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# COGNITIVE CHANGES ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM: A LITERATURE REVIEW

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**Abstract**: Objectives: Investigate cognitive changes associated with congenital hypothyroidism, understanding the mechanisms, impact on cognitive development and possible therapeutic interventions. Methodology: Bibliographic review study nthe PubMed and Scielo databases using the descriptors "congenital AND cognitive hypothyroidism". Of the 127 articles found, 21 met the inclusion criteria, published between 2013 The 2023.Results: The different types of studies analyzed point to iodine deficiency, thyroid dysgenesis and thyroid dyshormonogenesis as common causes of congenital hypothyroidism (CH). Genetic analyzes identified variants in the IGSF1, TBL1X and IRS4 genes associated with HC. As for the underlying mechanisms, thyroid hormone deficiency affects brain formation and white matter, with abnormalities and cognitive problems. In addition, neuropathological changes are observed, with possible repercussions on development and behavioral expression. With regard to cognitive changes, HC affects specific skills at different stages of development. Patients may have deficits in motor skills, language, attention, and memory, Treatment with levothyroxine is fundamental in CH, preventing intellectual disability. The initial dose of 10-15 mg/kg/day, adherence to treatment and continuous monitoring are essential. Final considerations: Investigating the cognitive alterations and mechanisms of congenital hypothyroidism is crucial to ensure adequate child development. Hormone replacement is of paramount importance in preventing intellectual deficit, promoting healthy physical and mental growth.
**Keywords**: Hypothyroidism congenital; Neuroinfant development; Cognitive change.

## INTRODUCTION

Congenital hypothyroidism is a condition

recognized through neonatal screening and with an estimated incidence between 1:2,000 and 1:4,000 live births (ANDRADE et al., 2021). The impact of congenital hypothyroidism on neuropsychomotor development and subsequent cognitive skills is an avoidable challenge when establishing an early diagnosis and adopting appropriate therapeutic interventions (LAMÔNICA et al., 2020).

This endocrine dysfunction is characterized by the inability of the thyroid gland to produce sufficient amounts of thyroid hormones and can be etiologically classified as primary, when there is an alteration in the thyroid gland; secondary, when there is a pituitary deficit; or tertiary, when there is a hypothalamic deficit (ANDRADE et al., 2021). The absence of adequate treatment of the resulting hormone deficiency can lead to a significant impairment of growth and cognitive development, with manifestations that affect the patient's understanding, language, behavior and motricity (LAMÔNICA et al., 2020). In addition, the importance of other aspects of treatment is emphasized, such as adequate and continuous follow-up in the first years of life,

Given this context, the objective of this literature review is to investigate the cognitive changes associated with congenital hypothyroidism, understanding the mechanisms underlying these changes, the impact on cognitive development and the possible therapeutic interventions available to minimize these effects.

## METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or problem, variables and outcome. The development of the research was guided by the guiding question: ''What are the cognitive changes associated with congenital hypothyroidism, their underlying mechanisms and possible therapeutic interventions?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients diagnosed with hcongenital hypothyroidism, thepossible approachestherapeuticthe variables used in the present study, and the respective outcome, being the prognosis regarding the dysfunctionsconsequences of this framework. The searches were carried out through searches in the PubMed and Scielo databases. The descriptors were used in combination with the Boolean term "AND": "Congenital hypothyroidism AND Cognitive". From this search, 127 articles were found, subsequently submitted to the selection criteria. Inclusion criteria were: articles in Portuguese, Spanish and English; published from 2013 to 2023, which addressed the themes proposed for this research and fit the typology of systematic review, retrospective observational, cross-sectional observational, prospective observational, longitudinal cohort, narrative review and randomized clinical trial studies, available in full. Exclusion criteria were: duplicate articles, available in abstract form, that did not directly address the proposal studied and did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 21 articles were found. Of which, 112 articles belonged to the PubMed database and 15 articles to Scielo. After applying the inclusion and exclusion criteria, 19 articles were selected from the PubMed database and 2 articles from Scielo, using a total of 21 studies to compose the collection.

## RESULTS

### MECHANISMS UNDERLYING COGNITIVE CHANGES

Congenital hypothyroidism (CH) is a complex condition that can be caused by both genetic and environmental factors. Deficiency of thyroid hormones (TH) can occur from fetal life due to disturbances in the functioning of the thyroid gland. Thyroid hormone deficiency during pregnancy, as well as its severity and duration, are determining factors in the formation and organization of the fetal brain (UCHIDA K.; SUZUKI M., 2021). In addition, some other risk factors include the baby's gender, premature birth, country of origin, health condition of the newborn and being small for gestational age (LIPSKA E. et al., 2022).

Iodine deficiency is still the main cause of CH in many countries and is associated with complications such as goiter and severe intellectual disability. However, in countries with adequate iodine supplies, other causes are more prevalent. Thyroid dysgenesis, which encompasses agenesis, hypotrophy, hemiagenesis and ectopy of the thyroid gland, is responsible for more than 50% of cases. Other causes include thyroid dyshormonogenesis, which is caused by mutations in genes involved in the synthesis and metabolism of thyroid hormones (LIPSKA E. et al., 2022).

Genetic analyzes have shown that dyshormonogenesis, a defect in the production of thyroid hormones, is involved in CH and its frequency seems to be increasing (LIPSKA E. et al., 2022). These analyzes revealed genetic variants associated with isolated congenital central hypothyroidism in a high proportion of tested patients, with emphasis on variants in the IGSF1, TBL1X and IRS4 genes. Such genetic variants affect the function of a set of amino acids important for the development and proper functioning of the pituitary gland, leading to a decrease in the production of the hormone TSH (NAAFS JC. et al., 2020a).

During fetal and infant development, thyroid hormones play an essential role in the proper maturation and migration of nerve cells, as well as in the formation of synapses and neuronal connections. Deficiency of thyroid hormones interferes with these processes, resulting in abnormalities in brain architecture (UCHIDA K.; SUZUKI M., 2021). Analyzes of brain white matter using diffusion tensor magnetic resonance reveal quantitative and microstructural abnormalities in various brain regions of children with CH. These abnormalities are related to the severity of CH and correlate with worse cognitive outcomes. Such findings suggest that HC may interfere with the development of the white matter of the brain, affecting myelination, the migration of axons and dendrites, as well as synaptogenesis (PERRI K. et al., 2021).

In CH, neuropathological changes occur that affect different parts of the brain. These alterations include problems in the formation of Purkinje neurons in the cerebellum, decrease in the myelin sheath in myelinated nerves, and dysgenesis in the formation of dendritic spines, both during brain development and in adulthood. Furthermore, the effects of thyroid hormone deficiency are not restricted to local brain cells only, but also impact neural structure and signal transmission between the cerebral hemispheres via the corpus callosum, which is the main communication pathway between them ( UCHIDA K.; SUZUKI M., 2021). These neuropathologic features may contribute to the cognitive problems seen in congenital hypothyroidism. Correlations have already been found between white matter microstructural changes and clinical scores, especially in the frontal, parietal, and temporal lobes of the brain. Compromising these regions is associated with cognitive deficits, including attention, perceptual-visual

reasoning, reading and memory (PERRI K. et al., 2021).

Importantly, the abnormalities seen in the commissural fibers are not just limited to hypothyroidism, but are also found in autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD), indicating that defects in brain structures involved in the integration functional affect behavioral expression. Therefore, thyroid hormones play a key role in various aspects of brain development, affecting neural architecture, the formation of neural connections and behavioral expression (UCHIDA K.; SUZUKI M., 2021).

**COGNITIVE CHANGES**

During the gestational period, the lack of thyroid hormone affects different cognitive abilities depending on the stage. In early pregnancy, problems with attention, visual processing, and gross motor skills occur. In the last trimester, there is a risk of changes in contrast sensitivity and visuospatial abilities. After childbirth, language and memory are the main areas affected. The reduction in hormone levels affects corticogenesis, neuronal migration and brain structure, resulting in deficits. Early treatment with thyroid hormone plays a crucial role in reducing neurological consequences. Starting treatment before the first two weeks of life can limit sequelae, although children with congenital hypothyroidism may still show lower scores in skills such as postural control, eye-hand coordination, visuospatial skills, auditory discrimination, attention, memory, and language (MORALES L.G. et al., 2020; NUNEZ A. et al., 2017; ONTIVEROS M.E. et al., 2023).

A cross-sectional cohort study performed by Naafs JC et al. (2021b) evaluated the motor and cognitive performance of 87 patients with early diagnosed central congenital hypothyroidism (HC-C) compared to their euthyroid siblings. Using the full-scale intelligence quotient (FSIQ) as the basis for assessment, the study found that approximately two-thirds of patients with HC-C had multiple pituitary hormone deficiency (MPHD), which is associated with increased risks of developmental disabilities. due to the impairment of multiple endocrine systems (NAAFS JC et al., 2020b). The study demonstrated a mean FSIQ of 90.7 (95% CI 86.4-95.0) among patients with MPHD, while patients with HC-C alone scored a mean of 98.2 (95% CI 93.0 -103.5) and euthyroid siblings, 98.6 (95%CI 94, 5-102.8). Importantly, 69% of patients with MPHD had moderate to severe hypothyroidism based on T4 concentration before starting treatment, compared to 37% of patients with HC-C alone (NAAFS JC et al., 2021b).

As for the cognitive domains evaluated, both groups of patients with HC-C and MPHD obtained mean scores lower than those of euthyroid siblings in processing speed (with a mean difference of 10.3 and 10.5 points, respectively), although the result the end of the FSIQ was similar between patients with HC-C and their euthyroid siblings. This underscores the importance of thyroid hormones in the neurodevelopmental process before and after birth, and suggests the possibility that congenital hypothyroidism itself affects processing speed independently of patients' cognitive outcome (Naafs JC et al., 2021). In addition, a mild attention deficit has been observed in patients with isolated HC-C, which reinforces the need for research that assesses specific cognitive domains in these patients (NAAFS J.C. et al., 2020a).

Regarding primary congenital hypothyroidism (HC-T), a retrospective cohort study conducted by Pelaez J.M. et al. (2023) analyzed the FSIQ scores of 458 patients diagnosed with HC-T, relating

them to T4 levels at diagnosis (T4dx), age at treatment initiation, and maternal education level. T4dx levels less than 3.0 µg/dL were classified as severe HC-T and had lower FSIQ scores compared to non-severe cases. This was statistically significant for both the scores calculated from the Wechsler Intelligence Scale for Preschool and Primary School Age - Revised (WPPSI-R) and the Wechsler Intelligence Scale for Children - III Edition (WISC-III) ($p < 0.001$ and $p = 0.02$, respectively). These results reinforce the importance of thyroid hormones for neurodevelopment. However, there was no statistically significant difference in scores between patients who started treatment before and after 15 days of life, contrary to what was observed by Nunez A. et al. (2017). In addition, maternal education proved to be the variable with the greatest impact on scores, with patients whose mothers had a lower level of education obtaining lower scores ($p < 0.001$). Based on these results, the authors highlighted the need for further research that considers socioeconomic factors as impacting variables on cognitive outcome in HC patients (PELAEZ J.M. et al., 2023).

Furthermore, both in children and adults with congenital hypothyroidism, a significantly higher frequency of comorbidities in the neuropsychiatric field is observed. These comorbidities include impairment of higher brain functions, epilepsy, or psychiatric disorders. Compromised higher brain functions can manifest as cognitive deficits in areas such as memory, attention, language, and visuospatial skills. The most common psychiatric disorders associated with congenital hypothyroidism include attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), mood disorders such as depression and anxiety, and behavioral disorders.

Furthermore, it has been observed that women with congenital hypothyroidism have lower fertility rates. This association can be explained by the influence of thyroid hormones on the functioning of the reproductive organs and on the hormonal balance necessary for fertility.

Regarding the analysis that considered the type of congenital hypothyroidism, Ontiveros ME et al. (2023) observed that patients with athyreosis had significantly lower scores ($p < 0.001$) on the Verbal IQ (VIQ), Performance IQ (PIQ) and Global IQ (GIQ) scales compared to patients with dysgenesis. Furthermore, when assessing the effect of starting treatment on the VIQ scale, it was found that patients with athyreosis and late treatment initiation had lower scores compared to the group treated early. These patients also had significantly lower scores ($p < 0.005$) compared to the group of patients with dysgenesis and late initiation of treatment. The average scores obtained by patients with athyreosis (about 85 points) are below normal classification criteria. On the other hand, patients with athyreosis and early treatment initiation obtained scores within the normal classification range (ONTIVEROS M.E. et al., 2023).

## TREATMENT OF CONGENITAL HYPOTHYROIDISM

The treatment of congenital hypothyroidism is essential to ensure the proper development of the child and prevent intellectual disability. According to Esposito et al. (2022), this condition is considered one of the most frequent preventable causes of intellectual disability, but when properly treated with levothyroxine (L-T4) at the right time and in the correct dosage, it has great potential for normal growth and neurodevelopment results.

Hormone replacement with L-T4 is the main therapeutic method for congenital hypothyroidism. According to Leung and

Leung (2019), L-T4 acts in the deficiency of thyroid hormones, which are important for brain development, especially in the first 2 to 3 years of life, a period of greater brain growth. It is recommended to start treatment as soon as possible, around 2 to 3 weeks of life, according to neonatal screening (UNIGARRO et al., 2022).

The initial dose of L-T4 is 10 to 15mg/kg/day (LEUNG; LEUNG, 2019). The drug is administered in the form of crushed tablets and diluted in water or breast milk, usually once a day, according to Stagi et al. (2022). In cases where oral administration is not possible, the intravenous route can be used, with half the usual dose. Recently, a new formulation of levothyroxine containing glycerol and water was developed, with efficacy and safety similar to levothyroxine in pills, with the advantage of requiring less need for dose adjustment (TZIFI et al., 2022).

The aim of treatment is to normalize hormone levels and promote good physical and mental growth and development. According to Stagi et al. (2022), the treatment goals for congenital hypothyroidism are determined by the American Academy of Pediatrics (AAP) and the European Society of Pediatric Endocrinology (ESPE), which establish as a reference a free T4 value within the upper limit, according to age, and a serum TSH value below 5mg/dl. To reach these adequate values, regular hormonal monitoring is necessary and, frequently, dose adjustments as the child grows. Adherence to treatment is also fundamental and can be influenced by the means of administration, interaction with other drugs and intestinal malabsorption (STAGI et al., 2022).

Furthermore, high doses of levothyroxine can result in irreversible damage to the developing brain, affecting neurons and their fibers, as mentioned by Bongers-Schokking et al. (2013). Studies also indicate a possible association between high doses of levothyroxine and attention deficit hyperactivity disorder, as well as aggressive behavior (STAGI et al., 2022; ESPOSITO et al., 2022).

The presence of a suboptimal IQ in the first 2 years of life of children with congenital hypothyroidism underscores the importance of adequate follow-up to rescue neurodevelopment. Esposito et al. (2022) explain that thyroid hormone insufficiency can cause prenatal brain damage that is not completely prevented by transplacental supply of maternal thyroxine, nor completely reversed by postnatal treatment. Thus, continuous monitoring is essential. Suboptimal IQ is not directly related to age at diagnosis, initial levothyroxine dose, T4 and TSH normalization time, but rather to socioeconomic status and delay in bone age at diagnosis.

Currently, the proposed treatment regimens have been shown to be effective in achieving normal growth and neurodevelopment results in children with congenital hypothyroidism detected by neonatal screening (ESPOSITO et al., 2022). Careful follow-up is needed to make necessary adjustments and ensure that the child is receiving the proper drug dose. The prognosis for normal intellectual function, neuropsychological development, and growth is excellent when treatment is administered early and appropriately. (LEUNG; LEUNG, 2019).

## FINAL CONSIDERATIONS

It is extremely important to investigate the cognitive changes linked to congenital hypothyroidism in order to understand the triggering mechanisms and ensure normal development. Hormonal deficiency throughout pregnancy, together with thyroid hormone deficit, are factors that affect the formation and organization of the fetal brain, subsequently impacting attention,

visual-perceptual reasoning, reading and memory. Therefore, screening is essential to initiate hormone replacement, reducing the chances of inadequate development and preventing possible intellectual deficiencies in children, with a view to cognitive behavioral development.

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