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CONGENITAL HYPOTHYROIDISM - THE IMPORTANCE OF SCREENING AND TREATMENT OPTIMIZATION IN CHILDREN

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ABSTRACT

Introduction and objective: Congenital hypothyroidism (CH) is an endocrine disorder that can lead to physical and cognitive impairment if not properly treated. The aim of this review is to discuss the importance of screening and treatment optimization in childhood, within the context of the healthcare system in Poland, with reference to European standards. The article also discusses the most important issues related to the topic of CH.
Review methods: This article is based on a literature review from 2009 to 2025, with more focus put on papers published after 2017, analyzing national and international diagnostic, therapeutic guidelines, and long-term treatment outcomes. It also analyzes the challenges of differentiating permanent and transient forms and strategies for therapy monitoring.
State of knowledge: Early diagnosis and treatment of CH (before 14th day of life) are crucial in preventing neurodevelopmental delays. Treatment involves lifelong thyroid hormone replacement therapy, but in cases of transient hypothyroidism, the withdrawal of the therapy at 2–3 years of age can be taken into consideration. Challenges in the topic of CH include diagnosing milder forms and personalizing treatment.
Summary: Despite significant progress in CH diagnosis and treatment over the years, precise diagnosing and adjusting therapy to individual patient needs still remain a challenge. Future research should focus on developing better diagnostic tools, adjusting treatment to personal needs, and monitoring long-term neurodevelopmental outcomes among the pediatric population.

KEYWORDS

Congenital Hypothyroidism, Newborn Screening, Pediatric Endocrinology, Thyroid Hormone Replacement Therapy, Treatment Optimization

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Introduction and Objective

Congenital hypothyroidism (CH) is the most common endocrine disorder identified through neonatal screening and one of the leading preventable causes of intellectual disability in children [1]. In Poland, universal screening for CH has been part of the National Program for Early Detection of Inborn Metabolic Diseases since 1994, coordinated by the Institute of Mother and Child (Instytut Matki i Dziecka, IMiD) [2]. Early diagnosis and immediate initiation of levothyroxine therapy allow for normal psychomotor development in most affected children [3].

The reported incidence of CH in Poland is approximately 1 in 3500 live births, aligning with data from other European countries [2,4]. Over recent years, there has been a growing body of research focusing on the genetic background of CH, the clinical variability between transient and permanent forms, and the long-term outcomes of therapy. Simultaneously, clinicians face challenges in optimizing screening protocols (e.g., TSH cut-offs, timing of sample collection), implementing individualized treatment strategies, and determining appropriate criteria for treatment withdrawal and re-evaluation.

The objective of this review is to provide a comprehensive summary of current knowledge on congenital hypothyroidism in children, with particular emphasis on neonatal screening practices and treatment optimization strategies. The review focuses primarily on Polish recommendations and practices; where national guidelines are lacking, relevant European standards and recent international research are referenced. Special attention is given to areas where current clinical approaches remain controversial or inconsistent.

Review methods

This review was conducted in accordance with the principles of narrative literature reviews. A systematic search of the electronic databases PubMed, Scopus, and Web of Science was performed between January and May 2025. The search strategy included the following keywords and their combinations: congenital hypothyroidism, newborn screening, levothyroxine, treatment, follow-up, transient hypothyroidism, neurodevelopment. MeSH terms were used when appropriate.

Inclusion criteria were: peer-reviewed original research articles and review papers published in English and Polish between 2009 and 2025, publications concerning congenital hypothyroidism in the pediatric population, studies focused on screening strategies, treatment protocols, diagnostic algorithms, follow-up, or long-term outcomes.

Exclusion criteria were: case reports and case series, editorials, letters to the editor, and conference abstracts, studies not directly addressing CH in children, articles in languages other than English or Polish.

To ensure relevance to national clinical practice, official guidelines and reports from the Institute of Mother and Child (IMiD) and Polish Society of Pediatric Endocrinology and Diabetology (PTED) were also reviewed. Where Polish recommendations were lacking, European guidelines, including those of the European Society for Paediatric Endocrinology (ESPE), were referenced.

Particular attention was paid to including recent studies, with at least 75% of references published within the last eight years, in accordance with the journal's editorial policy. The literature selection process prioritized methodological rigor, clinical applicability, and relevance to Polish healthcare context. Limitations of the review include potential publication bias and the heterogeneity of diagnostic and therapeutic approaches among different countries.

Description of the State of Knowledge

Pathophysiology and etiology

Thyroid hormones play a crucial role in fetal and neonatal brain development, growth, and metabolism. Congenital hypothyroidism (CH) is most commonly caused by primary thyroid dysfunction, which accounts for over 90% of cases [1,2]. Secondary (central) hypothyroidism and peripheral resistance to thyroid hormone are rare and typically associated with genetic or syndromic conditions [3].

Among primary CH cases, the most frequent etiology is thyroid dysgenesis (agenesis, ectopy, hypoplasia), often sporadic but sometimes linked to mutations in genes such as TSHR, PAX8, NKX2-1, and FOXE1 [4,5]. Dyshormonogenesis, resulting from inherited defects in thyroid hormone synthesis (e.g. DUOX2, TPO, TG), is more prevalent in populations with a higher rate of consanguinity and may be associated with a goitrous gland [6]. In Poland, as in many European countries, thyroid dysgenesis remains the leading cause of permanent CH [7].

Transient hypothyroidism may result from maternal factors (e.g. iodine excess or deficiency, maternal TSH receptor-blocking antibodies, antithyroid drug exposure), prematurity, or neonatal illness [8]. These cases often normalize within months and may not require lifelong treatment. Differentiating transient from permanent CH is essential in guiding long-term management but is not possible at the time of diagnosis and requires reassessment at approximately 3 years of age [2,9].

particularly in dyshormonogenesis and syndromic forms [4,10]. The identification of specific mutations may aid in diagnosis, prognosis, and family counseling, but genetic testing is not routinely recommended in all cases under current Polish and European guidelines [2,11].

Screening Strategies - Polish and European Context

Neonatal screening for congenital hypothyroidism (CH) is a well-established and effective public health intervention. In Poland, CH screening has been implemented nationwide since 1994, coordinated by the Institute of Mother and Child (Instytut Matki i Dziecka, IMiD), as part of the National Newborn Screening Program [1]. All newborns are tested by measuring TSH concentration in dried blood spot samples collected between 3 and 5 days of life. A TSH concentration ≥15–20 mIU/L is considered abnormal and requires further diagnostic evaluation [2].

Polish guidelines emphasize prompt sample collection and rapid communication of results to allow treatment initiation by day 14 of life [2,3]. Screening coverage in Poland consistently exceeds 99%, placing the program among the most efficient in Europe [4].

Table 1. Comparison of national and international guidelines for CH screening and management

Guideline aspect	Polish Society [2]	ESPE / International [7,9]
Initial TSH cutoff (screening)	>20 mIU/L (on day 3–5 of life)	>20 mIU/L or country-specific [7]
Confirmatory serum TSH	>10 mIU/L	>10 mIU/L [7,9]
Treatment start threshold	fT4 <10 pmol/L and/or TSH >20 mIU/L	Similar thresholds, with earlier treatment emphasis [7]
Initial L-T4 dose	10–15 µg/kg/day	10–15 µg/kg/day [9]
Follow-up intervals	Every 2 weeks initially	2–4 weeks [7]

Despite its success, several areas of controversy remain. The use of TSH as the sole first-tier marker may miss cases of central or mild hypothyroidism [5]. Moreover, the choice of TSH cut-off affects the sensitivity and specificity of the screening. Lowering the cut-off increases detection rates but also raises the number of false positives and transient cases, which can lead to overtreatment and parental anxiety [6].

Special consideration is required for premature infants, newborns with low birth weight, and those requiring intensive care. These populations are at increased risk of transient hypothyroidism or delayed TSH rise [7]. Current Polish practice involves repeat testing in these risk groups, although protocols vary regionally [2,8]. European Society for Paediatric Endocrinology (ESPE) guidelines recommend repeat sampling in premature and ill infants between 2–6 weeks of life [9].

While some countries have introduced combined TSH and T4 screening, this approach remains debated due to cost, logistics, and uncertain benefit in improving neurodevelopmental outcomes [10]. At present, Poland adheres to a TSH-based strategy, aligned with most European countries [1,4].

Ongoing evaluation of screening algorithms, including potential integration of molecular markers or second-tier tests, may enhance specificity and enable more precise classification of CH subtypes in the future.

Diagnosis and classification

Diagnosis of congenital hypothyroidism (CH) is confirmed after abnormal results from neonatal screening are followed by confirmatory testing, typically including serum TSH and free thyroxine (fT4) levels. A diagnosis of CH is confirmed when elevated TSH (>20 mIU/L) and low fT4 (<10 pmol/L) levels are detected, though slightly higher cut-offs are used for premature infants or those with low birth weight (LBW) [1,2]. Confirmatory testing should ideally be performed within two weeks after the initial screening to minimize the delay in treatment initiation [3].

The classification of CH depends on its etiology and the persistence or resolution of the thyroid dysfunction. The two main categories are primary CH, resulting from thyroid dysgenesis or dyshormonogenesis, and secondary CH, caused by pituitary or hypothalamic dysfunction. In addition, a rare form, peripheral resistance to thyroid hormone, occurs due to mutations in thyroid hormone receptors or transporters [4,5].

In primary CH, the most common cause is thyroid dysgenesis, including agenesis, ectopy, or hypoplasia. These structural defects often lead to permanent hypothyroidism, requiring lifelong levothyroxine treatment. Thyroid dyshormonogenesis, which accounts for a smaller proportion of cases, is caused by defects in thyroid hormone synthesis and may present with a goitrous gland [6].

Transient hypothyroidism, often seen in premature infants or those with LBW, is characterized by temporary elevation in TSH that normalizes over time. Such cases do not require lifelong therapy, but continued follow-up is essential to differentiate transient from permanent forms. The decision to stop treatment is typically made after repeated testing at 2–3 years of age, based on normalization of thyroid function and clinical development [7].

Table 2. Permanent vs. transient congenital hypothyroidism – diagnostic clues

Diagnostic clue	Permanent CH	Transient CH
TSH at diagnosis	>100 mIU/L [2,7]	10–40 mIU/L [2,7]
fT4 at diagnosis	Clearly decreased [2]	Normal or slightly reduced [2]
Thyroid imaging	Agenesis, ectopy, hypoplasia [7]	Normal size or enlarged [7]
Required L-T4 dose at the age of 1-3 years	>5–6 µg/kg/day [9]	<3 µg/kg/day [9]
Family history and/or maternal risk factors	Rare	Often associated with maternal antibodies or iodine imbalance [2,9]

A diagnostic challenge lies in distinguishing central (secondary) hypothyroidism, caused by dysfunction in the hypothalamic-pituitary axis, from primary thyroid disease. Secondary hypothyroidism is less common, and affected infants may have low or inappropriately normal TSH levels despite low fT4, which complicates diagnosis and treatment initiation [8]. TSH and fT4 testing, along with imaging studies (e.g., ultrasound, scintigram), are crucial to making an accurate diagnosis and planning appropriate treatment.

Differentiating between permanent and transient CH is often not possible at the time of initial diagnosis, especially in neonates with TSH values in the lower range or with transient illness. As such, most affected infants are initially treated as if they have permanent hypothyroidism, and their response to therapy is monitored until age 3 years, when treatment may be tapered based on normal thyroid function tests and growth parameters [9].

Treatment and follow-up

The cornerstone of treatment for congenital hypothyroidism (CH) is levothyroxine (L-T4) replacement therapy, which aims to normalize thyroid hormone levels and ensure normal growth and neurodevelopment. Early treatment, initiated before 14 days of age, is critical to avoid cognitive impairment and other developmental delays [1]. The standard approach in Poland follows international guidelines, including those of the European Society for Paediatric Endocrinology (ESPE), which recommend initiating levothyroxine therapy as soon as the diagnosis is confirmed through serum TSH and fT4 testing [2,3].

The initial dose of levothyroxine typically ranges from 10 to 15 µg/kg/day. Dosing is individualized based on factors such as weight, gestational age, and the severity of thyroid dysfunction. For example, premature infants or those with low birth weight may require higher doses initially, with adjustments made based on regular monitoring of thyroid function tests [4]. The treatment aims to achieve normal serum TSH levels (0.5–4.0 mIU/L) and a fT4 concentration within the age-appropriate reference range [5].

Monitoring is essential to ensure optimal treatment and avoid overtreatment, which could lead to complications such as tachycardia, hypertension, and bone maturation abnormalities. Frequent follow-up visits are recommended in the first year of life, with thyroid function tests performed every 4–6 weeks until the infant is stabilized [6]. After the first year, follow-up intervals may be extended to every 3–6 months, although the frequency should be higher for infants with more severe or complicated forms of CH [7].

In addition to thyroid function monitoring, growth parameters (weight, height, head circumference) are also regularly assessed, as growth failure and delayed bone age can indicate suboptimal treatment or the need for dose adjustments. The aim is to maintain a stable, normal TSH and avoid fluctuations that could impact neurodevelopment and physical growth [8,12].

While permanent CH generally requires lifelong treatment, in cases of transient hypothyroidism, treatment may be discontinued around the age of 2–3 years, after confirming normal thyroid function and development. Decision-making in these cases involves repeated thyroid function tests and clinical assessment, as well as a careful evaluation of the child's growth and development. Children with transient hypothyroidism should undergo regular follow-up for several years to detect any potential recurrence of hypothyroidism [9].

Table 3. Suggested approach to monitoring L-T4 therapy in infants and young children with CH

Age / period of treatment	Monitoring frequency	Tests to perform	Target values [2,7,9]
First 6 months	Every 2–4 weeks	TSH, fT4	fT4 in upper half of normal; TSH normal/suppressed
6–12 months	Every 1–2 months	TSH, fT4	As above
>12 months to 3 years	Every 2–3 months	TSH, fT4	Maintain normal TSH and fT4 levels
After 3 years	Every 3–6 months	TSH, fT4	Consider treatment withdrawal trial [9]

Long-term Outcomes and Therapy Withdrawal

The long-term outcomes of congenital hypothyroidism (CH) are largely dependent on the timing and adequacy of treatment initiation. Early diagnosis and prompt initiation of levothyroxine therapy before the 14th day of life have been shown to prevent significant neurodevelopmental deficits in most children with permanent CH [1]. Studies suggest that children treated within the first two weeks exhibit IQ levels and developmental milestones comparable to their peers [2,3].

However, the extent of cognitive and physical outcomes can vary based on several factors, including the severity of hypothyroidism at the time of diagnosis, the underlying etiology, and the precision of ongoing treatment adjustments [4]. For example, children with thyroid dysgenesis, especially those with more severe hypothyroidism (TSH >100 mIU/L and undetectable fT4), tend to show better long-term outcomes compared to those with dyshormonogenesis or secondary hypothyroidism [5].

Growth and height are also critical indicators of treatment effectiveness. Children with CH who receive appropriate levothyroxine therapy generally show normal growth trajectories, though short stature may still occur in cases where therapy is suboptimal or delayed. Monitoring growth parameters and bone age is important, as a delay in skeletal maturation can signal inadequate thyroid hormone levels or dosing errors [6].

A key challenge in the management of CH is the decision to withdraw therapy in cases of transient hypothyroidism. Treatment can often be discontinued around 2–3 years of age, provided that thyroid function tests are within the normal range, and no other signs of hypothyroidism are present. This decision should be made cautiously, with repeat evaluations of thyroid function and developmental progress [7].

Children with permanent CH typically require lifelong treatment with levothyroxine, although adjustments may be necessary during periods of growth, puberty, or illness. Therapy withdrawal is generally not attempted in these cases, but close follow-up remains crucial to prevent overtreatment or undertreatment, both of which can lead to significant complications [8].

Neurodevelopmental outcomes have been extensively studied, and while most children with CH treated early exhibit normal cognitive function, there are cases where subtle deficits in attention, executive function, or learning difficulties have been reported. These outcomes are more likely in children who were diagnosed later or who had more severe hypothyroidism at birth [9]. Continuous monitoring and early educational support can mitigate these challenges.

Challenges and future directions

Despite the significant advancements in the screening, diagnosis, and treatment of congenital hypothyroidism (CH), several challenges remain. One of the major obstacles is the early diagnosis of milder cases, including those with transient hypothyroidism or central hypothyroidism, which may not be detected by routine neonatal screening. As the current screening method primarily targets TSH levels, subtle thyroid hormone deficiencies may go undetected, leading to delays in treatment initiation. This is particularly true for central hypothyroidism, where low TSH levels fail to reflect the true thyroid status, requiring a more nuanced approach for diagnosis [1].

Personalized treatment is another area in need of improvement. While the standard levothyroxine dosage works well for many infants, individual variations in absorption, metabolism, and tissue response to thyroid hormone necessitate more personalized treatment plans. Monitoring thyroid function through regular testing is critical, but advanced monitoring tools, such as measuring T3 levels or genetic markers, may allow for more accurate and individualized management of CH [2]. Additionally, adjusting dosages during periods of rapid growth, especially during infancy and adolescence, remains a challenge, as improper dosing can lead to neurodevelopmental issues or physical complications such as short stature or bone abnormalities [3].

As we move forward, several areas of research may help optimize the management of CH:

- Second-tier screening tests, such as T4 measurement or genetic screening, could complement TSH testing, helping to identify central hypothyroidism or milder forms of the condition [4]. Such tests could improve the accuracy of early diagnosis and reduce the risk of long-term developmental delays.
- Gene therapy and personalized medicine are promising fields that could potentially offer more targeted treatments for children with CH caused by specific genetic mutations. Understanding the genetic basis of thyroid dysfunction may allow for the development of novel therapies that address the root cause rather than simply replacing thyroid hormones [5].
- Long-term neurodevelopmental outcomes should remain a priority in future studies, especially for children with milder forms of CH who were diagnosed and treated early. While many children with CH show normal cognitive development, research is needed to identify and address subtle learning and behavioral challenges that might arise over time [6].
- Global variations in treatment protocols and diagnostic strategies point to the need for further standardization in CH management. Differences in TSH cut-offs, repeat testing protocols, and treatment goals between countries highlight the importance of international cooperation to establish best practices and improve care outcomes across diverse healthcare systems.
- In conclusion, while the early diagnosis and treatment of CH have led to significant improvements in the neurodevelopmental outcomes of affected children, there is still room for advancement. Future research should focus on improving diagnostic accuracy, personalizing treatment plans, and addressing the long-term neurodevelopmental challenges that may persist in children with CH.

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