the other hand, scores in Daily Living Skills, Socialization and Adaptive Behaviour Composite, in children

with CH were significantly lower than in normal population ($p < 0.05$). Table 6 and figure 4 present the scores of domains and composite evaluated by VABS.

Table 6 - Descriptive statistics for VABS

	n	Mean	Standard Deviation	Median	Percentile 25	Percentile 75	p-value
Daily Living Skills	21	82.0	22.3	84.0	71.0	91.0	0.002
Communication	21	102.1	19.0	104.0	89.0	119.0	0.559
Socialization	21	87.1	12.9	85.0	77.0	92.0	0.001
Motor Skills	5	97.8	26.0	114.0	73.0	116.0	0.686
Adaptive Behaviour Composite	21	87.8	15.7	89.0	74.0	97.0	0.002

Legend: The p-values were obtained using one-sample t-tests. No correction for multiple comparisons was performed.

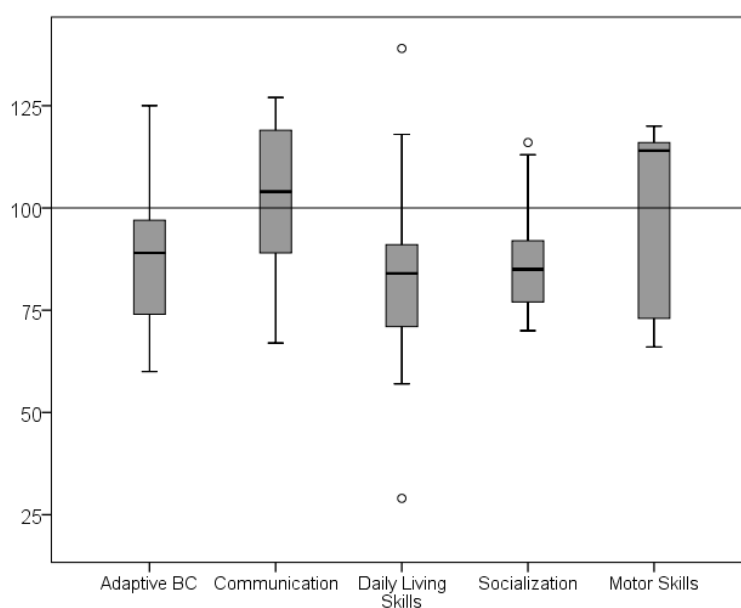


Figure 4 - The box plot shows the Adaptive Behaviour Composite and VABS domains: Communication, Daily Living Skills, Socialization and Motor Skills scores

Correlations

The correlation between quantitative variables was evaluated using Spearman's correlation tests.

Severity of CH

There is no correlation found between screening level of TSH and results in the three global scores (GDQ, FSIQ and Adaptive Behaviour Composite) of cognitive and functional assessment tests. No statistically meaningful correlation was found between screening level of TSH and GDQ ($\rho=-0.156$, $p=0.419$), between screening level of TSH and FSIQ ($\rho=-0.184$, $p=0.480$) or between screening level of TSH and adaptive behaviour composite ($\rho=-0.051$, $p=0.827$).

Graphs in figures 5 to 7 depict the lack of correlation between these variables.

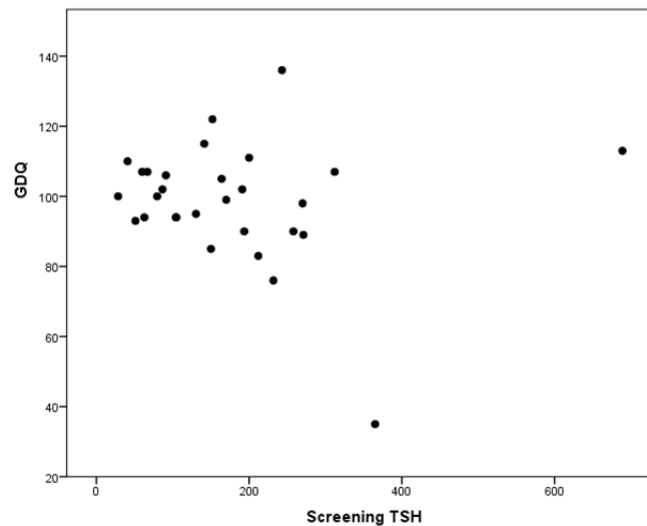


Figure 5 - Association between screening TSH level (mUI/L) and GDQ

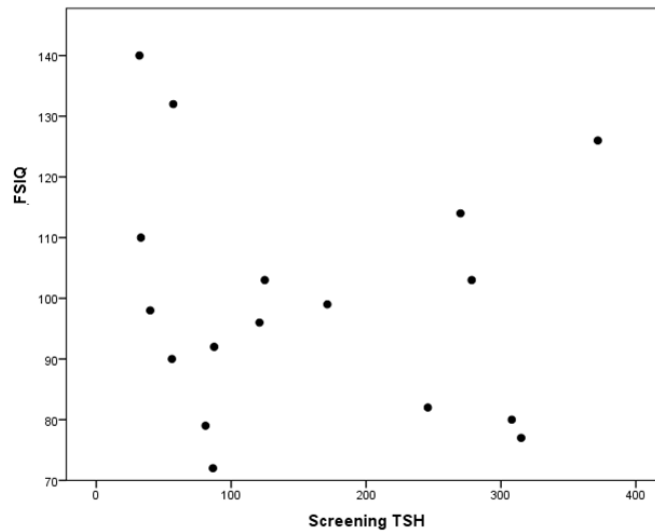


Figure 6 - Association between screening TSH level (mUI/L) and FSIQ

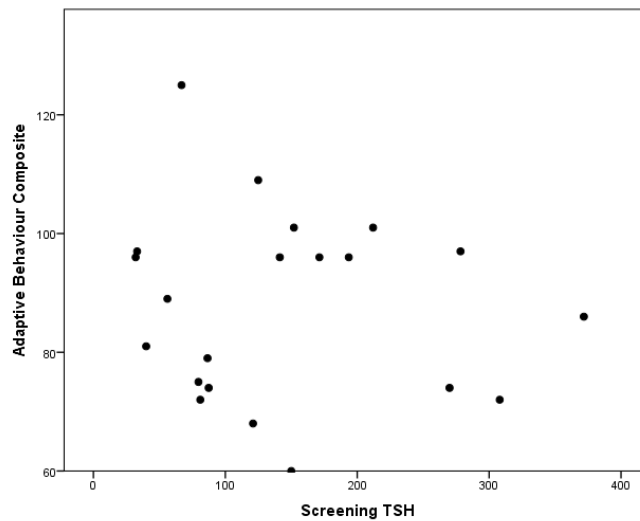


Figure 7 - Association between screening TSH level and Adaptive Behaviour Composite

Age of onset of treatment

We found no correlation between age of treatment initiation and results in the three global scores (GDQ, FSIQ and Adaptive Behaviour Composite). No statistically meaningful correlation was found between day of treatment start and GDQ ($\rho=0.310$, $p=0.101$), FSIQ ($\rho=0.269$, $p=0.297$) nor Adaptive Behaviour Composite ($\rho=-0.051$, $p=0.825$).

Graphs in figures 8 to 10 depict the lack of correlation between these variables.

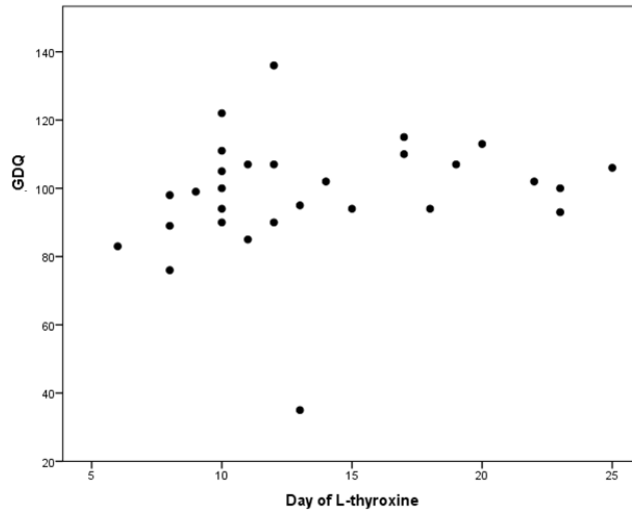


Figure 8 - Association between day of onset of treatment with L-thyroxine and GDQ

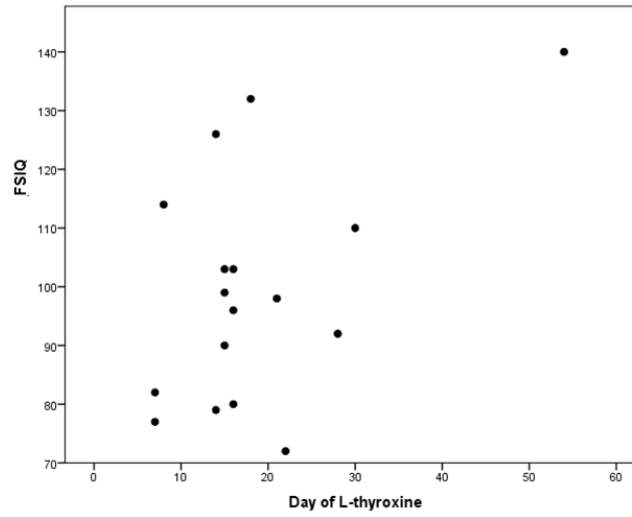


Figure 9 - Association between day of onset of treatment with L-thyroxine and FSIQ

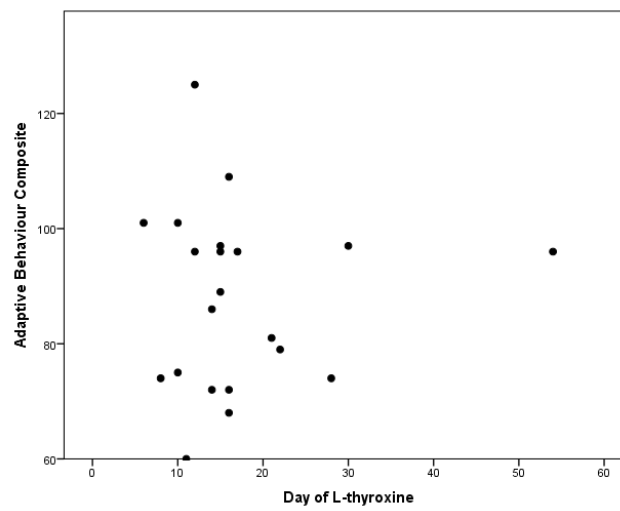


Figure 10 - Association between day of onset of treatment and Adaptive Behaviour Composite

Control of CH

To study the control of CH, we analysed mean values of TSH levels, fT4 levels and L-thyroxine mean dosage during follow-up in our Endocrinology Unit.

Regarding follow-up TSH levels, we found no correlation between mean TSH and results in the three scores (GDQ, FSIQ and Adaptive Behaviour Composite). No statistically meaningful correlation was found between mean TSH and GDQ ($\rho=-0.167$, $p=0.388$), between mean TSH and FSIQ ($\rho=-0.006$, $p=0.980$), nor between mean TSH and adaptive behaviour composite ($\rho=0.381$, $p=0.088$).

Also, there was no statistically correlation was found between mean fT4 and GDQ ($\rho=-0.076$, $p=0.694$), FSIQ ($\rho=-0.102$, $p=0.698$), nor Adaptive Behaviour Composite ($\rho=-0.365$, $p=0.103$).

Concerning mean dosage of L-thyroxine supplementation, a statistically meaningful correlation was found between mean L-thyroxine dosage and FSIQ ($\rho=-0.508$, $p=0.037$). In this group, a higher dosage of L-thyroxine correlates to a lower FSIQ (Figure 11). However, no correlation was found between mean L-thyroxine and GDQ ($\rho=-0.183$, $p=0.343$) nor Adaptive Behaviour Composite ($\rho=0.886$, $p=0.033$).

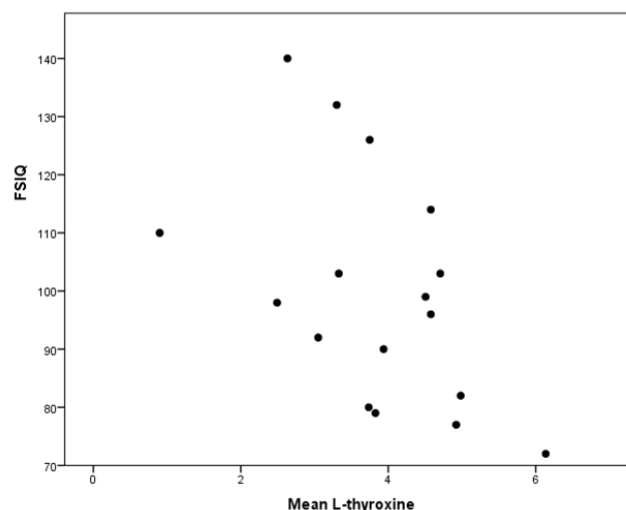


Figure 11 - Association between follow-up mean dosages of L-thyroxine supplementation.

Legend: A correlation was found between mean L-thyroxine dosage and FSIQ ($\rho=-0.508$, $p=0.037$), namely a higher dosage of L-thyroxine correlates a lower FSIQ.

Discussion

Regarding follow-up mean dosage of L-thyroxine supplementation, a statistically meaningful correlation was found between mean L-thyroxine dosage and FSIQ ($p < 0.05$). This may mean that a poor control of the disease, translated by the need of a higher dosage of L-thyroxine in order to normalize hormonal levels, can have a repercussion in the neurodevelopment outcome of a child with CH. On average, our group was supplemented with 4.3 $\mu\text{g}/\text{kg}$ of L-thyroxine per day. Guidelines recommend an initial L-thyroxine dosage of 10 to 15 $\mu\text{g}/\text{kg}$ per day, with a higher initial dose in infants with severe disease and a lower dose for those with mild to moderate hypothyroidism. (17) After adjustment of dosage, it is appropriate to recheck thyroid function (17) but it is difficult to titrate the optimal L-thyroxine dosage because both under- and overtreatment can result in adverse effects, such as decreased attention span, physical growth abnormalities, and craniosynostosis. (7,17) Therefore, careful monitoring of treatment adequacy in these children is essential. (6,7,22) Other authors have studied starting dosage of L-thyroxine effects on neurodevelopment and have reached the conclusion that higher initial thyroxine dosage combined with shorter time to normalization improved developmental outcome (18,26) but, as far as we know, this is the first study to compare follow-up mean L-thyroxine dosage and neurodevelopment results.

In a review of the literature of 11 studies comparing starting treatment at an earlier age (12-30 days of life) *versus* at a later age (> 30 days of life), infants started at the earlier age averaged higher Intelligence Quotient points than those at a later age. (1) However, in our study, no correlations were found between this variable and neurodevelopment outcome – a finding corroborated by a larger cohort study in Netherlands. (24)

It has been stated that one of the major neurodevelopment prognosis factors is severity of CH. (6,7,14,20-22,24,35) A potential limitation of this study is that, despite the criteria for

CH severity based in levels of fT4 present in *European Society for Paediatric Endocrinology* consensus guidelines (17), we used TSH levels from neonatal screening alone as CH severity criteria. Portuguese neonatal screening program is specially based on TSH levels and until 2012 we did not have data regarding fT4 levels before treatment initiation. Moreover, in Portugal, prior to 2012, when parents were told their child's condition, it was common practice to start a low dose L-thyroxine supplementation until the first consult in a reference centre, where plasma TSH and fT4 values were measured. By that time, those values no longer reflect the original severity of CH because there have been some prior supplementation. Even though it is not present in the guidelines, a study has compared TSH screening values and found that individuals with higher TSH levels performed significantly worse than children with lower TSH values. (23) Still, in our study, we found no correlation between screening level of TSH and neurodevelopment outcome in these children.

We also noted that ADHD were among the most common diagnosis, accounting for 15.9%. Taking into account that ADHD occurs in most cultures in about 5% of children (32), there is higher prevalence of ADHD in this group. According to the guidelines of *European Society for Paediatric Endocrinology*, (17) patients with CH have no increase in the risk of ADHD but may have more sustained attention problems related to episodes of overtreatment. It should be interesting to investigate whether there is a correlation between ADHD and mean dosage of L-thyroxine in a larger group of patients.

A major aim of this study was to examine CH effects in neurodevelopment. On one hand, according to literature, a significant percentage of children with CH have lower intellectual quotients than the normative population. (1,5,13,18) A study has shown children with CH treated early in life due to newborn screening may have lower IQ relative to their siblings. (18) Other studies have evaluated intellectual development with WISC (19,24-25), Kaufman Assessment Battery for Children and *Motoriktest fur vier-bis sechsjahrigre Kinder (MOT)* 4-6

(23) and concluded that children with this disease have Intelligence Quotients similar to the normative population. Ours shows that these children's global development quotients (GDQ and FSIQ) evaluated by GSMD or WISC-III are within the normal range. The reason may be in the success of neonatal screening and an early treatment that may grant them a global neurodevelopment as the normal population.

The neurodevelopmental alterations most encountered in the literature are motor (balance, coordination, fine motor and ball skills deficits) (20,22-23), alterations in performance and verbal domains in children evaluated with WISC-III (19-20) and some impairments in communication skills. (10,13,19,36)

Regarding motor skills, our subgroup's mean LDQ score, a subscale that evaluates gross motor skills (including the ability to balance and to coordinate and control movements), is even higher than normative population.

In what concerns Communication Disorders, Developmental Language Disorder accounted for 11.4% and Speech Sound Disorder for 13.6%. Results in VIQ in WISC – III and Communication in VABS did not fully demonstrate this finding, showing that there were no statistical differences language skills between our group of children with CH and normal population. Nevertheless, even though the comparison of HSDQ, which evaluates expressive and receptive language, did not show a statistical difference between this group and the normative population, an analysis to the amplitude of values of this score corroborates the fact these children do have some impairments in language skills.

A neurodevelopment impairment found was a lower PRDQ subscale, which evaluates the capacity in resolving practical problems. Such a result may predict a future subtle cognitive impairment in executive functions.

We also studied the adaptive abilities with VABS in a subgroup of these children. Adaptive Behaviour Composite, Daily Living Skills and Socialization domains were

significantly lower than in normal population. This result reflects lower cognitive and social competences acquired by the child to respond to daily life demands. To our knowledge, our study is the first to apply VABS to evaluate children with CH.

Our study is the first to explore the age of acquisition of early development milestones in children with CH. Although analysing mean values, we found no delay in their acquisition. This finding can indicate that early development milestones are not a useful tool to screen CH children.

A strength of this study is that, to our knowledge, this is the first study on neurodevelopment outcomes of CH in Portugal.

There are potential limitations in the present study. Not all children were evaluated using the same neurodevelopment test, introducing some variability in the results. A larger group size could be beneficial for conclusions. Outcome assessment in a larger group of children with CH rather than a centre-based study could provide more reproducible data.

Also, we would like to point out that our sample consists in children prospectively followed in our Child Development Centre that were signalized by our Endocrinology Unit.

Well-controlled studies in order to achieve more valid results, different thyroid-related predictors must be taken into account and included in the models of analysis. This implies complex sets of variables and the need for large data sets. A difficulty also referred by other authors. (14)

Conclusion

To sum up, despite neurodevelopment prognosis of CH has greatly improved in developed countries since introduction of neonatal screening, careful monitoring of cognitive, motor and behaviour development is vital, particularly during childhood, to ensure earlier

detection of any developmental disability requiring intervention, thereby optimizing neurodevelopmental outcomes.

It is crucial to ensure that children managed according to guidelines are systematically and prospectively assessed by a multidisciplinary neurodevelopment team in order to ameliorate outcomes.

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Appendix A – Supplementary Material

Neurodevelopmental Disorders DSM-5 diagnostic criteria: (32)

Intellectual disability

Intellectual disability is a disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social, and practical domains. The following three criteria must be met:

- A. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
- B. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
- C. Onset of intellectual and adaptive deficits during the developmental period.

Global development delay

This diagnosis is reserved for individuals *under* the age of 5 years when the clinical severity level cannot be reliably assessed during early childhood. This category is diagnosed when an individual fails to meet expected developmental milestones in several areas of intellectual functioning, and applies to individuals who are unable to undergo systematic assessments of intellectual functioning, including children who are too young to participate in standardized testing. This category requires reassessment after a period of time.

Language Disorder

- A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:
 - 1. Reduced vocabulary (word knowledge and use).
 - 2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).

3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).
- B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.
 - C. Onset of symptoms is in the early developmental period.
 - D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Speech Sound Disorder

- A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages.
- B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination.
- C. Onset of symptoms is in the early developmental period.
- D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurological conditions.

Attention-Deficit/Hyperactivity Disorder

- A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
 1. Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

 - a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
 - b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).

- c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
 - d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
 - e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
 - f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
 - g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
 - h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
 - i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
2. Hyperactivity and impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
- Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
- a. Often fidgets with or taps hands or feet or squirms in seat.
 - b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
 - c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless).
 - d. Often unable to play or engage in leisure activities quietly.
 - e. Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
 - f. Often talks excessively.
 - g. Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).

- h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
 - i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
- B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
 - C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
 - D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
 - E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Griffiths Scale of Mental Development

This scale is composed of six subscales:

- Locomotor (LDQ): evaluates gross motor skills including the ability to balance and to co-ordinate and control movements (ex.: climbing stairs, shooting a ball, riding a bike);
- Social/ Personal (SPDQ): evaluates proficiency in activities of daily living, level of independence and interaction with other children (ex.: dressing and undressing, playing with other children, birthday);
- Hearing/Speech (HSDQ) – evaluates expressive and receptive language (ex: nomination of objects and colours, describe a Picture, questions of daily life situations understanding);
- Hand/Eye co-ordination (HEDQ) – evaluates fine motor skills, manual dexterity and visual motoring skills (ex: using a scissors, copying geometric figures);
- Performance (PDQ) – evaluates visuospatial skills including speed of working and precision (ex: fittings of geometric figures, building of patterns with cubes);
- Practical Reasoning (PRDQ) – evaluates ability to solve practical problems, understanding of basic mathematical concepts and understanding of moral issues (ex: days of the week, digit memory, concepts of big/small, high/low, long/short).

The scale allows us to obtain results of Development Quotient and Mental Age for each of the areas evaluated by the subscales and global. (27)

Wechsler Intelligence Scale for Children - Third Edition - WISC-III

It is a cognitive assessment tool of individual administration, which evaluates the intelligence of subjects aged between six to sixteen years and eleven months. It has been adapted and standardized for the Portuguese population by Simões and colleagues in 2003.

This evaluation instrument consists of thirteen subtests ($M = 10$; $SD = 3$) spread over two subscales: Verbal and Performance, each one evaluating a different aspect of intelligence. The performance of the subjects in the various subtests is clustered in three composite results: a general intelligence measure (Full Scale Intelligence Quotient, FSIQ) and two ratios divided by the nature of its subtests: the Verbal Intelligence Quotient (VIQ), measurement of verbal intelligence, and the Performance Intelligence Quotient (PIQ), a nonverbal intelligence measure.

The subtests that compose the WISC-III enable a first distinction between skills or psychological functions, providing a reference point for the examination of higher cortical functions.

The WISC-III yields three composite IQs scores ($M = 100$; $SD = 15$): VIQ, PIQ and FSIQ, and four index scores: VCI, POI, PSI and FDI resulting from groupings of the subtests.

The various composite scores correspond to different levels of interpretation. The first level of interpretation is the FSIQ, determined by the sum of the standardized results of subtests of the subscales Verbal and Performance. The analysis of VIQ and PIQ defined, respectively, by the sums of standardized results in verbal and performance subtests, refers to the second level of interpretation. In this level, the comparison of results between VIQ and PIQ is valued. (28)

Vineland Adaptive Behaviour Scale

It is a standardized, semi-structured parent interview frequently used to measure adaptive abilities. The VABS consists of three main domains: Communication, Daily Living Skills, and Socialization. Additionally, it includes an optional motor skills domain which assesses gross and fine motor skills for children under 6 years old and a maladaptive behaviour domain for those over 5 years of age. Each domain contains several subdomains that further encapsulate the broad domain.

The subdomains for the Communication domain are expressive, receptive and written.

The subdomains for Daily Living are as follows: personal, domestic and community.

The subdomains for the Socialization domain are interpersonal, play and leisure, and coping.

VABS has also a total score, the Adaptive Behaviour Composite that is calculated via summing the raw scores from the VABS domains used. For the purposes of this study, the three main domains were used. In addition, comparisons were made using each participant's overall measure, the Adaptive Behaviour Composite, which represents the individual's global adaptive functioning profile.(29)