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Clinical manifestations and management of congenital hypothyroidism: A systematic review

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on Congenital Hypothyroidism, seeking to identify the main clinical manifestations, as well as the main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on

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understanding the main aspects of Congenital Hypothyroidism. The research was guided by the question: "What are the main signs and symptoms of Congenital Hypothyroidism in the pediatric population, as well as what are the therapeutic resources used in clinical practice?". To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 88 articles. 11 articles were selected for analysis. Results: Congenital Hypothyroidism (CH) is a metabolic condition present at birth, resulting from problems in the hypothalamic-pituitary-thyroid axis. It can be primary (in the thyroid) or central (in the hypothalamus/pituitary). Neonatal screening is crucial for early diagnosis and treatment with levothyroxine (L-T4), preventing sequelae. Continuous monitoring is essential to optimize development and avoid long-term complications. Conclusion: Congenital hypothyroidism (CH) is a condition that should be detected early through neonatal screening. Treatment with levothyroxine (L-T4) is crucial to normalize hormones and promote proper development. Collaboration between healthcare providers, parents, and caregivers is essential for successful treatment. Ongoing research is important to improve knowledge and management of the condition. In summary, rapid diagnosis and treatment are key to a good prognosis.

Keywords: Congenital Hypothyroidism, Pediatrics, Clinical Manifestations.

INTRODUCTION

Congenital hypothyroidism (CH) is a common endocrine condition in newborns, associated with a lack or decrease in thyroid hormones (THs) (ANDRADE et al., 2021). Primary congenital hypothyroidism (CH) is a frequent endocrine and metabolic disorder in infants, occurring in about 1 to 4 out of every 2,000 to 4,000 newborns annually. This disease is characterized by increased levels of thyroid-stimulating hormone (TSH) due to insufficient production of thyroid hormones during newborn screening. If left untreated, CH can result in signs and symptoms of metabolic impairment, affecting motor and cognitive development. About 85% of cases of congenital hypothyroidism (CH) are sporadic, while 15% have a genetic origin (autosomal recessive) (UTHAYASEELAN et al., 2022) (DA et al., 2021)

CH has been related to maternal perinatal factors, such as advanced maternal age and gestational complications, and to neonatal-perinatal factors, such as female gender, preterm birth, low birth weight, post-mature birth, other congenital malformations, and birth as part of multiple pregnancies. CH is classified into transient and permanent forms. Transient form refers to temporary TH deficiency detected at birth but resolves within the first few months or years of life, while permanent CH is a TH deficiency that requires lifelong treatment (UTHAYASEELAN et al., 2022).

Thyroid hormone plays a crucial role in energy metabolism, body temperature regulation, growth, bone formation, and central nervous system development. Because thyroid hormone is essential for the formation of the myelin sheath during the fetal, neonatal, and infant periods, thyroid hormone dysfunction in these periods causes irreversible impairment of intelligence. In addition, thyroid hormone stimulates growth hormone secretion, insulin-like growth factor 1 production, and bone maturation. Therefore, insufficient thyroid hormone activity can cause growth retardation and early osteoporosis in adulthood (MINAMITANI, 2021). There are two active thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Both T4 and T3 are secreted by the thyroid gland, although most of the circulating T3 is derived from the deiodination of T4 in peripheral tissues. The deiodination of T4 into T3 is catalyzed by a group of enzymes known as iodothyronine deiodinases (WEINER et al., 2020).

The hypothalamic-pituitary-thyroid (HPT) axis functions to maintain a stable concentration of thyroid hormone. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the thyrotrophic cells of the pituitary gland to produce thyroid-stimulating hormone (TSH). TSH, in turn, stimulates thyroid follicular cells to produce T4 and T3. Underfunctioning of the thyroid gland usually results in increases in the production of TRH and TSH, except in cases of pituitary or hypothalamic dysfunction (central hypothyroidism) and pituitary resistance to thyroid hormone feedback (WEINER et al., 2020).

The fetal thyroid gland becomes visible in the fourth week of gestation and begins to retain iodine in the 10th week of gestation. In the first trimester, most of the active fetal thyroid hormone results from maternal thyroid hormone that crosses the placenta. Maternal hypothyroidism during early pregnancy is a significant risk factor for impaired psychomotor development. The fetal HPT axis becomes active around the 18th week of gestation and, from then on, functions independently of the pregnant woman, with negligible transfer of TSH to the placenta. T4 levels increase continuously after 18 weeks of gestation and T3 levels increase after 30 weeks of gestation. In healthy infants, there is an increase in the production of TRH and TSH soon after birth, which has been attributed to exposure to cold, leading to an increase in T4 and T3 levels in the first 24 to 36 hours after birth (WEINER et al., 2020).

Most cases of congenital hypothyroidism (CH) are asymptomatic at diagnosis. Symptoms may include excessive sleepiness, constipation, and inadequate/slow eating. On examination, neonates may present with macroglossia, umbilical hernia, dry skin, rough and swollen face, and an enlarged anterior fontanelle with delayed reflexes and hypotonia on neurological examination. In some cases of thyroid dyshormonogenesis, the goiter may be palpable. Prolonged neonatal jaundice, specifically conjugated hyperbilirubinemia, should be an indicator to assess thyroid function as well as to assess for panhypopituitarism. If performed, the X-ray may reveal the absence of femoral epiphysis due to delayed skeletal maturation in patients with severe hypothyroidism (WEINER et al., 2020). Neonatal screening plays an essential role in the early identification of these cases, allowing immediate initiation of L-thyroxine (L-T4) replacement therapy (RASTOGI; LAFRANCHI, 2010).

This systematic review article aims to compile and analyze the scientific evidence on the clinical manifestations and management of congenital hypothyroidism (CH). The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the clinical manifestations of Congenital Hypothyroidism (CH) in pediatric patients, as well as to demonstrate the main methods used in the treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the main signs and symptoms of Congenital Hypothyroidism in the pediatric population, as well as what are the therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Congenital Hypothyroidism, Clinical Diagnosis, Pediatrics, and Signs and Symptoms. The search strategy used in the PMC database was: Congenital Hypothyroidism AND Clinical Diagnosis, Congenital Hypothyroidism AND Pediatrics, and Congenital Hypothyroidism AND Signs and Symptoms. From this search, 88 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 88 articles were found. After applying the inclusion and exclusion criteria, 16 articles were selected from the PubMed database, and a total of 11 studies were used to compose the collection.

DISCUSSION

Congenital hypothyroidism (CH) is a condition in which there is a dysfunction in the hypothalamic-pituitary-thyroid (HPT) axis present from birth. This results in inadequate thyroid hormone (TH) production, which can range from severe to mild deficiency. CH can be caused by abnormalities in the development or function of the thyroid gland, as well as the hypothalamus and pituitary gland. In addition, the impaired action of thyroid hormones can also contribute to the condition. In 2014, an international consensus guideline on HC was published, covering the scientific literature up to 2013. In addition, the ENDO-European Reference Network (ERN) has launched an initiative approved by the European societies of paediatric endocrinology and general endocrinology, with the aim of updating the practical guidelines for the diagnosis and treatment of HC (VAN TROTSENBURG et al., 2021).

Congenital Hypothyroidism (CH) is a metabolic disorder resulting from genetic defects in specific enzymes or proteins, leading to blockages in the normal metabolic processes of proteins, carbohydrates, or lipids. These conditions can cause severe symptoms and, if not diagnosed early, can lead to significant complications (MANSOOR, 2020).

Studies have identified more than 20 genes and approximately 800 variants associated with CH, including the thyroid hormone receptor (TSHR). TSHR is responsible for the synthesis and secretion of thyroid hormones (T3 and T4) by thyroid cells when stimulated by TSH. Pathogenic variants in TSHR can cause dysfunction in the TSH-TSHR axis. Some pathogenic genotypes are related to thyroid overfunction, while others cause non-autoimmune hypothyroidism. Global research

on TSHR sequencing in patients with CH aims to identify high-risk populations for these variants and understand their clinical characteristics, aiding in treatment and prognosis (DA et al., 2021).

There are two main forms of CH: primary CH, caused by defects in the thyroid gland, and central CH, related to hypothalamic or pituitary dysfunctions. Newborn screening (NBS) plays a crucial role in the early detection of these conditions, allowing for appropriate interventions and preventing irreversible brain damage. Primary CH is more common and usually results from thyroid dysgenesis, which includes absence (thyroid agenesis), incorrect displacement (thyroid ectopy), or underdeveloped development (thyroid hypoplasia) of the thyroid gland. Thyroid dysgenesis (TD) refers to a failure in the formation of the thyroid gland, whereas dyshormonogenesis refers to a defect in the production of HT, both of which can highlight the primary CH. TD accounts for the majority of primary CH (80%) and includes a variety of anomalies, such as agenesis, ectopic gland, or hypoplastic. The cause of TD is generally considered sporadic. Research has suggested that genetic factors contribute to the disease. According to recent findings, the development of the embryonic thyroid gland and its migration from the base of the tongue to the anterior part of the neck is a multi-stage process involving highly regulated biochemical phases, requiring the activation of transcription factors such as thyroid transcription factor 1 (TTF-1), forkhead box protein E1 (FOXE1), the homeobox 1 NK2 (NKX2-1), the paired box gene 8 (PAX-8), and transcription regulators. The remaining 10-15% of primary CH is due to thyroid dyshormonogenesis. Low T4 and T3 levels are standard in infants with primary CH, with elevated TSH and TRH levels due to a feedback signal to the hypothalamus and pituitary gland (BOELEN et al., 2023) (UTHAYASEELAN et al., 2022).

Central CH results from hypothalamic insufficiency and/or inadequate pituitary stimulation. Most patients with central CH have multiple pituitary hormone deficiency (MPHD), involving at least two anterior pituitary hormones. Genes such as TSHB, TRHR, and IGSF1 are associated with central HC. Most NBS programs are based on thyroid-stimulating hormone (TSH). However, the Dutch algorithm utilizes the combined measurement of T4, TSH, and TBG, allowing detection of primary and central CH. Early detection is crucial to avoid long-term complications. Studies show that most patients with central CH treated early have moderate to severe hypothyroidism. The long-term cognitive outcome is reassuring, with nearly 90% of patients having normal Full Scale Intelligence Quotient (FSIQ) scores. However, more research is needed to compare early and late detected patients. Neonatal detection of central CH is essential for the proper care of patients. International collaboration and prospective studies are needed to fully understand the benefits of newborn screening. Early detection can prevent brain damage and improve the clinical and cognitive outcomes of these patients (BOELEN et al., 2023).

These hormones are essential for the development of the auditory pathway. Children with CH may develop hearing problems, as TH are essential for the maturation of the auditory pathway. Early

sensory deprivation can impair language skills, literacy, and behavioral development. In this review, we describe clinical and molecular aspects that link CH to hearing loss. In addition, CH can be classified as permanent or transitory, with different etiologies. Neonatal screening is crucial for early diagnosis and appropriate treatment (ANDRADE et al., 2021).

Thyroid hormones play a vital role in brain development and neural function. In this review, we explore the complex interaction between thyroid hormones, parvalbumin-expressing neurons, and their relationship to neuropsychiatric disorders. We investigated studies that address congenital hypothyroidism, Rett Syndrome and other conditions, seeking to understand the underlying mechanisms and their clinical implications. Thyroid hormones (T3 and T4) are essential for brain development, synaptic plasticity, and neuronal homeostasis. They affect neuronal migration, cell differentiation, and synapse formation. In addition, parvalbumin-expressing neurons play a crucial role in the regulation of cortical excitability and the synchronization of neural networks. Studies in mice with congenital hypothyroidism have revealed a significant decrease in the number of parvalbumin-expressing neurons. This hormone deficiency during the perinatal period affects brain formation in fetuses and newborns. Recovery of hormone levels after treatment with antithyroid agents does not completely restore parvalbumin neuron counts, suggesting a critical period of sensitivity to thyroid hormones. (UCHIDA; SUZUKI, 2021).

Rett syndrome (RTT), caused by mutations in the MeCP2 gene, presents histological abnormalities similar to those observed in congenital hypothyroidism. Patients with RTT also exhibit thyroid dysfunction, with contradictory results regarding serum T4 levels. The relationship between MeCP2 and thyroid function still requires investigation, but studies suggest reciprocal interactions. Understanding these interactions is crucial to advance research on neuropsychiatric disorders. Comparative analysis with schizophrenia and autism may provide clues about the pathogenesis of developmental delay. In addition, the search for biomarkers and the study of animal models continue to unravel the mysteries of these complex conditions. The relationship between thyroid hormones, parvalbumin neurons, and neuropsychiatric disorders is multifaceted and continues to be explored. Research in this area promises significant improvements in the understanding and treatment of these conditions, positively impacting mental health and brain development (UCHIDA; SUZUKI, 2021).

Neonatal screening, which began in the 1970s, plays a crucial role in the early detection of this disorder. The goal is to identify newborns with elevated levels of thyroid-stimulating hormone (TSH) above a specific threshold. Screening programs, such as the one established in Scotland in 1979, are essential to detect permanent and transient cases. The anatomy and physiology of the fetal and neonatal thyroid are fundamental to understand changes in thyroid function in newborns. The synthesis of thyroxine (T4) and triiodothyronine (T3) involves complex steps, and frequent monitoring of hormone levels is essential in the first months of life. Levothyroxine treatment should

be started as soon as possible after diagnosis in order to maintain free T4 or T4 levels in the upper half of the normal range. In addition, clinical evaluation, thyroid imaging tests, and reevaluation are an integral part of the follow-up of these babies. The intellectual outcome depends on the severity of intrauterine hypothyroidism, and it is crucial to avoid sequelae through appropriate treatment. Each case is unique, and individualized monitoring is essential to ensure the best development of these children (TORRESANI, 2014).

Screening for early detection of primary hypothyroidism results in the diagnosis of 1 in 2,000 live births. Pilot programs for screening for hypothyroidism were developed in Quebec, Canada, and Pittsburgh, PA, in 1974. In addition to the clinical benefit, the cost of screening for CH is significantly lower than the cost of diagnosing CH at an older age. The ideal time to perform neonatal screening tests is 48 to 72 hours after birth, to avoid the physiological increase in TSH that occurs in the first hours after birth. To perform newborn screening, capillary blood from a heel puncture is placed in circles of specialized filter paper, dried, and sent to a centralized laboratory (WEINER et al., 2020).

A TSH value <20 mIU/L in the first 72 hours after birth is considered normal. If the TSH value is elevated (usually defined as >20–40 mU/L), confirmatory serum testing via venipuncture of blood is required to confirm the diagnosis of CH. Confirmatory serum tests should ideally be obtained within the first 2 weeks of age. Serum samples should be sent to measure the TSH level and the total T4 or FT4 level. The total T4 test is less expensive and can be reported within a few hours; however, FT4 values are not affected by changes in TBG and represent biologically relevant T4. The results should be compared with age-normalized values for full-term and preterm infants. Immediate consultation with a pediatric endocrinologist is recommended if the results are abnormal for age (WEINER et al., 2020).

TSH concentration is the most sensitive indicator of the HPT axis. Before 2 weeks of age, venous TSH values greater than 20 mIU/L, and after 2 weeks, TSH values greater than 10 mIU/L suggest primary CH. Low serum T4 or FT4 with elevated TSH confirms the diagnosis of primary hypothyroidism and treatment should be initiated immediately. For subclinical hypothyroidism (also known as) with hyperthyrotropinaemia, a TSH value between 6 and 20 mIU/L with normal FT4, it is reasonable to proactively monitor serum thyroid tests and delay the initiation of LT4 unless the TSH level continues to increase or the FT4 level decreases below normal (WEINER et al., 2020).

Thyroid ultrasound is usually the first test performed to determine the etiology of primary hypothyroidism. Color Doppler can be useful in identifying an ectopic thyroid gland. An iodine uptake scan, with iodine 123 or sodium pertechnetate 99m, is the most accurate imaging tool for determining the size and location of thyroid tissue. It can be used to diagnose aplasia, hypoplasia, or ectopic thyroid gland. Patients with TRAbs blockade, TSH receptor inactivating mutations, and

iodine retention defects also did not have any uptake, but will have normal or enlarged thyroid on ultrasound. Alternatively, thyroglobulin levels can also be used to assess the presence of a thyroid gland (WEINER et al., 2020)

The treatment of CH is based on replacement therapy with L-T4. As soon as the diagnosis is confirmed, L-T4 administration begins, with a recommended starting dose of 10-15 mcg/kg/day, and should be administered 30 minutes before feeding. Subsequent adjustments are made based on the results of thyroid function tests. It is important to ensure adherence to treatment and avoid interactions with substances that may interfere with L-T4 absorption (RASTOGI; LAFRANCHI, 2010).

Absorption is hampered by foods and products with soy, iron, calcium, and aluminum. A crushed LT4 tablet is typically mixed with 1 to 2 mL of breast milk, formula, or water, and the suspension is placed on the cheek. Recently, a commercial oral solution of levothyroxine sodium has become available for the treatment of hypothyroidism and pituitary TSH suppression. It is the first liquid formulation of LT4 approved by the Food and Drug Administration. However, the treatment of choice remains the tablet form of LT4. If intravenous therapy is required, the dose should be 50% to 80% of the oral dose (WEINER et al., 2020).

Treatment should be started within 2 weeks of birth. However, in patients with adrenal insufficiency in addition to central hypothyroidism or in those in whom adrenal insufficiency cannot be excluded, assessment of adrenal function, followed by appropriate glucocorticoid therapy, is required for 48 to 72 hours prior to LT4 supplementation. The AAP recommends monitoring thyroid function 2 and 4 weeks after starting LT4 treatment and every 1 to 2 months during the first 6 months of age. The goal is to normalize T4 and TSH in 2 and 4 weeks, respectively. The goal is T4 and FT4 concentrations in the upper half of the reference range for age, with normalization of TSH (WEINER et al., 2020).

Infants with suspected transient disease should be reassessed after 3 years of age. Early treatment is essential to avoid cognitive and behavioral sequelae. Studies show that mental retardation associated with untreated CH has been largely eradicated by newborn screening. However, controversies persist about subtle cognitive deficits in more severely affected infants. Factors such as the time to normalization of thyroid hormone levels, maternal IQ, socioeconomic and ethnic status also influence the result. Long-term problems can affect areas such as memory, language, fine motor coordination, attention, and spatial vision. Therefore, ensuring adherence to treatment and long-term monitoring are essential to optimize the development of these children. In conclusion, CH, when properly diagnosed and treated, has a good prognosis. Collaboration between health professionals and parental awareness are essential to ensure positive outcomes and better quality of life for patients with CH. (RASTOGI; LAFRANCHI, 2010).

CONCLUSION

Congenital hypothyroidism (CH) is a complex condition that requires careful attention from the first days of life. Newborn screening plays a key role in early detection, allowing for timely interventions and avoiding cognitive and behavioral sequelae. Treatment with levothyroxine (L-T4) aims to normalize hormone levels and optimize the development of these children.

Collaboration between healthcare providers, parents, and caregivers is essential to ensure positive outcomes. In addition, continued research into the underlying mechanisms of HC, including its relationship to the auditory pathway and parvalbumin neurons, is crucial to enhance our knowledge and patients' quality of life. Intervention proposals include awareness-raising, improvement in screening programs, multidisciplinary follow-up, and research. In summary, early diagnosis and appropriate treatment of CH are essential for a favorable prognosis. With continued efforts in the medical field and public awareness, we can significantly improve the care and well-being of children affected by this condition.

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