

# CONGENITAL HYPOTHYROIDISM: INFLUENCE FOR LANGUAGE AND BEHAVIORAL SKILLS: STUDY REVIEW

## *Hipotireoidismo congênito: influência para as habilidades linguísticas e comportamentais: estudo de revisão*

Fernanda da Luz Anastácio-Pessan<sup>(1)</sup>, Dionísia Aparecida CusinLamônica<sup>(1)</sup>

### ABSTRACT

Congenital hypothyroidism is a systemic metabolic disorder characterized by insufficient production of thyroid hormones. The literature shows that infants with congenital hypothyroidism may have cognitive, language and behavioral problems, even when the diagnosis and treatment started early. The objective of this study was to describe the language, cognitive, psycholinguistic abilities and / or behavior changes in patients with congenital hypothyroidism from published national and international studies in the period 2004-2013. The database research included: LILACS (Latin American and Caribbean Health Sciences), MEDLINE (MedlarsenLINE– International Literature) and SciELO (Scientific Electronic Library Online). When evaluating children with congenital hypothyroidism, the literature indicates that the severity of changes in the development of motor skills, cognitive and language abilities was related to the age the child was diagnosed and the start of treatment. However, disorders in these abilities have been observed in congenital hypothyroidism children even when the diagnosis and early treatment were within the standards considered adequate. The magnitude of these changes depends on factors as congenital hypothyroidism etiology, time of its beginning (pre-or post-natal), severity of hormone deficiency and age of the start of hormone replacement therapy.

**KEYWORDS:** Congenital Hypothyroidism; Language; Intellectual Disabilities; Learning

### ■ INTRODUCTION

Congenital hypothyroidism (CH) is a metabolic disorder characterized by insufficient production of thyroid hormones due to malformation or malfunction of the thyroid gland. It is the leading cause of preventable intellectual disability and is diagnosed and timely treated<sup>1,2</sup>. It occurs in 1:2000 to 4000 live births and it affects females twice as much<sup>1</sup>.

Thyroid hormones have great influence on the development of the central nervous system (CNS) during fetal life and during the first years of life<sup>3</sup>. Of these hormones, it depends on vascularization processes of the CNS, myelination, dendritic branching, synapse formation, neuronal migration, cell differentiation and gene expression. Since these processes typically exhibit a peak from the

fifth month of pregnancy and after birth, depending on the type of process and its location in the brain, adequate levels of thyroid hormone are essential<sup>4</sup>.

The deleterious effects of lack of thyroid hormones during pregnancy can be avoided by transplacental transfer of hormones from mother to fetus<sup>1,5</sup>, however, from birth to maternal hormone transfer to the fetus disappears, and those newborns untreated after the third month of life usually present delayed physical and cognitive development, with the possibility of intellectual disability of varied grade<sup>5</sup>.

Already in the first three months of life, children with CH may present clinical signs of this metabolic alteration, such as lethargy, drowsiness, hypotonia, hypothermia, prolonged jaundice, edema, puffy eyes, large fontanelles, bloating, goiter, macroglossia, "facies syndrome", hoarse cry, nasal obstruction, difficulty breastfeeding, breathing difficulties, constipation, cold skin, pale, dry, scaly and carotenemia and umbilical hernia. After the third month, these signals become increasingly evident and delayed

<sup>(1)</sup> Universidade de São Paulo, Bauru, SP, Brasil.

Source: CAPES

Conflict of interest: non-existent

growth and neuropsychomotor development can be observed<sup>1</sup>.

These clinical features may not appear ready due to the relative and transient protection of maternal thyroid hormones during pregnancy and since the sequels start before the first month these children may develop normally until the fourth or fifth month<sup>5</sup>. For this reason, the clinical diagnosis is difficult and unusual to be accomplished before the third month of life and detection of CH during the first week of life becomes essential for the rapid initiation of treatment and, consequently, to prevent its manifestations and sequelae<sup>6</sup>.

Treatment of CH is performed by means of hormone replacement with levothyroxine. The dosage should be individualized and tailor to the need of the individual so that the thyroid hormones are kept within the standards of normality<sup>5</sup>.

Thyroid hormones accelerate most biological processes, and have metabolic and metamorphic effects. The metamorphic effects refer to somatic growth and differentiation related to the development of CNS tissues, causing poor brain oxygenation, leading to brain damage and consequent developmental delay and intellectual disability. Due to the large involvement of thyroid hormones in brain development, the longer the hormone deficiency, the greater the severity and extent of brain damage and, the sooner the start of hormone replacement with levothyroxine, less is the child affected<sup>7,8</sup>.

To verify the performance of children with CH, the literature has found that the severity of changes in the development, motor, cognitive and linguistic skills, was related to the age of the child to get diagnosed and start treatment<sup>9</sup>.

However, changes in these abilities have been observed in children with CH, even when the diagnosis was made early and treatment was considered within adequate standards<sup>5,7-10</sup>. The extent of these changes depends on factors such as CH etiology, time of initiation (pre-or post-natal), severity of hormone deficiency and age of the child to start spare hormonal treatment<sup>7,9</sup>.

The objective of this study was to describe the changes in language, of cognition, psycholinguistic abilities and / or behavior in patients with CH from previous studies in this regard by the national and international scientific community.

## ■ METHODS

Starting from the literature review, we conducted a study of the literature published between 2004 and 2013. The literature survey was conducted by research bases of national and international data: (Latin American and Caribbean Literature on Health Sciences) and SciELO (Scientific Electronic Library Online) LILACS, MEDLINE (MEDlarsen LINE Literature-International), according to the following inclusion criteria:

- Articles with information about changes in receptive and expressive language in individuals with CH;
- Articles with presentation of results of scientific research with experimental and control groups;
- Completed scientific work, including monograph, dissertation and doctoral thesis.

## ■ LITERATURE REVIEW

The presentation of the studies followed numerical order, according to the chronological order of publication, facilitating the reading of the tables.

Table 1 shows the selected studies, with respective year of publication and names of the authors who developed the work with CH focusing on changes in language, cognition, psycholinguistic abilities and / or behavior are presented as well as the number of participants with CH evaluated in each.

Table 2 shows the abilities studied in the body of knowledge published in the studies described above.

**Table 1 - Study, year of publication, authors and number of participants with Congenital Hypothyroidism**

Study	Year	Authors	Number of Participants with HC
1	2004	Androvandi e Nunes <sup>8</sup>	22
2	2004	Simonset <i>al</i> <sup>11</sup>	59
3	2004	Torres <i>et al</i> <sup>12</sup>	37
4	2005	Bongers-Schokkinget <i>al</i> <sup>9</sup>	45
5	2005	Oerbecket <i>al</i> <sup>13</sup>	49
6	2005	Rovet <sup>7</sup>	42
7	2006	Bargagnaet <i>al</i> <sup>10</sup>	52
8	2006	Kemperset <i>al</i> <sup>5</sup>	70
9	2007	Kemperset <i>al</i> <sup>14</sup>	58
10	2008	Gejão e Lamônica <sup>15</sup>	35
11	2008	Sluijset <i>al</i> <sup>16</sup>	69
12	2009	Blasiet <i>al</i> <sup>17</sup>	15
13	2009	Dimitropouloset <i>al</i> <sup>18</sup>	63
14	2009	Gejãoet <i>al</i> <sup>19</sup>	43
15	2009	Correiaet <i>al</i> <sup>20</sup>	17
16	2011	Wheeleret <i>al</i> <sup>3</sup>	35
17	2012	Wheeler <i>et al</i> <sup>2</sup>	14
18	2012	Sluijset <i>al</i> <sup>21</sup>	95
19	2013	Komuret <i>al</i> <sup>22</sup>	41

**Table 2 - Results of reviews**

Skills studied	Studies																			T
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Cognitive Development	+	-	-	+	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+	13
Neuro psychomotor Development	-	-	-	+	-	-	-	-	-	+	+	+	-	-	-	-	-	+	-	5
Motor Skills	-	+	-	-	-	-	+	+	+	+	+	-	-	+	-	-	-	+	+	9
Communication	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	+	3
Behavioral Problems	-	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Linguistic- verbal Skills	-	-	-	+	-	-	+	-	-	-	-	-	-	+	-	-	-	-	+	4
Visual motor Skills	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	2
Changes educational, reading and comprehension	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Mathematical Skills	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Attention	-	-	+	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	3
Memory	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	+	+	-	-	4
Social Skills	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	2
Self-care	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	2
Anxiet and Depression	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	1
Integrity of Hippocampus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-	3

T= Total

+ present

- absent

Table 1 presented the study, year of publication, number of authors and participants with CH. These works are important references for the contribution to the current knowledge of language, cognitive and behavioral characteristics in individuals with this metabolic alteration.

In Table 2 it is possible to observe the skills and behaviors studied. We emphasize that cognitive development was assessed in 13 studies. In all, the authors observed intellectual development of people with CH below expectations for their age, compared with their healthy peers.<sup>5-8,10,14-19,21,22</sup>, even in the absence of intellectual disability.

Some of these studies have evaluated the index of the Intelligence Quotient (IQ) of the participants, subdividing it in full, verbal and execution<sup>8,14</sup> or even comparing the IQ with the subjects' performance on psychomotor, verbal skills and compartmental changes<sup>5-7,18,21,22</sup>. The results showed that children or young people with CH are considered at risk for experiencing cognitive, linguistic and behavioral changes<sup>5-8,10,14-19,21,22</sup>.

In the treatment of congenital hypothyroidism, a major concern is the prevention of intellectual disability that can bring devastating effects to the lives of these subjects<sup>5,12,18</sup>. What is discussed in the literature is the presence of multiple variables involved in intellectual development and the interference of the risk factors in CH. Among these, in addition to the diagnosis and treatment started early, are listed: the severity and etiology of CH, drug dosage of synthetic hormone, individual appropriateness of this dosage during the treatment, the normalization time of CH, the presence of comorbidities and socio-economic level<sup>10,11,18</sup>.

Thyroid hormones have great interest in the developing brain, and the longer the period of hormonal insufficiency, the increased severity and extent of cerebral damage<sup>7</sup>. The literature also shows that the dosage of hormone replacement should be individualized and appropriate to the needs of each individual and that the greater the dose of levothyroxine at the beginning of treatment, lower are the rates of change of development<sup>7,15</sup>.

In cases of CH in which the mother has normal thyroid function and the fetus has some thyroid dysfunction during pregnancy, the most affected areas of the nervous system are those related to postnatal development, ie, cerebellum, hippocampus and cortex, especially visual and auditory. This is because the deleterious effects of lack of thyroid hormones during pregnancy can be avoided by transplacental transfer of hormones from mother to fetus<sup>5</sup>. In the cortex, the hormone deficiency reduces the length and branching of pyramidal neurons, the density of axon terminals and the

number of dendritic spines. In the cerebellum, deficits in the number, density and branching of dendrites occur. Therefore, in the presence of CH, the decreasing of the absolute size of the cerebellum and brain can be observed, as well as atrophy of the cerebral convolutions. These irreversible damages to neuronal tissue not only cause intellectual disabilities, but other neurological, metabolic and maturational changes that may reflect difficulties in oral communication and learning processes<sup>4</sup>.

Thyroid hormones depend on vascularization processes of CNS myelination, dendritic branching, synapse formation, neuronal migration, cell differentiation and gene expression. Changes in neuronal connections reduce the ability of neuronal transmission, affecting intellectual functioning. Depending on the timing of hormone deficiency, cognitive abilities are also affected<sup>3</sup>, interfering with the processing of auditory and visual information reflected on the psycholinguistic skills<sup>15,19</sup>.

The hormonal deficit in the brain regions responsible for cognitive activities cause perceptual changes<sup>7</sup>. Cognitive deficits have been observed in children, adolescents and adults with CH, especially when treatment starting is delayed and / or the hormonal change is more grave<sup>5,7,13,14</sup>.

The severity of changes in development is related to the age of the child to be diagnosed at the beginning of treatment and quality monitoring of this development<sup>9</sup>.

The early treatment with high levels of levothyroxine minimize these limitations, but not exclusively<sup>5-7,15,18,22</sup>, once it has detected slow progression of neurological development in children with CH<sup>21</sup>, this cognitive impairment may be a consequence of prenatal hypothyroidism or thyroid hormone deficiency in early life<sup>7,21</sup>.

Motor and psychomotor changes are also commonly found in patients with CH. Authors showed that children, youth and adults with CH showed significant motor changes when compared with the control group<sup>5</sup>. Dividing the participants according to the severity of CH (mild, moderate and severe), some authors claim that the three subgroups present significant motor changes, however, these were more pronounced in the group with severe CH<sup>14</sup>. Moreover, in all three disease subgroups, lower levels of psychomotor development were observed<sup>21</sup>.

Complaints about behavioral changes are common, particularly involving attention, impulsivity, hyperactivity, sleep disturbances, agitation, among others<sup>12,13,19</sup>.

Complaints of learning difficulties are also common in children with congenital hypothyroidism<sup>19</sup>. Some studies show that there is

an association between CH and attention problems, motor deficits, defects in visual-spatial skills, language, and memory contributing to producing specific learning difficulties<sup>9,19</sup>.

The development of school education of individuals with CH is a process that requires constant monitoring. Clinical practice has shown that these children have been diagnosed as having learning difficulties and require additional monitoring to meet school demands.

One study showed that children with CH treated with levothyroxine levels  $\leq 40$  nmol/L had poorer performance in educational, behavioral and motor skill aspects when compared to healthy children and that have CH, but are treated with levothyroxine levels  $> 40$  nmol/L. The reading rate, accuracy and comprehension were similar in all three groups, but the mathematical skills and motor skills were significantly lower in the group treated with a low dose of levothyroxine. Behavioral problems were more frequently observed in both groups with CH, particularly regarding hyperactivity and difficulty in calming. And even individuals treated early have educational changes<sup>11</sup>.

Some necessary skills for learning may also be lower than expected in children with CH. Studies show that children or adults with CH treated early present performance in verbal memory and attention tests significantly lower when compared with adults without metabolic abnormalities<sup>12,13</sup>.

Memory is the ability to acquire (acquisition), storage (consolidation) and retrieve (recall) available information. Faulty memory tasks interfere with learning, problem solving and academic performance. The deprivation of thyroid hormone effects are long term on the hippocampal function and may be responsible for memory problems in congenital hypothyroidism<sup>2,3</sup>. Studies in subjects with congenital hypothyroidism have showed losses involving working memory<sup>2,3,13,20</sup>. Changes in brain metabolism also contribute to these findings<sup>17</sup>.

Visual motor and verbal skills are lower in children with CH and the index of behavioral

changes is superior<sup>6</sup>. In the assessment of visual spatial skills through functional magnetic resonance imaging (fMRI), differences were found in latencies of responses and the percentage of correct answers, concluding that poverty in the performance of children with CH in visual spatial tests may be related to decreased activation of important brain areas for mental representation of spatial features of objects, with increased recruitment of regions involved in the representation of somatosensory information<sup>17</sup>.

Children with CH treated early were evaluated for motor, language and cognitive skills. The authors concluded that children with very low levels of levothyroxine before the start of treatment for CH and less privileged socioeconomic levels had greater changes in the evaluated performance skills<sup>10</sup>.

Advances in the treatment of CH have considerably improved the sequelae of this disease on neuropsychological development. The implications of the CH motor and cognitive development have been extensively studied in the literature, however, there are few studies that focus on the social and emotional consequences of this disease in affected individuals. Results indicate negative influence on the quality of life of individuals such as low self-esteem. The authors suggest additional support is necessary for these people in the emotional and educational aspects<sup>16</sup>.

## ■ CONCLUSION

Based on the studies, it was found that individuals with CH are considered at risk for learning disabilities, behavioral, motor, psychomotor, linguistic and psycholinguistic ability changes. Early initiation of treatment and the proper maintenance tends to minimize this risk, but not exclude it. Changes in psycholinguistic skills such as attention and memory are commonly found in individuals with CH. This interferes negatively in the academic development of these individuals, requiring additional monitoring to meet their educational demands.

**RESUMO**

O hipotireoidismo congênito é um distúrbio do metabolismo sistêmico caracterizado pela produção deficiente dos hormônios tireoidianos. A literatura apresenta que estas crianças podem apresentar alterações cognitivas, linguísticas e problemas comportamentais, mesmo quando o diagnóstico e o tratamento iniciaram precocemente. O objetivo do presente trabalho foi descrever as alterações de linguagem, de cognição, de habilidades psicolinguísticas e/ou de comportamento em sujeitos com hipotireoidismo congênito, a partir de estudos já publicados pela comunidade científica, no período de 2004 a 2013. O levantamento bibliográfico foi realizado por meio de pesquisa em bases de dados nacionais e internacionais: LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), MEDLINE (MEDlarsónLINE–Literatura Internacional) e Scielo (*Scientific Eletronic Library Online*). A literatura evidencia que a gravidade das alterações no desenvolvimento das habilidades motoras, cognitivas e linguística, esteve relacionada à idade da criança ao receber o diagnóstico e ao iniciar o tratamento. Entretanto, alterações nestas habilidades têm sido observadas em crianças com hipotireoidismo congênito, mesmo quando o diagnóstico foi precoce e o tratamento foi considerado dentro de padrões adequados. A magnitude de tais alterações depende de alguns fatores como a etiologia do hipotireoidismo congênito, época de seu início (pré ou pós-natal), gravidade da deficiência hormonal e idade da criança ao iniciar o tratamento de reposição hormonal.

**DESCRITORES:** Hipotireoidismo Congênito; Linguagem; Deficiência Intelectual; Aprendizagem

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Mailing address:

Dionísia Aparecida Cusin Lamônica

Alameda Octávio Pinheiro Brisolla nº 9-75 - Vila

Universitária

Bauru – SP – Brasil

CEP: 17012-901

E-mail: dionelam@uol.com.br