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Review Article

Congenital hypothyroidism: An updated review of its pathogenesis

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ABSTRACT

Congenital Hypothyroidism is a frequently occurring daunting disorder of the metabolic system affecting the new-born infants and is particularly associated with the impairment of the normal physiology of the thyroid gland or the thyroid hormones. It may possibly occur due to any condition which results in inadequate secretion of the thyroid hormone; however, only in the extreme cases does a condition occur in which no hormone is synthesized at all or due to some other circumstances which cause the peripheral cells to become resistant to thyroid hormones. This impairment of normal synthesis of the thyroid hormones or their impaired effect may either be due to the anatomic or physiologic defects incurred in the thyroid gland of the infant. Other reasons include hereditary causes – i.e., mutations of certain genes which when inherited by the infant from the parents lead to the progression of congenital hypothyroidism. The severity of this disorder is exceptionally extreme as it may cause serious intellectual disability, impeded growth and development, heart ailments, irreversible neurologic disorders and infertility problems, if left untreated. Therefore, such possible outcomes of this disorder validate the necessity of its diagnosis and cure at the right time. If diagnosed within safe interval of time, this disorder could be cured completely and no complications of it would be encountered by the infant in the later life.

Key words: Thyroid dysgenesis, Thyroid stimulating hormone (TSH), Hypothalamus- pituitary-thyroid axis

INTRODUCTION

Congenital hypothyroidism is a common conditions associated with dysfunction of the thyroid gland in the infants from birth. This may most commonly occur due to two reasons – first, incomplete, improper or immature development of the thyroid gland (which is called thyroid dysgenesis) – which may include dispositioning of the thyroid gland during embryonic development, aplasia or hypoplasia of the thyroid gland and second, inability of the thyroid gland to synthesize sufficient thyroid hormone (which is known as dyshormonogenesis) [1-3]. Both of these conditions result in reduced levels of thyroid hormone in the body which could lead to serious impairments in the body whose physiological regulation was to be monitored by this hormone. This above category accounts for the 85% of the total cases of congenital hypothyroidism whose occurrence is sporadic in nature while the rest of the 15% cases are of hereditary etiology in which the synthesis of thyroid hormone, its secretion or utilization is impaired due to some defects inherited by the infants from his parents [4]. This disorder is associated with severe abnormalities in children such as cardiac disorders [5], aberrant neurological development [6], anomalies in the genitourinal formation [7], improper growth of various body parts and Intellectual disabilities [8].

Epidemiology

According to a survey conducted in the United Kingdom, every one child in the 4000 live children born is affected by this disorder with females being almost two times more prone to it than males [4]. Another one conducted in New York state saw an increase in the incidence of this disease from 1 affected child in 4,094 live children born in 1987 to 1 affected child in 2,372 live births in 2002 [9]. Some countries namely – Bangladesh, China, Peru, Chad, Indonesia, Nepal and Zaire were found to be epidemiologically more prone to this disorder owing to the epidemic of iodine deficiency prevalent in them, thus leading to an increased risk in the occurrence of it [10-13]. Another study conducted on Italian population by Italian National Registry of Infants with Congenital Hypothyroidism (INRICH) suggests that the occurrence of

this disorder is almost three folds more in women with multiple pregnancies, although the reason for it is still unknown [14].

Signs and Symptoms

The extent of the severity of visible signs and symptoms vary widely. While some children may have typical sharp characteristic symptoms which can be easily noticed, some others may have very mild symptoms which could go unnoticed and thus prove to be dangerous afterwards if the infant remains undiagnosed. Many infants may show no symptoms due to some of the thyroid hormone passed on to their body via their mother's circulating system during their development in the womb. But some of the symptoms otherwise commonly found are: -

- Excessive sleeping or somnolence
- Low frequency of crying (or hoarse cry)
- Lesser extent of muscle tone
- Constipation or irregular bowel movement
- Bradycardia
- Prolonged jaundice
- Lethargy
- Feeding difficulties
- Visible facial cretinism
- Reduced body temperature or hypothermia
- Umbilical hernia
- Macroglossia or abnormally large tongue
- Myxedema or thickening and swelling of skin
- Wide posterior fontanel [15-20]

Etiology and Pathogenesis

The occurrence of congenital hypothyroidism may be due to any of the following reasons –

i. Due to the defects in the anatomy of the thyroid gland e.g., an ectopic or feebly developed or immature thyroid gland which could not produce thyroid hormones adequately
ii. Due to the disorders of the metabolism of the thyroid hormones
iii. Due to the abnormal development of the hypothalamus-pituitary-thyroid axis which is responsible for the production of thyroid hormones through the stimulus of thyroid stimulating hormone (TSH) released by the anterior pituitary gland [21-22].

The etiology of the congenital hypothyroidism may be classified as follows: -

Primary Causes: -

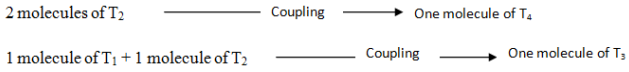
The primary causes of congenital hypothyroidism are the ones which directly affect the thyroid gland. These include:

Thyroid dysgenesis: -

This refers to the altered development of the thyroid gland. According to various researches, the development of thyroid gland in the embryo and its correct positioning in the infant is dependent on numerous transcription factors. The most studied transcription factors in this regard Include – TTF-1 (thyroid transcription factor-1), TTF-2 and PAX-8. TTF-1, which is also known as thyroid specific enhancer binding protein, has a critical role in the etiology of congenital hypothyroidism. It is a homeobox transcription factor of NK-2 gene which is responsible for the encoding of several transcription-regulatory proteins which have a crucial role in the anatomical development of the body. It is also said to be involved in the regulation of the transcription of TG and TPO genes, which are the thyroid stimulating hormone receptor genes in the follicular cells of the thyroid gland. Some studies also suggest the role of TTF-1 in the development of human brain due to some facts presented by various studies, like hypotonia, persistent ataxia, dysarthria, choreoathetosis and microcephaly – which are encountered due the mutations caused in TITF-1 gene (which is located on chromosome 14q). Many deletion mutations have been reported in this gene, which is probably responsible for the progression of thyroid dysgenesis [23-30]. TTF-2 is a transcription factor which winged helix domain protein family, many members of which have a role in the embryonic development and regulating the specification of the region of the organs descending into the embryo. A recent study described an indispensing role of TTF-2 in the derivatives of pharyngeal endoderms such as tongue, palate, epiglottis and esophagus; and in human thyroid, hair follicle and prepubertal testis. A missense mutation (A65V) has been reported in the gene TITF-2 gene, which is also known as FKHL-15 or FOXE-1. This mutation is said to be responsible for the pathogenesis of thyroid dysgenesis. After incurring this mutation, the transcription factor TTF-2 shows a much altered behavior with impairment in the DNA binding and loss of typical transcriptional functions. Thus, the role of TTF-2 mutations is also considered important in the progression of congenital hypothyroidism [31-34]. PAX-8 is a transcriptional factor belonging to the nine-membered mammalian paired homeodomain family. The PAX genes have a pivotal role in the development of embryo. PAX-8 gene which is located on chromosome 2q12-14 consists of 11 exons. Its most specific function reported by various studies is the initiation of the differentiation of the thyroid cell as well as maintaining this differentiating state, which is essential for the proliferation of the thyroid cell which results in the development of thyroid gland. The mutant PAX-8, formed due to various mutations which occur in PAX-8 gene, is associated with reduced DNA binding, which accounts for impaired PAX-8 physiology. This results in impairment of efficient transcription by thyroid peroxidase (TPO) because it is crucially dependent upon PAX-8 for its function. Thus, resulting in defects in the organification [35-37].

Thyroid dyshormonogenesis: - In a normal human being, a fully normally developed hypothalamus-pituitary-thyroid axis is responsible for the production of thyroid hormones. Sodium iodide symporter, which is a protein located at the basolateral membrane of the follicular cells of the thyroid gland, is responsible for actively transporting and concentrating iodide in the gland. It is then further oxidized

in the presence of hydrogen peroxide. This oxidized product readily binds to the tyrosine amino-acid residues in the thyroglobulin and leads to the formation of iodotyrosine. A number of such inert iodotyrosine residues specifically – monoiodotyrosine (T_1) and diiodotyrosine (T_2) – after undergoing coupling reactions, form Triiodothyronine (T_3) and tetraiodothyronine (T_4), which is also called - thyroxine.



These T_3 and T_4 are known as the thyroid hormones. An enzyme called thyroid peroxidase (TPO), also known as thyroperoxidase), is responsible for the oxidation, organification and coupling reactions. Any alterations in this physiology lead to the condition called thyroid dyshormonogenesis, which is characterized by the progression of congenital hypothyroidism and goitre. The molecular basis of the alterations lies in the mutations of various genes associated with them. Most of these mutations are inhertited in an autosomal recessive pattern [38]. The various defects associated in the progression of thyroid dyshormonogenesis are: -

i. Sodium-iodide symporter (NIS) protein defects are caused due to mutations like G93R, Q267E, C272X, T354P, Y531X and G543E on the NIS gene are a part of the pathogenesis of congenital hypothyroidism [39]
ii. Thyroid peroxidase enzyme defects which are caused due to the mutations on the thyroid peroxide (TPO) gene – which is located on the chromosome 2p25 – such as (Arg491His, Leu458Pro, etc) leads to the progression of congenital hypothyroidism [40]
iii. Hydrogen peroxide generation defects, caused by the mutations such as DUOX2 or THOX2 and DUOXA2 gene mutations are responsible for producing various alterations which lead to congenital hypothyroidism [41-42]
iv. Thyroglobulin protein defects which occur on thyroglobulin gene (located on chromosome 8q24.2-8q24.3) due to the mutations such as p.R277X, p.C1058R, p.C1977S, p.R1511X, p.A2215D and p.R2223H results in the progression of congenital hypothyroidism [43]
v. Iododtyrosine deiododinase defects, which are caused due to DEHAL1 and SECISBP2 gene mutations are also responsible for the pathogenesis of congenital hypothyroidism [44-45]

Resistance to TSH binding and signaling: - TSH (Thyroid stimulating hormone or thyrotropin stimulating hormone) is responsible to stimulate the thyroid gland to produce T_3 and T_4. Any alterations which cause resistance to the stimulus of TSH leads to congenital hypothyroidism. These various alterations may be: -

i. TSH receptor defect: - These defects are caused due to the various mutations (such as deletions of 18 nucleotides at positions 1217-1234 and 4 novel bp insertions) in the thyroid hormone receptor – beta gene results in a frame-shift and premature termination of the coding sequence which lead to the consequence of induced resistance of the thyrotropin receptor towards TSH. This resistance has a critical role in the pathogenesis of congenital hypothyroidism [46-47].
ii. G-protein mutation: - The G-protein alpha subunit gene (GNAS1) is located on chromosome 20q at position 13. It has a stimulating effect on the release of thyroid hormones due to its intrinsic GTPase activity. G-proteins are responsible for the signal transductions across the cellular membranes and coupling extracellular receptors (also the ones which bind TSH). The mutations in GNAS1 (such as c.1100_1101insA) results in the alterations of the normal physiology of signal transductions due to frame-shift and premature truncation of bases downstream resulting in pseudohypothyroidism 1A with congenital hypothyroidism [48-50].

Secondary Causes: - The congenital hypothyroidism caused by secondary causes is also known as central hypothyroidism. These causes are mainly related to the dysfunction of pituitary gland or hypothalamus. The results of this dysfunction are: -

i. Inadequate secretion of TSH (thyroid stimulating hormone), which is necessary for the release of thyroid hormones.
ii. Inadequate stimulation of the thyroid gland by insuuficient amount of TSH secreted by the anterior pituitary gland [51-52].

Apart from the above reasons, there are also some other secondary causes (related to genetic mutations in various genes) which are responsible for the pathogenesis of central hypothyroidism. These are as follows: -

a) Defects in the transcription factor due to the mutations in various genes (such as PIT-1, PROP-1 LHX3 or HESX1) which are responsible for the development of pituitary gland [53-54].
b) Mutations in the thyroid stimulating hormone alpha subunit gene such as: -

i. Non-sense mutation in the thyroid-stimulating hormone beta-subunit gene [55]
ii. G29R mutation in exon 2 [56]
iii. Non-sense mutation at codon 49 (Q49X) [57]
iv. Frame-shifting 1-base pair deletion in codon 105 (313[DELTA]T: C105V) in exon 3 [58-59]
v. Homozygous mutation in the thyrotropin beta-subunit gene follows an autosomal-recessive inheritance [60-61]

Peripheral hypothyroidism: - It is a condition in which the various cells of the body stop responding to thyroid hormones. It occurs due to the peripheral defects in the metabolism of the thyroid hormone. 90% of the cases of

peripheral hypothyroidism are due to genetic mutations caused in various genes such as: -

i. Thyroid receptor beta mutations: - Some mutations in the beta receptor gene of thyroid are also responsible for inducing resistance against thyroid hormones in the peripheral target cells. These mutations are inherited in dominant pattern. Infants having these mutations are generally euthryoid (i.e., the functioning of their thyroid gland is normal). The levels of T_3 and T_4 are slightly elevated (as a result of compensatory mechanism of the body) and TSH levels are also normal. Therefore, such infants would pass undetected under newborn screening, which would result in serious problems later [62].

ii. Mutations in transport gene: - Several plasma membrane transporters such as monocarboxylase transporter 8 (*MCT8*) facilitate the transport of thyroid hormones into the peripheral cells. Any mutation which occurs in the gene encoding this transporter would lead to the disruption of its function, thus leasing to peripheral resistance against thyroid hormones. Moreover, the defective transporter also seems to disrupt the passage of T_3 into the neurons which results in various neurologic complications such as mental retardation and quadriplegia. Besides, this disrupted transport leaves the body with elevated levels of T_3 and low levels of T_4 while the levels of TSH appear normal. This condition is known as Allan-Herndon-Dudley syndrome [63].

Transient congenital hypothyroidism: - It is a condition characterized by low levels of the thyroid hormones and elevated levels of TSH. The various reasons accounting for the pathogenesis of transient congenital hypothyroidism are as follows: -

i. Maternal intake of anti-thyroid drugs: - The intake of anti-thyroid drugs such as propylthiouracil or methimazole by a pregnant woman could lead to the risk of progression of congenital hypothyroidism in the fetus. Even low doses of such drugs are severe enough for the fetud due to its extreme sensitivity [64].

ii. Transplacental passage of maternal TSH receptor blocking antibodies: - The passage of thyroid stimulating hormone receptor blocking antibodies from the mother's body to the fetus could lead to transient blockage in the neonatal thyroid physiology and thus cause hypothyroidism [65].

iii. Maternal and neonatal iodine deficiency or excess: - Due to the low iodine reserves and immaturity of the hypothalamus-pituitary-thyroid axis in fetus, it is extremely sensitive to the low levels of iodine. Besides, the high levels of iodine are equally harmful because the immature thyroid gland of the infant is unable to reduce the uptake of iodine when exposed to high load. Thus both these conditions lead to congenital hypothyroidism [66].

iv. Heterozygous mutations of DOUX2 (THOX2) or DUOXA2: - These genes are responsible for the production of hydrogen peroxide which is essentially required by the thyroid gland for the oxidation process required in the formation of thyroid hormones. Thus, any mutation in these genes would result in alterations in the normal physiology, decreasing the levels of thyroid hormones which lead to congenital hypothyroidism [67].

CONCLUSION

The deficiency of thyroid hormones could cause serious impairments of various elements of the body because of which the quality of life could be smashed to smithereens. The pathogenesis of the congenital hypothyroidism, which is very well studied and understood, tells us about the various elements involved in this disorder. Moreover, various diagnostic measures are available which could screen the new born children for such disorders. Thus, every possible way should be adopted to prevent and cure it so that the infants born with this disorder, after appropriate treatment, could be saved from its drastic consequences and be given the privilege to live normal lives.

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