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Diagnosis and Management of Congenital Hypothyroidism: An Updated Overview

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Abstract

Context: Hypothyroidism describes an endocrine disorder that occurs when the thyroid gland cannot secrete adequate thyroid hormones. Congenital hypothyroidism refers to a lack of thyroid hormone among newborns.
Evidence Acquisition: The ISI Web of Sciences, Scopus, PubMed, and Google Scholar databases were reviewed for relevant articles published from 2000 to 2022.
Results: Congenital hypothyroidism, occurring in approximately one in 2,000 to one in 4,000 newborns, ranks among the most frequent causes of intellectual disability that can be prevented. The screening of newborns, confirmation assessments, interpretation of thyroid function tests accurately, prompt and therapeutic treatment, and regular follow-up contribute to a very good neurocognitive outcome later in life. Since the timely diagnosis of congenital hypothyroidism is critical in preventing mental retardation, clinicians must be kept abreast of this disorder and educate nursing and medical students regarding accurate interpretations of diagnostic testing and the recognition of associated symptoms. Most newborns with congenital hypothyroidism present no symptoms, even though their TSH or T4 levels are likely to have fluctuated significantly. As a result, congenital hypothyroidism was rarely detected in newborns before the introduction of neonatal screenings.
Conclusions: We provide an overview of the etiology, epidemiology, manifestation, diagnosis, and treatment of congenital hypothyroidism based on the latest studies.

Keywords: Congenital Hypothyroidism, Manifestation, Epidemiology, Treatment, Screening

1. Context

Hypothyroidism describes an endocrine disorder that occurs when the thyroid gland cannot secrete adequate thyroid hormones (1). The thyroid gland lies just beneath and laterally to the thyroid cartilage on the anterior neck side. The structure comprises two large lobes on each side linked by a thin isthmus, which passes anteriorly to the second and third tracheal rings (2). This organ releases two kinds of hormones: amino acid hormones containing iodine (thyroxine and triiodothyronine) and a peptide hormone (calcitonin). Thyroxine (T4) and triiodothyronine (T3) constitute a couple of crucial metabolic hormones involved in cellular differentiation and organogenesis at the developmental stage, in addition to maintaining thermogenesis and metabolic equilibrium through increasing the body's basal rate of metabolism (3).

Congenital Hypothyroidism (CH) refers to a lack of thyroid hormone among newborns. The condition arises either from defects occurring during the formation or functioning of the thyroid gland (primary congenital hypothyroidism) or when the pituitary gland or the hypothalamus fails to sufficiently stimulate the thyroid gland (central congenital hypothyroidism) (4). Congenital hypothyroidism is among the leading factors of intellectual disability worldwide that can be prevented. The screening of newborns, confirmation assessments, interpretation of thyroid function tests accurately, prompt and therapeutic treatment, and regular follow-up are all contributing factors to a very good neurocognitive outcome later in life (5, 6).

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Significant progress has been made over the past 40 years since congenital hypothyroidism was first introduced in understanding congenital hypothyroidism pathophysiology, etiology, clinical manifestations, and epidemiology, as well as the most effective strategies to screen and treat this disorder (7, 8). Since a timely diagnosis of congenital hypothyroidism is essential to preventing mental retardation, clinicians must be kept abreast of this disorder and educate nursing and medical students on accurate interpretations of diagnostic testing and the recognition of associated symptoms (9). Therefore, in this study, we provide an overview of the etiology, epidemiology, manifestation, diagnosis, and management of congenital hypothyroidism based on the latest studies.

2. Evidence Acquisition

Based on the results of related studies, this is a review of the diagnosis and management of congenital hypothyroidism. The ISI Web of Sciences, Scopus, PubMed, and Google Scholar databases were reviewed for relevant articles published from 2000 to 2022. The keywords used included Congenital, Hypothyroidism, Manifestation, Epidemiology, Treatment, and Diagnosis.

3. Results

3.1. Pathophysiology, Etiology, and Risk Factors

In the hypothalamus-pituitary-thyroid axis, thyrotropin-releasing hormone (TRH) is secreted from the hypothalamic neurons to stimulate the pituitary gland to produce Thyroid-stimulating Hormone (TSH), thereby stimulating the production and release of thyroid hormone (10). This hormone has a negative feedback effect, acting primarily using the thyroid hormone receptor $\beta 2$, inhibiting TRH and TSH synthesis. Therefore, reducing thyroid hormone levels increases TSH release and enhances its stimulation by TRH. Defects at each stage of the thyroid axis may result in tertiary hypothyroidism (hypothalamus), secondary hypothyroidism (pituitary), or primary hypothyroidism (thyroid) (11).

Primary congenital hypothyroidism occurs when the thyroid gland cannot provide sufficient thyroid hormone due to thyroid gland defects. A biochemical characteristic of this condition involves lower serum-free T4 (FT4) levels and higher TSH levels than the reference interval (12). Nevertheless, the serum-free T4 concentration in subclinical primary hypothyroidism remains within normal limits. A primary defect in the thyroid gland can occur due to either the defective development of the gland (dysgenesis) or a normally structured gland that fails to synthesize enough thyroid hormone (dyshormonogenesis) (13). Permanent congenital hypothyroidism results primarily from thyroid dysgenesis, including thyroid agenesis, hypoplasia, and ectopy. Thyroid dysgenesis is typically sporadic, and only 2 - 5% of cases are linked to specific genetic mutations (14). When certain genes are disrupted, notably NKX2-1 (formerly known as TTF1), FOXE1 (formerly known as TTF2), and PAX8, which are essential transcription factors responsible for thyroid morphogenesis and differentiation, along with the thyroid-stimulating hormone receptor (TSHR), they may cause dysfunction in the formation of the thyroid gland (15). Transcription factors also play an important role in the development of different types of tissues, causing further syndromic characteristics, including interstitial lung disease and chorea (NKX2-1), renal abnormalities (PAX8), or cleft palate, choanal atresia, spiky hair, and bifid epiglottis (FOXE1) (16).

Congenital hypothyroidism is mostly associated with thyroid dysgenesis. However, dyshormonogenesis incidence has significantly increased over the past few decades. In contrast to thyroid dysgenesis, which presents with a monogenic cause in a very small percentage of cases, dyshormonogenesis is often caused by a defect within the genome that affects the components of thyroid hormone production (17). Some genetic defects have been implicated as responsible for thyroid dyshormonogenesis, such as mutations in thyroglobulin (TG), dual oxidase 2 (DUOX2) and its accessory protein (DUOXA2), thyroperoxidase (TPO), the sodium-iodide symporter or NIS (SLC5A5), iodotyrosine deiodinase (IYD), and the chloride-iodide transport protein pendrin (SLC26A4) (18, 19). Gene mutations affecting NIS and pendrin cause functional impairments in iodide uptake into follicular cells and iodide efflux into proteinaceous colloids, which are uncommon but notable contributing factors to congenital hypothyroidism. An important point to note is that Pendrin syndrome, which results from mutations in the Pendrin gene, results in impaired iodine organification, goiter, and sensorineural deafness (9). Conversely, individuals with congenital hypothyroidism with mutations in thyroglobulin genes responsible for producing the iodinated precursor glycoprotein of active thyroid hormone in thyroid follicles exhibit goiter and low serum thyroglobulin levels (20, 21).

Infrequently, thyroid function in neonates can be temporarily compromised due to external factors. These factors include antithyroid medications administered by the mother, such as methimazole or propylthiouracil, TSH receptor-blocking antibodies (TRBAb) that result from passage through the placenta in Graves' disease, and maternal or infant iodine deficiency (Endemic Goiter) or excessive amounts of iodine. The latter can occur due to the administration of iodine-containing antiseptics and drugs, such as amiodarone or radiocontrast agents, either in the infant or the mother (5, 12).

Central congenital hypothyroidism and insufficient TSH are conditions related to the pituitary gland or hypothalamus development defects. Central congenital hypothyroidism can be described biochemically by an FT4 concentration lower than the reference interval in conjunction with slightly elevated, insufficient, or normal TSH (22). Central congenital hypothyroidism is not detectable using the screening approach based on TSH, used in most newborn screening programs worldwide. Screening programs may detect the condition by measuring T4 levels in all infants, in addition to measuring TSH in tandem or in only a small proportion of infants who have low levels of T4. Even so, this method might not be sufficiently sensitive and may not detect central hypothyroidism in all cases (18, 22, 23). A combination or multiple deficiency of pituitary hormones occurs in approximately 75% of newborns with congenital hypothyroidism. As a result, infants with this condition are likely to exhibit hypoglycemia, persistent jaundice, micropenis or cryptorchidism in boys, or midline defects, including midline cleft lip or palate or midface hypoplasia (24). There are reports of central congenital hypothyroidism associated with deficiency of multiple pituitary hormones resulting from mutations of transcription factors involved at the developmental stage of the hypothalamus or pituitary, including HESX1, LHX3, SOX3, OTX2, LHX4, POU1F1, and PROP1 (14). Furthermore, genetic mutations of the TRH receptor (TRHR), TSH subunit beta (TSHB), and TBL1X have been reported as rare genetic factors associated with isolated central congenital hypothyroidism. In addition, congenital hypothyroidism is a temporary disorder in newborns whose mothers have been hyperthyroid during gestation (Table 1) (14, 22, 24-30).

Apart from genetic factors contributing to the abnormal formation of the thyroid and its dysfunction, congenital hypothyroidism is also associated with several acquired factors. Maternal and perinatal risk factors, including advanced maternal age, multiparity, and pregnancy-related conditions, namely Gestational Diabetes Mellitus (GDM), hyperthyroidism, and hypertensive disorder during pregnancy, all contribute to congenital hypothyroidism in the child (31). Even though thyroid dysfunction has always been associated with diabetes in studies, there is no clear causal link between GDM and congenital hypothyroidism in offspring. As mentioned previously, antithyroid medications taken by pregnant women are capable of crossing the placenta and causing fetal goitrous hypothyroidism (32). Female sex, low birth weight, being born as part of multiple births (such as twins), preterm (before 37 weeks of gestational age), and post-term (over 41 weeks of gestational age) births constitute neonatal risk factors for congenital hypothyroidism. Also, additional research is required to pinpoint the factors contributing to congenital hypothyroidism more precisely (33-35).

3.2. Main Clinical Manifestations

For several years prior to 1878, "myxedema" was used to describe severe hypothyroidism in infants and adults. It has been later discovered that the clinical characteristics of congenital hypothyroidism often appear mild (36). Congenital hypothyroidism is commonly characterized by swollen necks, poor feeding, inadequate weight gain, failure to thrive, alopecia, brittle hair, dry skin, prolonged or recurrent jaundice, cold intolerance, umbilical hernia, macroglossia, swelling of the face, hands, and feet (myxedema), hypotonia, constipation, and lethargy (18, 23). Goiter, hypothermia, a widened posterior fontanelle (greater than 0.5 cm), bradycardia, continuous indirect hyperbilirubinemia, and peripheral edema may be signs or symptoms of CH. It should be noted that hypothyroidism rarely occurs in association with obesity (37). It has already been mentioned that infants with congenital hypothyroidism are not generally affected by these symptoms, provided that maternal thyroid hormone is provided. This may sometimes result in a significant delay in initiating treatment and maximizing the development. As a result, worldwide screening strategies must be implemented effectively. Unless hypothyroidism is treated, it may result in greater physical changes over time (19, 38-42).

3.3. Epidemiology

Congenital hypothyroidism, occurring in approximately one in 2,000 to one in 4,000 newborns, ranks among the leading causes of intellectual disabilities

that can be prevented. Congenital hypothyroidism incidences have increased in recent decades worldwide. This disease's prevalence is estimated to have increased from one in 6,700 children before the implementation of screening programs to one in 3,500 in the first two decades following their introduction (43). Newborn screening (NBS) for congenital hypothyroidism represents one of the greatest advances in pediatric preventive medicine over the past 50 years. As such, it is alarming that nearly 71% of newborns worldwide do not live in areas with an established newborn screening program, despite developed countries having been screening newborns for more than five decades (44). Additionally, a contributing factor to the change in congenital hypothyroidism incidence could be the increased screening of individuals at greater susceptibility. This applies to premature newborns and ethnic groups, including Hispanics and Asians (45). Changing screening algorithms and decreasing the TSH cutoff for screening, thereby detecting milder cases, have also contributed to the approximate doubling of congenital hypothyroidism incidence from 1: 3500 to 1: 1714 in the past few years (46). Overall, congenital hypothyroidism epidemiology has changed significantly in recent decades and appears mostly artifact, demonstrating that detection by newborn screening (NBS) and treatment have significantly reduced mental retardation. More than 1,400 of the 3.4 million newborns in the United States of America (USA) receive a congenital hypothyroidism diagnosis each year (47). While the findings of several epidemiological investigations indicate that the prevalence of congenital hypothyroidism is higher in Iran than in other countries (48, 49).

3.4. Diagnosis and Screening by Expressing Newest Methods

In the first 16 weeks of pregnancy, the fetus relies entirely upon the maternal T4 being delivered transplacentally. In this manner, maternal T4 is transmitted transplacentally, accounting for approximately one-third of fetal T4 levels upon birth (50). As a result, most newborns with congenital hypothyroidism present with no symptoms, even though their TSH or T4 levels are likely to have fluctuated significantly. This disease is therefore detected early through neonatal screening tests. As a result, congenital hypothyroidism was rarely detected in newborns before the introduction of neonatal screenings (51).

Identifying congenital hypothyroidism in newborn babies involves screening a specific geographical region's population of newborns. This screening process is efficiently carried out by state or provincial public health laboratories in collaboration with birthing hospitals or centers in that area. Newborn screening programs involving a diverse team can provide comprehensive care for identified cases (52). These programs engage in effective communication with the infant's Primary Care Provider (PCP) and ensure continuous education of pediatric providers and birthing hospitals or centers (Table 2) (53).

Neonatal screening, sometimes called a heel-prick test, is recommended 48 to 72 hours following birth. A heel-prick blood sample is collected on filter paper and, once dried, taken to a central laboratory for analysis (65). The initial step in most screening programs involves measuring TSH levels only. Nevertheless, there are three methods of screening for congenital hypothyroidism: primary TSH measurement, primary total T4 measurement, and a combination of TSH and total T4 (66). To summarize, the condition is referred to as primary hypothyroidism in the case of elevated TSH and normal or decreased free T4. A primary hypothyroid condition is classified into two categories: Clinical, in which TSH levels increase and free T4 levels decrease, and subclinical, in which TSH is increased but free T4 is not decreased. Furthermore, central hypothyroidism occurs when TSH levels are normal or reduced and free T4 levels are low (5).

Though a primary TSH assessment can detect moderate to severe primary hypothyroidism in infants, potentially leading to intellectual disability if undiagnosed, it may miss central hypothyroidism or primary congenital hypothyroidism if there is a delayed rise in TSH (67). Since central hypothyroidism is a relatively rare condition, the most sensitive screening method would be only measuring TSH in newborns. Thus, most programs for newborn screening in the United States, Canada, Iran, and other countries rely on a primary TSH measurement method. As part of this routine approach, screening tests showing abnormal results are followed by confirmation measurements of free T4 and TSH levels in serum samples (8).

During the initial screening step, methods that measure total T4 (with or without TSH) can detect primary hypothyroidism, central hypothyroidism, delayed onset TSH elevation, and deficiency of thyroxine-binding globulin (TBG) (68). Most screening programs do not measure free T4 due to technical limitations. Compared to the primary TSH method, the primary T4 method has lower sensitivity to detect subclinical hypothyroidism

Table 2. Characteristics of Newborn Screening Programs in Different Countries

Country of the Study	Year	Screening Strategy	Cutoff Value in the First Step of the Screening Program	Total Screened Infants	Confirmed Cases of Congenital Hypothyroidism	Incidence	Case per 10000
Argentina (54)	1997 - 2002	TSH - based screening program	TSH >15 mU/L (until 12/2002)	310,805	119	3.83 per 10,000	1: 2,206
	2003 - 2010		TSH >10 mU/L (Thereafter)	459,258	230	5 per 10,000	
	Total			770,063	349	4.53 per 10,000	
Canada (55)	1990 - 2009	TSH - based screening program	TSH >15 mU/L during 20 years (except in the year 2001: TSH>5 mU/L)	1,660,857	620	3.73 per 10,000	1: 2,679
China (56)	2013 - 2018	TSH - based screening program	Varied in different provinces, for instance: TSH >10 mU/mL in Shaanxi province or TSH >8.5 mU/mL in Shandong province	91,921,334	42,861	4.66 per 10,000	1: 2,145
France (57)	1982 - 2012	TSH - based screening program	Varied in different years and methods, for instance: TSH>20 - 30 mU/L (until 2001) TSH>20 - 25(Thereafter)	23,669,598	6,622	2.8 per 100,000	1: 3,574
Iran (58)	2011 - 2014	TSH - based screening program	TSH $\geq$5 mU/L	452,918	1,085	24 per 10,000	1: 417
Ireland (59)	1979 - 2016	TSH - based screening program	TSH >8 mU/L	2,361,174	1,063	4.5 per 10,000	1: 2,221
Mexico (60)	2000 - 2004	TSH - based screening program	TSH >15 mU/L in capillary blood and TSH >30 mIU/mL in umbilical cord blood	2,777,292	1,286	4.63 per 10,000	1: 2,160
Netherlands (61)	2007 - 2017	T4 - reflex TSH - reflex TBG	Referral if T4 $\leq$ - 3 SD and TBG >40 nmol/L; if T4 < -1.6 SD TBG measurement; referral if T4/TBG ratio $\leq$17 in first and second NBS result	1,963,465	612	3.12 per 10,000	1: 3,028
New Zealand (62)	1993 - 2001	TSH - based screening program	TSH >15 mU/L	1,053,457	330	2.65 per 10,000	1: 3,192
	2002 - 2010					3.60 per 10,000	
	Total					3.1 per 10,000	
Turkey (63)	2008 - 2010	TSH - based screening program	TSH >15 mU/L	3,223,765	4,966	15.4 per 10,000	1: 649
United States (64)	1994 - 1997	T4 backup TSH testing	Varied in different years and methods	542,945	241	4.44 per 10,000	1: 2,253
	1998 - 2003	Tandem T4 and TSH testing		754,722	594	7.87 per10,000	1: 1,271
	2003 - 2007	Primary TSH, no serial testing		432,615	225	5.2 per 10,000	1: 1,923
	2007 - 2010	Primary TSH, plus serial testing		395,463	259	6.55 per 10,000	1: 1,527
	Total			2,125,745	1,319	6.20 per 10,000	

Abbreviations: TSH, thyroid-stimulating hormone; T4, thyroxine; TBG, thyroxine-binding globulin.

characterized by increased TSH but with normal T4. Clearly, measuring TSH and T4 together at first in a screening program incurs a greater financial cost and takes more time than primary TSH or T4 programs (5, 8).

Imaging techniques, such as thyroid ultrasonography or scintigraphy, are emerging as new methods for screening purposes. When conducted by experienced centers, these imaging techniques can help determine the underlying cause of congenital hypothyroidism. However, there is a debate regarding the usefulness of routine thyroid imaging in congenital hypothyroidism patients. Imaging can be informative in predicting the prognosis if it detects abnormalities like an ectopic or dysgenic thyroid gland, which suggests a permanent form of congenital hypothyroidism. It can also guide the likelihood of the disease recurring in future children from the same parents. Nevertheless, in most cases, imaging does not significantly impact the clinical management of patients until they reach three years of age. Thyroid ultrasonography, which does not involve radiation exposure, can identify the presence and location of thyroid tissue and can be performed at any time after the congenital hypothyroidism diagnosis. It is important to note that scintigraphy generally has higher sensitivity than ultrasonography in detecting ectopic thyroid (69).

Genetic testing is another approach used to diagnose congenital hypothyroidism. In most cases, congenital hypothyroidism has a complex and sporadic etiology. However, it can also be linked to specific monogenic causes or broader syndromes. Monogenic causes of congenital hypothyroidism are generally classified into two categories: Thyroid dysgenesis and dyshormonogenesis. While thyroid dysgenesis is typically sporadic, rare cases have been associated with mutations in specific genes. Many of these genes encode transcription factors that play a crucial role during embryonic development in various tissues. Recent advancements in genetic testing have enabled the simultaneous assessment of multiple genes at a lower cost and with quicker results than before. Although genetic information can be highly valuable for families, genetic testing comes with challenges, such as cost and the interpretation of inconclusive results. Additionally, it is important to note that in many cases, a genetic diagnosis may not significantly alter the clinical management of the condition (30).

3.5. Therapeutics Management by Expressing Newest Methods

Once the diagnosis of congenital hypothyroidism has been confirmed, preferably during the first two weeks of childbirth, levothyroxine (LT4) should be administered orally. By starting levothyroxine treatment later, there is an increased risk of poorer neurodevelopmental outcomes (12). Despite this, a recent study conducted in the Netherlands reported that overtreatment of congenital hypothyroidism, as indicated by elevated FT4 measurements, led to a significant decrease in IQ (intelligence quotient) at the age of 11. The FT4 may be a sensitive indicator of over-treatment. Recent approvals of oral LT4 solutions have occurred in Europe and the United States.

Considering that 80% of circulating T3 is produced by deiodination circulating T4, levothyroxine alone is sufficient to return serum T4 and T3 levels to normal (70). Thyroid alternative medications, such as thyroid products containing T3, are not recommended. Also, LT4 is initially administered at a dosage of 10 - 15 μg/kg/day, and the dose is adjusted according to TSH levels monitored periodically (once every 1-2 months during the first six months and then once every 2-4 months between six months and three years of age) (71). Additionally, when the dose of LT4 is changed, it is recommended to check both TSH and FT4 levels after four weeks. When a patient does not respond to treatment as expected, it should be considered that the patient is not adhering to the treatment (72). Initial LT4 treatment normalizes serum FT4 and TSH levels. Accordingly, normalization of serum TH levels within a short period of time improves neurocognitive results, the ultimate objective of the treatment. When neonates are born prematurely with birth weights below 1000 g and before 28 weeks of gestation, some physicians recommend levothyroxine therapy administered at 4 μg/kg; however, no consensus has been reached (7). Multiple treatment modalities and medications are employed to manage congenital hypothyroidism. However, avoiding the improper use or excessive reliance on diagnostic techniques and therapeutic drugs is essential, as these practices can lead to increased treatment-related side effects and are unethical. Following globally and locally accepted governmental guidelines is recommended to address these concerns. These guidelines serve as valuable references for pediatricians, aiding them in effectively screening and treating CH, as demonstrated in the context of appropriate antibiotic utilization and prescription (73).

4. Conclusions

Central congenital hypothyroidism results from reduced levels and/or bioactivity of thyroid-stimulating

hormone resulting from either hypothalamic or pituitary disorders (23). It was discovered in 2012 that IGSF1 is responsible for central congenital hypothyroidism and macroorchidism associated with an X-linked syndrome. Recently, mutations in TBL1X and IRS4 were found to be causally responsible for central congenital hypothyroidism (14). Pituitary and hypothalamic expression of TBL1X encodes a protein that functions as a crucial component of the NCoR-SMRT co-repressor complex. This protein interacts with thyroid hormone receptors and plays a crucial role in mediating the regulation of genes dependent on thyroid hormone (74). Researching to demonstrate how prompt treatment of central hypothyroidism benefits neurological development is challenging as the condition rarely occurs; however, these new data demonstrating congenital hypothyroidism severity provide helpful information for newborn screening cost-benefit analysis (23).

Recent findings have indicated that central congenital hypothyroidism is a more severe condition than previously recognized. In the neonatal period, clinical diagnosis of central congenital hypothyroidism is frequently overlooked, even during hospital admission, due to issues such as feeding difficulties, hypoglycemia, and prolonged jaundice. However, thanks to early detection through newborn screening (NBS) followed promptly by accurate diagnostics and appropriate treatment, children with central congenital hypothyroidism demonstrate a remarkable neurodevelopmental prognosis, whether isolated or as part of central hypothyroidism (CPHD). In fact, their developmental outcomes are comparable to those of unaffected siblings (22).

In the United States and Japan, newborn screening for congenital hypothyroidism was initially performed primarily by measuring total thyroxine (T4) in dried blood spots; however, increased serum TSH levels are now considered more reliable indicators of primary hypothyroidism (22). When a newborn is found to have a positive congenital hypothyroidism screening report, immediate clinical evaluation is necessary. Diagnostic tests performed on newborns with a positive congenital hypothyroidism screening result are to confirm hypothyroidism and determine the cause of the condition (75).

The existing protocols utilized for identifying and treating congenital hypothyroidism have generally led to favorable neurocognitive outcomes in most patients. Nevertheless, there is still some uncertainty surrounding the importance and optimal management of certain subtypes of congenital hypothyroidism, such as delayed TSH rise and central hypothyroidism. Conducting additional studies that focus on outcomes could provide valuable insights into these matters, leading to further improvements in the care provided to infants affected by these conditions.

4.1. Limitations

It should be noted that the current study had several limitations. Most of the studies included in this article were retrospective cross-sectional, and a small percentage of the included studies were prospective or interventional. On the other hand, more studies do not evaluate the sensitivity of diagnostic tests.

Footnotes

Authors' Contribution: Sh. K.: Design, literature search, data collection/processing, and writing. A. B.: Concept development, data collection/processing, and writing. Sh. P.: Design, data collection/processing, and writing. B. M.: Concept development, design, supervision, and writing

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Table 1. Clinical Features of Genetic Syndromes Associated with Primary and Central Congenital Hypothyroidism

Gene (OMIM)	MOI	Typical Thyroid Phenotype	Other Associated Phenotypes
Genes Associated with Thyroid Dysgenesis			
NKX2-1 (600635)	Autosomal dominant	Variable	Brain-Lung-Thyroid syndrome: characterized by congenital hypothyroidism, neurological symptoms (hypotonia evolving to benign hereditary chorea, and pulmonary symptoms (respiratory distress)
FOXE1 (602617)	Autosomal recessive	Athyreosis, severe hypoplasia	Bamforth-Lazarus syndrome: characterized by thyroid dysgenesis (in most cases athyreosis), cleft palate, and spiky hair, with or without choanal atresia, and bifid epiglottis
PAX8 (167415)	Autosomal dominant	Variable	Urogenital tract malformation (horseshoe kidney, renal agenesis, ureter, and testes anomalies)
NKX2-5 (600584)	Unclear	Thyroid in situ, variable hypothyroidism	Congenital cardiac anomalies
GLIS3 (610192)	Autosomal recessive	Variable	Neonatal diabetes, polycystic kidneys, and cholestasis
JAG1 (601920)	Autosomal dominant	Variable orthotopic hypoplasia	Cardiac malformations and Alagille syndrome (characterized by chronic cholestasis, butterfly vertebrae, posterior embryotoxon, and cardiovascular anomalies)
TBX1 (602054)	Autosomal dominant	Thyroid in situ	DiGeorge syndrome with congenital heart defects
NTN1 (601614)	Unknown inheritance	Thyroid ectopy	Arthrogryposis
CDCA8 (609977)	Autosomal dominant or autosomal recessive	Thyroid ectopy, athyreosis, hemiagenesis, thyroid asymmetry	
TUBB1 (612901)	Autosomal dominant	Thyroid dysgenesis	Congenital macrothrombocytopenia
Genes Associated with Thyroid Dyshormonogenesis			
TSHR (603372)	Autosomal dominant or autosomal recessive	Complete or partial resistance to TSH, mild hypothyroidism	
GNAS (139320)	Maternal inheritance, parental imprinting of gene locus	Partial resistance to TSH, mild hypothyroidism	Pseudohypoparathyroidism (multiple hormone resistances)
SLC5A5 (601843)	Autosomal recessive	Absent or low iodide uptake at scintiscan, variable hypothyroidism, and goiter	Congenital Iodide Transport Defect (ITD) due to sodium-iodide symporter (NIS) mutation
SLC26A4/PDS (605646)	Autosomal recessive	Partial iodide organification defect, mild to moderate hypothyroidism, goiter, high serum thyroglobulin	Pendred syndrome: characterized by sensorineural hearing loss with an enlarged vestibular aqueduct, predisposition to alkalosis
SLC26A7 (608479)	Autosomal recessive	Goiter, variable hypothyroidism, conserved iodide uptake, partial defect at perchlorate discharge, high serum thyroglobulin	Normal hearing
DUOX1/DUOX2 (606758/606759)	Autosomal dominant or autosomal recessive	Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity, high serum thyroglobulin	

DUOXA2 (612772)	Autosomal recessive	Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity, high serum thyroglobulin	
TPO (606765)	Autosomal recessive	Complete iodide organification defect, severe hypothyroidism, goiter, high serum thyroglobulin	
TG (188450)	Autosomal recessive	High iodide uptake, variable hypothyroidism, congenital or rapidly growing goiter, low serum thyroglobulin	
IYD/DEHAL (612025)	Autosomal recessive or autosomal dominant with Incomplete penetrance	Conserved iodide uptake, negative perchlorate discharge test, goiter, variable hypothyroidism, high serum thyroglobulin, and MIT or DIT concentrations in serum and urine	
Genes Associated with Isolated Central Congenital Hypothyroidism			
TSHβ (188540)	Autosomal recessive	Neonatal onset of severe hypothyroidism with low TSH	High glycoprotein hormone α-subunit (αGSU) and normal prolactin serum levels, pituitary hyperplasia reversible on levothyroxine
TRHR (188545)	Autosomal recessive	Normal TSH and low prolactin serum levels blunted TSH and prolactin responses to TRH	Based on a few described families: Male index cases with growth retardation and overweight during childhood; one female proband with prolonged neonatal jaundice
TBL1X (300196)	X-linked	Mild isolated central congenital hypothyroidism in males with normal TSH serum levels and normal response to TRH stimulation test; low-normal FT4 values to mild hypothyroidism in females	Sensorineural hearing loss
IRS4 (300904)	X-linked	Mild isolated central congenital hypothyroidism in males with normal TSH serum levels, blunted TSH response to TRH; low-normal FT4 values in females	
Genes Associated with Multiple Pituitary Hormone Deficiencies			
IGSF1 (300137)	X-linked	Normal TSH serum levels and blunted response to TRH test; males are preferentially affected	Low prolactin levels and variable GH deficiency (childhood), acromegaloid facies (adulthood), possible transient mild hypocortisolism and metabolic syndrome; late adrenarche and delayed pubertal testosterone rise in males, dissociated from testicular growth leading to postpubertal macroorchidism
PROP1 (601538)	Autosomal recessive	Variable age of onset	Combined pituitary hormone deficiencies (including GH, prolactin, LH, and FSH) and delayed ACTH deficiency, small to large pituitary gland volume
POU1F1 (173110)	Autosomal dominant or autosomal recessive	Variable age of onset	GH and prolactin deficiencies, prominent forehead, mid-face hypoplasia, saddle nose, and deep-set eyes
HESX1 (601802)	Autosomal dominant or autosomal recessive	Central congenital hypothyroidism	Hypopituitarism associated with septo-optic dysplasia (SOD)
SOX3 (313430)	X-linked	Central congenital hypothyroidism	Hypoplastic anterior pituitary with ectopic posterior pituitary, persistent craniopharyngeal canal, and learning difficulties

OTX2 (600037)	Autosomal dominant	Central congenital hypothyroidism	Anterior pituitary hypoplasia with ectopic posterior pituitary and ocular defects (ano- or micro-ophthalmia and early-onset retinal dystrophy)
LHX3 (600577)	Autosomal recessive	Central congenital hypothyroidism	Hypopituitarism with variable ACTH deficiency, small to large pituitary gland volume, short and rigid cervical spine, and variable hearing loss
LHX4 (602146)	Autosomal dominant or autosomal recessive	Central congenital hypothyroidism	Variable hypopituitarism, anterior pituitary hypoplasia with ectopic posterior pituitary, Arnold-Chiari syndrome, hypoplasia of the corpus callosum
LEPR (601007)	Autosomal recessive	Central congenital hypothyroidism	Hyperphagia, obesity, and combined with hypogonadotropic hypogonadism
SOX2 (184429)	Autosomal dominant	Central congenital hypothyroidism	Variable hypopituitarism, pituitary hypoplasia, microphthalmia, variable learning difficulties
Genetic Defects Variably Associated with Central Congenital Hypothyroidism			
PROKR2 (607123)	Autosomal dominant or autosomal recessive	Variable TSH defects	Variable hypopituitarism associated with septo-optic dysplasia or pituitary stalk interruption syndrome
NFKB2 (164012)	Autosomal dominant	Variable TSH defects	Deficient anterior pituitary with variable immune deficiency syndrome associated with ACTH deficiency and variable GH deficiency
CHD7 (608892)	Autosomal dominant	Variable TSH defects	Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies (CHARGE) syndrome with ectopic posterior pituitary and variable LH, FSH, and GH defects
FGFR1 (136350)	Autosomal dominant	Variable TSH defects	Kallman syndrome and normosmic congenital hypogonadotropic hypogonadism, a variable related to other pituitary hormone defects including TSH deficiency, septo-optic dysplasia, and ectopic posterior pituitary
FGF8 (600483)	Autosomal recessive	Variable TSH defects	Kallman syndrome and normosmic congenital hypogonadotropic hypogonadism, a variable related to other pituitary hormones' defects including TSH, holoprosencephaly, and corpus callosum agenesia
FOXA2 (600288)	Autosomal dominant	TSH defects	Hypopituitarism with craniofacial and endodermal organ abnormalities and hyperinsulinism

Abbreviations: OMIM, online mendelian inheritance in man; MOI, mode of inheritance; TSH, thyroid-stimulating hormone; MIT, monoiodotyrosine; DIT, diiodotyrosine; TRH, thyrotropin-releasing hormone; FT4, free thyroxine; GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ACTH, adrenocorticotropic hormone.