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Congenital hypothyroidism: A theoretical approach

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Giovanna Batista Nogueira
Undergraduate student of the seventh period of Medicine
University Center of Caratinga – UNEC

Jovino Marcelino Fernandes Neto
Graduating from the tenth period of Medicine
University Center of Caratinga – UNEC

Diego Guzella Pinto Lopes
Graduating from the seventh period of Medicine
University Center of Caratinga – UNEC

Juscélio Clemente de Abreu
Doctor in Cytogenetics
University Center of Caratinga – UNEC

ABSTRACT
Congenital hypothyroidism (CH) is a rare endocrine disease that manifests chronically and insidiously in children. Historically, HC is linked to regions with high rates of malnutrition, lack of prenatal care, and late diagnosis. In addition, studies show that the risk is higher in female children, high maternal age, prematurity and the birth of twins. The disease is based on the alteration of thyroid hormone or Thyroid Stimulating Hormone (TSH) levels, so the main complications are in bone development, which can lead children to short stature and growth retardation, and in neurological development, which can lead to mental retardation. Thus, the delay in diagnosis, especially until the second or third month of life, can impair the physical and cognitive development of the newborn, generating irreversible complications. Newborn screening is challenging, as a significant portion of children appear to be normal at birth. It relies on a heel prick to detect high TSH levels and low thyroxine (T4) or free T4 levels. After diagnosis, treatment is instituted, through hormone replacement with levothyroxine, to avoid irreversible deficits and long-term metabolic complications. Treatment is also challenging, as hormone replacement is regularly adjusted based on the child's growth and development to keep hormones within the age range, which makes regular medical follow-up essential.

Keywords: Congenital hypothyroidism, Thyroid disease, Hypothyroidism in pediatrics, Thyroid dysfunction in childre.

1 INTRODUCTION

Congenital hypothyroidism is a medical condition in which a child is born with an underactive or absent thyroid, resulting in low thyroid hormone levels. (KLOSINSKA, 2018).

Treatment involves hormone replacement with levothyroxine, usually for life. It is important to start treatment as early as possible to prevent possible development and growth problems (BRITO, 2021), preferably within the first 15 days of life.

The dose of levothyroxine is adjusted regularly, as the child grows and develops, to keep thyroid hormone levels within the normal range.

Regular medical follow-up is essential to ensure that treatment is adequate and possible long-term complications are avoided. (KLOSINSKA, 2018). If treatment is not given early, congenital hypothyroidism can lead to short stature due to the low production of hormones, which are essential for the growth and development of the body, by the thyroid.

However, if hormone replacement treatment is started soon after birth, most children can reach a normal height. Therefore, theoretical studies on epidemiology and etiologies of short stature in children with congenital hypothyroidism are highly justified due to their clinical relevance and impact on the quality of life of these children.

In addition, there is a need for constant updating of scientific information on the subject, to support health professionals, generate new technical-scientific contributions and enhance improvements in public health policies aimed at the prevention and treatment of this condition.

This study aims, mainly, to contribute theoretically to the advancement of knowledge in the area of pediatric endocrinology, indirectly benefiting children affected with congenital hypothyroidism.

2 DEVELOPMENT

2.1 GETTING TO KNOW THYROID DISEASES

2.1.1 Hypothyroidism

Hypothyroidism is the main thyroid dysfunction, manifesting in a chronic and insidious way. There are three classifications: primary, secondary, and tertiary. (KLOSINSKA, 2018)

Primary hypothyroidism, the most prevalent, results from intrinsic dysfunction of the thyroid gland, leading to hormone deficiency with elevated TSH and free T4 levels below normal limits. The secondary, in turn, is characterized by dysfunction in the pituitary gland, which does not secrete enough thyroid-stimulating hormone (TSH) to stimulate the production of thyroid hormones. This dysfunction can originate both in the pituitary itself and in the hypothalamus, which regulates the release of hormones by the pituitary. Tertiary, on the other hand, involves a failure in the hypothalamus, which does not produce the adequate amount of thyrotropin-releasing hormone (TRH), which is responsible for stimulating the release of TSH through the pituitary. Although it is less common, it can be caused by genetic factors or lesions in the hypothalamus (CARVALHO et al, 2022).

Autoimmune thyroiditis, especially Hashimoto's, is the most common cause, involving an inflammatory response mediated by T cells. Other causes include dietary iodine deficiency, surgical resection of the gland, and certain medications.

Central hypothyroidism refers to dysfunctions in the secretion of central hormones, TSH or TRH, and is rare and associated with disorders that compromise hypothalamic and pituitary thyroid control (KASPERAVICIUS, 2020).

Subclinical hypothyroidism is characterized by elevated TSH levels and normal T3 and T4 levels. Risk factors include older age, family history of thyroid disease, radiation therapy to the head and neck, among others. The disease has nonspecific symptoms such as bradycardia, dry skin, fatigue, and weight gain. Diagnosis involves laboratory tests, and TSH measurement is the most reliable.

Treatment aims to normalize hormone levels, commonly using levothyroxine sodium, and continuous monitoring is effective in getting doses right and sustaining correct thyroid function.

Congenital hypothyroidism is a condition present from birth, often stemming from genetic defects that affect the formation of the thyroid gland. If not treated early, it can lead to developmental delays and cognitive impairment (PEDRO, 2022).

2.1.2 Hyperthyreoidism

Hyperthyroidism occurs due to excess circulating thyroid hormones, resulting from overproduction by the thyroid gland. Decreased TSH levels, below 0.1 mIU/L, and increased levels of free T3 and T4 characterize the condition.

Graves' disease is the most common cause, an autoimmune disease that stimulates the excessive production of T3 and T4. Other causes include adenomas, hyperplastic thyroid nodules, malignant thyroid neoplasms, and exposure to excess iodine. Diagnosis involves clinical evaluation and laboratory tests. Symptoms include nervousness, sweating, heat intolerance, weight loss, among others.

Treatment of hyperthyroidism may involve the use of beta-blockers to relieve adrenergic symptoms and antithyroid drugs.

In specific cases, radioactive iodine or thyroidectomy may be indicated. The association of Graves' disease with family history and its prevalence in women are observed. Hyperthyroidism can lead to complications such as bone metabolism disorders, panic disorders, changes in blood glucose and cardiovascular dysfunctions, especially atrial fibrillation and heart disease (MAIA, 2013).

2.1.3 Goiter

Goiter is characterized by any increase in the size of the thyroid gland, and is considered when it exceeds two standard deviations for age. The World Health Organization (WHO) classification divides goiter into four grades: grade 0 indicates the absence of goiter, grade 1 refers to a palpable goiter, grade 2 represents a visible goiter, and grade 3 describes a bulky goiter. The adaptive increase in thyroid-stimulating hormone (TSH) in response to factors that alter the synthesis of thyroid hormones is determinant for this growth, generating hyperplasia and hypertrophy of the follicular epithelium. The most common causes of goiter are simple goiter and Hashimoto's thyroiditis (SEGURA et al, 2019).

There are several etiologies for goiter: simple or colloid, which is not associated with hypothyroidism or frank hyperthyroidism and is not a consequence of inflammation or neoplasia, has genetic and environmental factors as possible causes. On the other hand, endemic goiter affects more than 10% of the general population and is a result of iodine deficiency. Although iodization programs

and the recommendation of iodized salt consumption have reduced the incidence, iodine deficiency is still a significant cause of goiter worldwide.

Autoimmune thyroid diseases, such as Hashimoto's thyroiditis, can also cause goiter, and is more common in children with chromosomal abnormalities, such as Down and Turner syndrome. Treatment with levothyroxine (LT4) is indicated in cases of goiter associated with subclinical hypothyroidism with persistently elevated TSH (BOWDEN and GOLDIS, 2023).

2.1.4 Tireoidite

Thyroiditis encompasses a heterogeneous group of processes with different etiologies and clinical characteristics, sharing the destruction of the normal structure of the thyroid follicle, but each process has specific characteristics. The following types of thyroiditis stand out:

i) Acute thyroiditis, also known as suppurative or pyogenic, is a rare form of thyroiditis caused by various microorganisms, especially bacteria such as S. *aureus, S.* hemoliticus, and *S. pneumoniae.* Symptoms include unilateral pain in the anterior part of the neck, radiating to the jaw, accompanied by fever, chills, and other general symptoms of bacterial infection. The diagnosis is established by fine needle aspiration (FNA), and treatment consists of early and parenteral administration of antibiotics, with the possible occurrence of permanent hypothyroidism in severe cases (BORGES et al, 2020).

ii) subacute thyroiditis or De Quervain's thyroiditis, which is characterized by an inflammatory process in the thyroid gland, with spontaneous remission. Its duration varies from 1-2 weeks to several months, and its cause is usually of viral origin. Symptoms include a prodromal period with fever, asthenia, arthralgias, odynophagia, and dysphagia, followed by severe pain in the thyroid region, high fever, and significant impairment of general condition. About half of the cases present with thyrotoxicosis in the first few weeks, followed by return to euthyroidism and, in some cases, development of transient hypothyroidism. Treatment varies according to the phase: initial phase treated symptomatically with acetylsalicylic acid, addition of β-blockers in cases of hyperthyroidism, and, if hypothyroidism occurs, levothyroxine sodium (LT4) (SEGURA et al, 2019).

iii) Hashimoto's thyroiditis or chronic lymphocytic thyroiditis, which is a chronic inflammation of the thyroid with autoimmune origin, often associated with goiter and may result in permanent hypothyroidism. It is the most common cause of thyroid disorders in children, being more prevalent in girls. Symptoms vary, and many cases are asymptomatic. The diagnosis is confirmed by the presence of antibodies, mainly antithyroglobulin and antiperoxidase. There is no etiological treatment; in the case of hypothyroidism, the

administration of LT4 is indicated, with withdrawal of treatment for evaluation of thyroid function after 6-12 months in cases of transient hypothyroidism. In situations of euthyroidism with positive antibodies, the administration of thyroxine is not necessary, but thyroid function should be monitored regularly (CARVALHO et al, 2021).

2.1.5 Graves' disease

Graves' disease (GD) is an organ-specific autoimmune condition, standing out for its more frequent association with increased end-organ function. It represents the most common cause of hyperthyroidism in individuals under the age of 50, characterized by lymphocytic infiltration into the thyroid gland and activation of the immune system. GD accounts for 60-80% of hyperthyroidism cases, with an annual incidence in women of approximately 0.5 per 1000 over a 20-year period (VIANA et al, 2015).

The pathogenesis of GD is associated with an autoimmune disorder that results in hyperthyroidism due to the presence of TSH receptor-stimulating autoantibodies. These antibodies, called TSI, promote the growth of thyroid cells and the secretion of thyroid hormones. The cause of this autoimmune process is not yet fully understood, but factors such as genetic susceptibility, sex hormones, changes in immune function, smoking, iodine intake, and the action of infectious agents can trigger the disease (BOWDEN and GOLDIS et al, 2023).

GD is characterized by hyperthyroidism, ophthalmopathy, and acromachy. Patients may experience a variety of symptoms, such as nervousness, palpitations, heat intolerance, weight loss, weakness, insomnia, tremors, among others. Goiter, formed by multiple thyroid nodules, is predominant, being detected in about 90% of patients under 50 years of age. Clinical manifestations also include cardiac abnormalities such as sinus tachycardia and atrial fibrillation (BRITO et al, 2021).

Excess thyroid hormones can lead to serious complications such as congestive heart failure, cardiomyopathy, arrhythmias, and increased risk of fractures in older women due to elevated bone resorption. Varied clinical manifestations may be exacerbated by comorbidities, highlighting the importance of a comprehensive approach in patient evaluation. Laboratory findings, including increased levels of free T4, TSI, and an elevated ^{131}I uptake, are crucial for the clinical diagnosis of thyrotoxicosis and for differentiating GD from other thyroid conditions. The measurement of suppressed TSH confirms the picture of hyperthyroidism associated with GD, contributing to the definition of severity and, occasionally, providing evidence of the underlying etiology (VIANA et al, 2015).

2.1.6 Thyroid cancer

Thyroid cancer, the most common neoplasm of the endocrine system, has seen a significant increase in incidence since the 1990s, although without substantial repercussions on mortality and survival of the populations studied globally. The difference between the magnitude of incidence and mortality suggests a more timely diagnosis and a favorable prognosis, especially for differentiated carcinomas, the most frequently identified histological types. These observations raise questions about the possible phenomenon of overdiagnosis, attributed to the introduction of new diagnostic technologies, which may result in the detection and treatment of low-risk tumors, generating permanent morbidity associated with therapeutic procedures (Borges et al, 2020).

Projections indicate that thyroid cancer could occupy the fourth position among the most frequent malignant neoplasms by 2030, according to North American data. This prediction, associated with the hypothesis of overdiagnosis, highlights the importance of examining the epidemiological situation of this condition. The descriptive analysis of the data, using information from hospital cancer registries (RHCs) in Brazil, reveals a predominance of thyroid cancer in women, with a sex ratio (F/M) of 5:1, in line with the female dominance associated with this neoplasm. In addition, the age group and histological types show patterns consistent with the literature, highlighting the complexity of this condition and the importance of targeted prevention and awareness strategies (Borges et al, 2020).

2.2 CONGENITAL HYPOTHYROIDISM

Congenital Hypothyroidism (CH) is a condition that affects newborns due to incomplete thyroid development, resulting in decreased levels of thyroid hormone or Thyroid Stimulating Hormone (TSH). This condition, historically associated with regions with poor nutrition, lack of prenatal care, and late diagnosis, has been a significant social concern. Delay in diagnosis, especially until the second or third month of life, can impair the cognitive and physical development of the newborn.

CH can be classified as permanent or transient, depending on the etiology and duration of hypothyroidism. There are different primary types of CH, such as thyroid dyshormonogenesis, TSH receptor insensitivity, central CH, transient CH, and thyroid dysgenesis. Genetic factors also play a role, contributing to inborn errors in thyroid hormone synthesis (PEDRO, 2022).

Statistics reveal that CH affects approximately 1 in 3,000 to 4,000 newborns, with higher rates in Asian, Native American, and Hispanic populations. In addition, the risk is higher in female children, with an increase associated with maternal age, prematurity, and twin birth. It is noteworthy that many cases remain undiagnosed in the first few months due to the presence of maternal hormones and underdeveloped thyroid tissues (SILVA et al., 2022).

It is notable that a significant portion of children with CH appear normal at birth, making diagnosis challenging. Follow-up studies indicate that delayed diagnosis can lead to neurological complications such as mental retardation, developmental disorders, stunted growth pattern, and short stature. In addition to neurological symptoms, clinical manifestations such as umbilical hernia, dry skin, cretinoid face, growth deficit, jaundice, and other problems may arise (SINGH et al., 2022).

Treatment is crucial to avoid irreversible deficits and long-term metabolic complications. Newborn screening plays a key role in this process, being performed through a heel prick to detect elevated TSH levels and low thyroxine (T4) or free T4 levels. Additional tests, such as thyroid radionuclide uptake and scanning, are used to confirm the diagnosis (VASIREDDY et al., 2023).

An integrative literature review was conducted using databases such as PubMed, Virtual Health Library and Directory of Open Access Journals. A total of 25 relevant articles were identified, highlighting the importance of early diagnosis, risk factors, screening methods, and treatment. The results indicate that early diagnosis, ideally during the neonatal period, is crucial to avoid long-term complications, including mental retardation. Newborn screening programs are implemented globally, with the heel prick test being an essential tool. Treatment, usually based on levothyroxine, aims to normalize hormone levels and ensure proper development. In conclusion, research highlights the importance of early diagnosis of CH, emphasizing the need for awareness, effective newborn screening programs, and appropriate therapeutic intervention. The knowledge and attention of health professionals play a crucial role in promoting the quality of life of affected children and preventing serious complications (PEDRO, 2022).

2.3 BONE DEVELOPMENT AND SHORT STATURE

Congenital hypothyroidism is an endocrine condition resulting from inadequate production of thyroid hormones during the neonatal period, having significant implications on the physical and neurological development of affected children. This endocrine disorder directly impacts bone development, interfering with the mineralization, growth, maturation, and structure of growing bones. The thyroid hormones, triiodothyronine (T3) and thyroxine (T4), play a vital role in regulating bone metabolism. The deficiency of these hormones compromises bone formation by decreasing the activity of osteoblasts, responsible for the production of bone matrix, and by increasing the activity of osteoclasts, which are involved in bone resorption. This dysregulation results in inadequate bone mineralization, impairing the incorporation of essential minerals into the bone matrix (MACIEL, 2013)

Longitudinal bone growth, which is essential for body stature, is compromised in congenital hypothyroidism. Thyroid hormones exert a direct influence on the closure of bone epiphyses and the control of skeletal growth. Hormone deficiency interferes with this process, resulting in slower bone growth and, consequently, below-average height. In addition, hypothyroidism affects skeletal

maturation, delaying bone age in relation to chronological age, evidencing a delay in bone maturity. This delay can impact the final structural development of the skeleton, influencing long-term bone health. Advanced clinical manifestations of hypothyroidism, such as myxedema, characterized by skin swelling and thickening, can have impacts on facial and cranial bone structure, altering bone conformation and physical appearance (KLOSINSKA, 2018)

Therefore, congenital hypothyroidism poses a substantial challenge in infant bone development, impacting the mineralization, growth, maturation, and structure of growing bones. Early detection and effective treatment are crucial to mitigate adverse effects and promote healthy and proper bone development in these children. (VIANA, 2023)

Short stature is defined as the condition in which the height of individuals is below the 3rd percentile on the World Health Organization curve, or is 2 standard deviations below the mean height of children of the same age and sex. Decreased growth can occur as a result of several factors, such as congenital hypothyroidism. (AGARDH, 2015)

Among the endocrine causes, congenital hypothyroidism is a clinical syndrome caused by thyroid hormone deficiency, resulting in altered metabolic processes and impaired neurodevelopment. These children develop a picture of reduced growth and mental retardation in varying degrees, and may also present delayed bone maturation and tooth eruption, the most common manifestation of hypothyroidism in children is related to decreased growth speed. Growth retardation can occur for several years before having other symptoms. Thus, any child with reduced growth velocity should be evaluated for hypothyroidism (Cooper, 2007).

In summary, short stature in children with congenital hypothyroidism is a direct manifestation of hormone deficiency that affects bone growth.

3 FINAL THOUGHTS

Academic theoretical studies are of great importance for clinical medicine, especially in relation to the present subject, which is always undergoing updates due to advances in molecular tests for early diagnosis.

Early recognition of congenital hypothyroidism is crucial to guide timely clinical interventions, ensuring optimal physical development and minimizing the adverse effects associated with this endocrine condition.

The contribution to a better physiological understanding of congenital hypothyroidism has had a direct impact on clinical practice and supportive management of this vulnerable pediatric population.

REFERENCES

AGARDH, D et al. Clinical features of celiac disease: a prospective birth cohort. J. Pediatrics 2015; 135:627.

ARES SEGURA, S. et al. Hipotiroidismo y bocio. Protoc diagn ter pediatr. 2019;1:183-203. Disponível em: https://www.aeped.es/sites/default/files/documentos/12_hipotiroidismo.pdf. Acesso em: 11 nov. 2023.

BORGES, Anne Karin da Mota et al. Câncer de tireoide no Brasil: estudo descritivo dos casos informados pelos registros hospitalares de câncer, 2000-2016. Epidemiologia e Serviços de Saúde, v. 29, n. 4, 2020. Disponível em: https://www.scielo.br/j/ress/a/8pPPFwPvxYXDWnqvtGJbQPg/?format=html#ModalTutors. Acesso em: 11 nov. 2023.

BOWDEN, Sasigarn A.; GOLDIS, Marina. Congenital Hypothyroidism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023 Jan. 2023. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32644339/. Acesso em: 20 set. 2023.

BRITO, Lara Novais Santos et al. ADHESION TO TREATMENT BY CHILDREN WITH CONGENITAL HYPOTHYROIDISM: KNOWLEDGE OF CAREGIVERS IN BAHIA STATE, BRAZIL. Revista Paulista de Pediatria, 2021 Apr 2; 39:e2020074. DOI: 10.1590/1984-0462/2021/39/2020074. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33825794/. Acesso em: 20 set. 2023.

CARVALHO, Idelândia Lacerda de et al. Tireoidite de Hashimoto como Etiologia Prevalente de Hipotireoidismo Primário: Aspectos Etiopatogênicos, Métodos Diagnósticos e Condutas Terapêuticas. Brazilian Journal of Development, Curitiba, v.8, n.7, p. 52525-52536, jul., 2022. Disponível em: https://ojs.brazilianjournals.com.br/ojs/index.php/BRJD/article/view/50474 Acesso em: 14 dez. 2023.

COOPER, D. et al. The thyroid gland. In: Greenspan FS, Gardner DG, editors. Basic & Clinic Endocrinology. 8th ed. New York: McGraw-Hill; 2007. p. 209- 80.

KASPERAVICIUS, Jéssica Pasquali. Prevalência de hipotireoidismo e de hipertireoidismo e fatores associados. Monografia. Universidade Federal da Fronteira Sul, Curso de Bacharelado em Medicina, Passo Fundo, RS, 2020. Disponível em: https://rd.uffs.edu.br/bitstream/prefix/4107/1/TCC%20J%c3%89SSICA%20PASQUALI%20KASPERAVICIUS.pdf. Acesso em: 11 nov. 2023.

KLOSINSKA, Martyna; KACZYNSKA, Agnieszka; BEN-SKOWRONEK, Iwona. Congenital Hypothyroidism in Preterm Newborns – The Challenges of Diagnostics and Treatment: A Review. Frontiers in Endocrinology, v. 13, 2022. DOI: 10.3389/fendo.2022.860862. Disponível em: https://www.frontiersin.org/articles/10.3389/fendo.2022.860862/full. Acesso em: 21 set. 2023.

KLOSINSKA, Martyna; KACZYNSKA, Agnieszka; BEN-SKOWRONEK, Iwona. Congenital Hypothyroidism in Preterm Newborns – The Challenges of Diagnostics and Treatment: A Review. Frontiers in Endocrinology, v. 13, mar. 2018. Congenital Hypothyroidism in Preterm Newborns - The Challenges of Diagnostics and Treatment: A Review - PubMed (nih.gov)

MACIEL, L. M. Z. et al. Hipotireoidismo congênito: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia. Arquivos Brasileiros de Endocrinologia & Metabologia, São Paulo, v. 57, n. 3, p. 184-192, 2013 SciELO - Brasil - Hipotireoidismo congênito: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e

Metabologia Hipotireoidismo congênito: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia

MAIA, Ana Luiza et al. Consenso brasileiro para o diagnóstico e tratamento do hipertireoidismo: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia. 2013. Disponível em <https://repositorio.ufba.br/ri/bitstream/ri/16832/1/Ana%20Luiza%20Maia.pdf. Acesso em: 13 nov. 2023.

PEDRO, Isabella Geraldi Augusto et al. Hipotireoidismo Congênito: Diagnóstico Precoce e Suas Complicações - Uma Revisão de Literatura. Revista Eletrônica Acervo Médico, Vol. 12, Universidade de Vassouras, Vassouras–RJ, 2022. Disponível em: https://acervomais.com.br/index.php/medico/article/view/10365/6267. Acesso em: 13 nov. 2023.

SILVA, Ivani Novato; MARÇAL, Lara Vieira; QUEIROZ, Dulciene Maria Magalhães. A infecção por Helicobacter pylori está associada à disfunção tireoidiana em crianças com hipotireoidismo congênito. Pediatria Frontal, 21 de junho de 2022; v. 10, 875232. DOI: 10.3389/fped.2022.875232. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35799701/. Acesso em: 21 set. 2023.

SINGH, Karam Chandrajit; DHILLON, Prabhkiran; THULASEEDHARAN, Thushara. A retrospective study on newborn screening for metabolic disorders. Bioinformation, v. 18, n. 12, p. 1122-1125, dez. 2022. DOI: 10.6026/973206300181122. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37701517/. Acesso em: 21 set. 2023.

VASIREDDY, Nayana Tara; ASIRVATHAM, Adlyne Reena; MAHADEVAN, Shriraam. Congenital hypothyroidism: clinical examination relevance. BMJ Case Reports, v. 16, n. 9, e256718, set. 2023. DOI: 10.1136/bcr-2023-256718. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37699738/. Acesso em: 21 set. 2023.

VIANA, Virgínia et al. Relato de CASO: Doença de Graves. Revista de Iniciação Científica da Universidade Vale do Rio Verde, Três Corações, v. 5, n. 1, p. 23-32, 2015. Disponível em: file:///C:/Users/marce/Downloads/2363-6895-1-PB.pdf. Acesso em: 11 nov. 2023.