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Congenital Hypothyroidism in Adulthood: A Literature Review

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ABSTRACT

Congenital Hypothyroidism (CH), the common pediatric endocrine disorder, resulting from their impairment at tissue level. Congenital Hypothyroidism is a major concern now a days. Congenital Hypothyroidism is broadly classified into Primary hypothyroidism, secondary hypothyroidism, peripheral hypothyroidism, syndromic hypothyroidism and transient congenital hypothyroidism. Factors affecting congenital hypothyroidism include thyroid dyshormonogenesis, thyroid dysgenesis, resistance to Thyroid Hormone binding, defects in T3 and T4 release or genetic factors. Thyroid hormone is essential for normal brain development.

Keywords: Congenital Hypothyroidism, Mental Retardation

INTRODUCTION

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. A well- known endocrine disorder primarily associated with neonates and infants, characterized by deficient thyroid hormone production due to various genetic or developmental abnormalities of the thyroid gland [(1)]. Many newborns, infants get undiagnosed at birth due to the subtle clinical features of Congenital Hypothyroidism. This is due to passage of maternal thyroid hormone across the placenta, so it provides a protecting effect and also masking the clinical signs [(2)].

Thyroid hormone plays a major role in growth, energy, metabolism and neurodevelopment. Thyroid hormone acts on neuronal differentiation, synapsis development, myelination in the prenatal and newborn periods and regulating central nervous system development. Thyroid hormones originate from the amino acid tyrosine and are synthesized by the thyroid gland upon stimulation by Thyroid-Stimulating Hormone (TSH) from the anterior pituitary. The release of TSH is governed by Thyroid Releasing Hormone (TRH), which originates from the hypothalamus. This regulatory mechanism is known as Hypothalamic Pituitary Thyroid (HPT) axis. The two primary active thyroid hormones are thyroxine (T4), and triiodothyronine (T3) [(3)].

Thyroid gland secretes both T3 and T4, with the majority of circulating T3 originating from peripheral tissue conversion of T4. This conversion is facilitated by a group of

enzymes called iodothyronine deiodinases. Both T4 and T3 inhibit the secretion of TSH, directly and indirectly by suppressing the release of TRH. Other factors that suppress TSH release include glucocorticoids, somatostatin and dopamine. Most circulating T3 and T4 are tightly bound to serum proteins, such as T4 Binding Globulin (TBG), with only a small fraction being unbound, known as free T4 and free T3, which are biologically active[3].

Congenital hypothyroidism is classified into primary hypothyroidism, secondary hypothyroidism, peripheral hypothyroidism, syndromic hypothyroidism, and transient congenital hypothyroidism. Factors affecting Congenital Hypothyroidism (CH) may include thyroid dyshormonogenesis, thyroid dysgenesis, resistance to TH binding, defects in T3 and T4 release, or even genetic factors. Environmental factors that increase the risk of thyroid disease include radiation exposure, both from nuclear fallout and medical radiation, increased iodine intake, as well as several contaminants in the environment that influence the thyroid[3]. Historically, CH has been predominantly studied and managed in pediatric populations, given its critical implications for early neurodevelopment and growth. Screening programs have been conducted in most developed countries [1].

PREVALENCE

Prevalence rates may vary by region and population, the implementation of universal newborn screening programs has helped ensure that affected infants receive timely intervention, ultimately improving their long-term outcomes. Early detection and management of congenital hypothyroidism are essential for minimizing the risk of cognitive impairment and optimizing the child's overall health and development.

ETIOLOGY

Congenital Hypothyroidism may be thyroidal or central origin. Thyroid dysgenesis or dyshormonogenesis defects in the thyroid gland were two main causes of primary Congenital Hypothyroidism. Thyroid dysgenesis includes a range of abnormalities such as agenesis, ectopic or hypoplastic gland. Although mutations in the genes (TSH receptor or transcription factors PAX8, NKX2-1 or FOXE1) responsible for thyroid gland formation may be detected in 2-5% of instances, thyroid dysgenesis is almost usually sporadic or nonhereditary [4].

The condition may be temporary due to iodine excess or shortage, maternal thyroid blocking antibodies or transplacental passage of maternal anti- thyroid drugs. These defects can induce persistent Congenital Hypothyroidism (CH). Iodine deficiency, particularly in areas with low iodine level, is still a major global cause of CH. Because of the transitory inhibition of thyroid hormone synthesis caused by the Wolff-Chaikoff effect, newborns exposed to excess iodine (e.g., iodine-containing antiseptics or radiographic contrast agents) may develop hypothyroidism. Secondary or tertiary hypothyroidism, a pituitary or hypothalamic anomaly, causes central CH, which is an uncommon condition [5].

PATHOPHYSIOLOGY

The most frequent cause of hypothyroidism is a localized thyroid gland disease that reduces the synthesis of thyroid hormones. Normal thyroid function involves daily release of 100–125 mol of T4 and very little T3. The pituitary gland secretes more TSH when there is less T4 being produced. TSH increases thyroid T4-5'-deiodinase activity as well as thyroid gland hyperplasia and hypertrophy. Thyroid then releases more T3 as a result of this. Since thyroid hormone is necessary for all cells that are metabolically active, a deficiency in the hormone can have a variety

of repercussions. Derangements in metabolic processes or direct effects from myxedematous infiltration - the aggregation of glycosaminoglycans in the tissues - are the sources of systemic consequences [3].

Step 1: The active uptake of iodide from the blood circulation via the sodium-iodide symporter (SLC5A5)

Step 2: The facilitated efflux of iodide into the colloid via an apical anion channel (SLC26A4)

Step 3: Iodination of tyrosine groups of thyroglobulin (TG) catalyzed by thyroid peroxidase (TPO)

Step 4: Subsequent coupling of iodinated thyrosines within TG via ether-bond formation to iodothyronines.

Steps 3 and 4: require hydrogen peroxide as co-substrate, which is provided by a hydrogen peroxide generating NADPH-oxidase constituted by dual oxidase 2 (DUOX2) and its maturation factor (DUOXA2) following endocytosis, iodothyronines (T4>T3) are liberated by lysosomal degradation of the TG matrix protein concomitantly released iodothyrosines are dehalogenated by iodothyrosine d [3].

EVALUATION

Newborn screening (NBS) can identify infants with congenital hypothyroidism, which frequently manifests as absence of symptoms at birth. On filter paper cards, dried whole blood spot samples are pricked with a heel pin to acquire NBS. The majority of nations in the globe routinely use NBS for CH. In the US and other nations, there are differences in the criteria for diagnosing CH and the methods for detecting NBS. Early primary CH detection is the NBS's top priority. A TSH measurement is the most specific test for identifying primary CH, but the T4 test is more sensitive since it can identify infants with the uncommon hypothalamic-pituitary-hypothyroidism [6].

Gives the dynamic nature of infant thyroid physiology, a number of factors could influence the outcome of a thyroid screen. The newborn screening procedure, the newborn's age at specimen collection, their preterm status, and their clinical condition must all be considered when interpreting the thyroid function test. Ideally, NBS for CH should be carried out between the second and fourth day of life. Testing ought to be completed before discharge from the hospital if this is not feasible [7].

There are 3 screening methods

1) First TSH with a backup T4 reading. TSH cutoff is usually between 20 and 50U/L. Europe, Canada, Japan, and US this method.
2) Initial T4 with backup TSH measurement. This method will miss some vases of primary CH (subclinical hypothyroidism) where T4 is normal, but TSH is elevated. Initial T4 level can detect central hypothyroidism.
3) Simultaneous T4 and TSH measurements. This is an ideal screening method but little bit expensive.

Repeated Screening

The reduction of TSH secretion brought on by hypothalamic-pituitary immaturity, drug administration, and the consequences of severe neonatal sickness can conceal primary CH. In 50% of preterm newborns, there is delayed TSH elevation (defined as raised TSH in the second neonatal screening following normal TSH in the initial screening). For low-birth-weight, preterm (less than 37 weeks gestational age), and sick newborns admitted to the neonatal intensive care unit (NICU), a second screening is advised by the American and European Pediatric Societies to identify those with delayed elevations in TSH concentration. Screening protocols for preterm infants (less than 32 weeks gestation) include measurement on days 3 to 5 and at 1

week, 2 weeks, 4 weeks, and term-corrected gestational age or the day of discharge home, whichever comes first. The TSH cutoff level of 10 mU/L or greater is considered to be positive for CH. If there is a worry about fetal blood mixing, a second test should be performed at two weeks of age or when the baby is discharged from the hospital. When an infant is exposed to iodine, it is important to watch them for up to one month in order to detect iodine-induced hypothyroidism (characterized by low T4 and increased TSH). A venous sample confirmation for thyroid function testing (free T4 and TSH) should be taken right after upon reporting abnormal results on the NBS for CH. It is not necessary to wait to start treatment while more research is done to determine the cause of CH [(8)].

Other Laboratory Investigations [(9)]

1. Thyroid Imaging Studies
2. Thyroid Ultra Sound
3. Thyroid Autoantibodies
4. Thyroid Radio Nuclear Uptake Scan
5. Serum Thyroglobulin
6. Urine Iodine Concentration

Differential Diagnosis

A post-delivery increase in thyroid stimulating hormone (TSH) may occur in neonates who were released from the hospital early and whose NBS was collected during the first 24 hours of life. As a result, a second screening test is necessary and leads to false-positive results. Between two and four days of life, when TSH levels have dropped, is the best time to get NBS for CH.

Extra care should be give to premature babies: A premature baby's undeveloped HPT axis can cause hypothyroxinemia of prematurity, which is defined by low free T4 and normal TSH. Complicated thyroid profiles caused by non-thyroidal illnesses or secondary to central hypothyroidism make it difficult to interpret TFT in preterm newborns. As previously said, TFT should be repeated. Most patients will have a normal TFT by 6 to 10 weeks [(10)].

Management

Following the diagnosis of congenital hypothyroidism (CH), treatment with levothyroxine (L-T4) must begin right way. It is possible to avoid intellectual deficiencies and improve neurodevelopmental outcomes by implementing NBS programs and starting Levothyroxine (L-T4) treatment early (before two weeks of life). The preferred course of treatment is Levothyroxine (L-T4) alone. Starting dose is depends upon the severity of Congenital Hypothyroidism. It is advised to start with a greater first dose of L-T4 (10–15 ug/kg/day) or 50 ug/day for full-term newborns with severe CH. This is especially important for neonates whose pretreatment T4 level was extremely low. Two weeks of therapy and three days for serum T4 and TSH normalization are possible with a high starting dose of L-T4. To prevent overtreating, most full-term newborns with severe CH need a short-term high dose of L-T4 (50 ug per day), which is subsequently reduced to 37.5 ug per day once TSH returns to normal.

L-T4 tablets crushed and mixed with a small amount (1 to 2 ml) of water or breast milk may be administered orally via a small spoon or syringe. L-T4 should be given at the same time each day and at a different time of the day from calcium, iron, and soy to avoid interference with the absorption of the L-T4.

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Toxicity Management

Cognitive and behavioural changes were reported in patients who are over treated with

Levothyroxine L- T4. Careful monitoring of Thyroid Function Test after starting, adjusting L- T4 doses [11].

Complications

Cardiac malformations includes- septal defects, Renal abnormalities, Neurodevelopmental disorders, etc[12].

Patient Education

Parents must be informed about congenital hypothyroidism (CH), how to diagnose it, and how to receive appropriate medication as soon as possible to avoid negative neurodevelopmental effects. For administering L-T4, caregivers should get sufficient and unambiguous instructions. It is imperative to underscore the significance of conscientious follow-up appointments and thyroid laboratory surveillance [12].

CONCLUSION

The review indicates the factors associated with congenital hypothyroidism. Congenital Hypothyroidism (CH) is one of the common preventable causes of mental retardation. Etiology of Congenital Hypothyroidism (CH), thyroid dysgenesis. The aim of neonatal screening is to prevent cerebral damage due to lack of thyroid hormone by enabling early and adequate T4 supplementation. Cognitive deficits were observed in both verbal and performance domains, and motor deficits were found in balance, fine motor, as well as ball skills. Deficits were most pronounced in patients with severe CH and were comparable to those measured during childhood. The best way to detect infants with CH is the newborns screening.

Declaration by Authors

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REFERENCES

1. Alam A, Ashraf H, Khan K, Ahmed A. Uncovering Congenital Hypothyroidism in Adulthood: A Case Study Emphasizing the Urgency of Screening and Clinical Awareness. Cureus. 2023 Sep 20;15(9):e45611. doi: 10.7759/cureus.45611. PMID: 37868446; PMCID: PMC10588732.
2. Pankaj Agarwal, Rajeev Philip, Saran Sanjay, Gutch Manish et al. Congenital Hypothyroidism. Indian Journal of Endocrinolo Metab. 2015;19(2):221-227.
3. Samiran Sana, Sadiur Rahman Sajon, Sohel Rana, Zobaida Mostarin Nishi and Niaz Mahmud. A short review on congenital hypothyroidism, environmental thyroiditis and current status of thyroid disease in Bangladesh. The Pharma Innovation Journal 2017; 6(10): 328-335.
4. Olivieri, Donaldson, J. Leger, et al. Congenital Hypothyroidism Consensus Conference Group. European Society for Pediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. Horm Res Pediatrics. 2014;81(2):80-103.
5. Brown RS, Public Health Committee, Lawson Wilkins Pediatric Endocrine Society. Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK. American Academy of Pediatrics. Rose SR, Section on Endocrinology and Committee on Genetics, American Thyroid Association Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006 Jun;117(6):2290-303.
6. Alzahrani AS, Al Mourad M, Hafez K, Almaghamsy AM, Alamri FA, Al Juhani NR, Alhazmi AS, Saeedi MY, Alsefri S, Alzahrani MDA, Al Ali N, Hussein WI, Ismail M, Adel A, El Bahtimy H, Abdelhamid E. Diagnosis and Management of Hypothyroidism in Gulf Cooperation Council (GCC) Countries. Adv Ther. 2020 Jul;37(7):3097-3111.
7. Bakker B, Kempers MJ, De Vijlder JJ, Van Tijn DA, Wiedijk BM, Van Bruggen M, Vulsma T. Dynamics of the plasma concentrations of TSH, FT4 and T3 following thyroxine supplementation in congenital hypothyroidism. Clin Endocrinol (Oxf). 2002 Oct;57(4):529-37.

8. Park ES, Yoon JY. Factors associated with permanent hypothyroidism in infants with congenital hypothyroidism. BMC Pediatr. 2019 Nov 22;19(1):453.
9. Bhansali A, Aggarwal A, Parthan G, Gogate Y. Clinical Rounds in Endocrinology. New Delhi: Springer; 2016. Disorders of growth and development: clinical perspectives; pp. 1–44.
10. Anne RP, Rahiman EA. Congenital hypothyroidism in India: a systematic review and meta-analysis of prevalence, screen positivity rates, and etiology. Lancet Reg Health Southeast Asia. 2022;5:100040.
11. Philip R, Saran S, Gutch M, Gupta K. An unusual case of precocious puberty and macroorchidism. Thyroid Res Pract. 2013;10:29–31.
12. Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. Thyroid. 1998; 8:827-856.

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