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Congenital Hypothyroidism-A Review

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ABSTRACT:

Congenital hypothyroidism is a well known but a serious clinical disease. The reported incidence vary according to various population studied but still significant number of undetected congenital hypothyroidism particularly in developing countries is a reality and this may lead to permanent clinical neuro-developmental delay and compromised intelligence. Many developed countries has their own universal screening program for timely detection and appropriate clinical management, which has proven to prevent from permanent clinical complications, but in counties like India, still we lack any such universal screening strategy. There are various proposed screening strategies with their own merits and limitations but TSH used initially for screening is most accepted and universally adopted method. Starting of thyroxine treatment in appropriate doses as soon as clinically suspected and diagnosed is the best policy to reduce the burden of permanent complications.

Key-words: Congenital hypothyroidism, athyrosis, dys-hormogenesis, muataion, TSH, neonatal screening.

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INTRODUCTION:

The term 'congenital hypothyroidism' was first introduced more than 60 years ago when Radwin *et al.* reported children with hypothyroid-associated features of severe intellectual disability and growth retardation.[1] Today, this definition of congenital hypothyroidism has to be revisited, as the diagnosis of the disease is made before the onset of severe clinical symptoms, on the basis of biochemical measurement of TSH and thyroid hormone levels alone.[2,3] Primary congenital hypothyroidism, the most common form of congenital hypothyroidism, occurs either as a result of developmental defects of the thyroid gland, known as thyroid agenesis or dysgenesis, or is due to disruptions in thyroid hormone biosynthesis, also known as thyroid dyshormonogenesis.

In the majority (80%) of cases, a structural defect of the thyroid gland is present which can be an ectopic gland, sometimes lingual or other position, thyroid gland hypoplasia; or the complete absence of thyroid tissue.[4,5,6] Minor variants of thyroid dysgenesis include the absence of the thyroid isthmus or a lack of one in most cases the left-lobe of the thyroid. This thyroid hemi-agenesis can be found with a frequency of 1 in 1,000-2,000 individuals without a pre-existing diagnosis of hypothyroidism and its finding in children with neonatal elevated levels of TSH, therefore, does not confirm the diagnosis of congenital hypothyroidism.[7]

The remaining 20% of children with congenital hypothyroidism have normal or enlarged thyroid. These children are affected by a defect of thyroid hormone synthesis, which occurs in most cases as an autosomal recessive trait of inheritance. Secondary congenital hypothyroidism, also termed as

central congenital hypothyroidism, is caused by deficiencies in TSH, for example, in infants with pituitary insufficiency or structural abnormalities of the pituitary gland or hypothalamus. Over the time, TSH cut-off levels used in confirmatory diagnoses have been lowered, leading to the diagnosis of congenital hypothyroidism in patients who exhibit elevated TSH levels without decreased peripheral thyroid hormone concentrations or clinical symptoms. This mild form of congenital hypothyroidism occurs as the result of either a transient or permanent rise in TSH levels and has been named 'subclinical hypothyroidism'. However, given that this condition does not reflect a true state of hypothyroidism, nor causes an obvious developmental defect, this form would be more accurately labelled as 'hyper-thyrotropinemia'.

Definition and Classification:

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. Thyroid hormone deficiency at birth is most commonly caused by a problem with thyroid gland development (dysgenesis) or disorder of thyroid hormone biosynthesis (dyshormonogenesis).These disorders result in primary hypothyroidism. Secondary or central hypothyroidism at birth results from a deficiency of thyroid stimulating hormone (TSH). Congenital TSH deficiency may rarely be an isolated problem (caused by mutations in the TSH b subunit gene), but most commonly it is associated with other pituitary hormone deficiencies, as part of congenital hypopituitarism. Peripheral hypothyroidism is a separate category resulting from defects of thyroid hormone transport, metabolism, or action.

Congenital hypothyroidism is classified into permanent and transient CH. Permanent CH refers to a persistent deficiency of thyroid hormones that requires life-long treatment. Transient CH refers to a temporary deficiency of thyroid hormones, discovered at birth, but then recovering to normal thyroid hormone production. Recovery to euthyroidism typically occurs in the first few months or years of life. Permanent CH can be further classified into permanent primary and secondary (or central) CH; transient primary CH has also been reported. In addition, some forms of CH are associated with defects in other organ systems; these are classified as syndromic hypothyroidism.

Neonatal Screening:

Klein and co-workers were the first to show that the IQ of a child with congenital hypothyroidism dramatically depends on the time of clinical diagnosis and initiation of replacement therapy.[8] The observation that the diagnosis and treatment of CH only before the age of 3 months enables normal mental development led the researchers to propose the introduction of screening programs. Neonatal screening for congenital hypothyroidism became a feasible option only after the development of specific, robust and sensitive radio immunoassays for TSH and T_4.[9] Subsequently, the results of two pilot screening programs were published in the early 1970s.[10,11]

There is normally transient rise of TSH in the first 48 hr after birth,[12] therefore, either cord blood samples or dried blood spots taken from heel pricks at birth or after the third day of life were used to measure either TSH alone as done in Europe and Japan[3] or T_4 followed by TSH in neonates if initial T_4 concentration were below the 10th percentile screening used in North America.[2] Both strategies aimed to identify children with primary congenital hypothyroidism but not those with central congenital hypothyroidism. The results of these first screening programs were encouraging and confirmed that early diagnosis and treatment can offer a normal intellectual outcome in a disease that was historically thought to result in severe mental retardation.[2,3]

The incidence of congenital hypothyroidism that was observed in inital screening programs were similar, with a rate

of 1 in 3,000-4,000, which was twofold higher than the incidence calculated by clinical diagnosis in the pre-screening era.[13-17] Further neonatal screening programs have confirmed an incidence of 1 in 3,500 in a wide range of different geographic and ethnic populations.[18] But there were two exceptions in US screening programs, which observed Hispanic neonates exhibiting an increased incidence of 1 in 2,000, and neonates of African American origin had a reduced incidence of 1 in 10,000.[19] Interestingly, a female preponderance was observed in all screening cohorts, similar to that seen in cohorts studied before the introduction of screening.[20]

Over the past four decades, increasing overall incidence rates have been observed in the USA, without an obvious identifiable reason. Several factors have been proposed to underlie this observation: the diagnosis of more subtle cases of congenital hypothyroidism due to lower TSH cut-off levels; the increasing number of preterm children, who can be affected by a transient rise in TSH levels; and a change in study populations, with a higher proportion of neonates with a Hispanic background.[21]

A summary of the New York State program during the years 2000 to 2003 showed some interesting demographic variations in the incidence of congenital hypothyroidism (Table-1).[5] As compared to the overall incidence of congenital hypothyroidism, the incidence was somewhat lower in Whites (1:1815) and Blacks (1:1902), somewhat higher in Hispanics (1:1559), and highest in the Asian population (1:1016). In addition, New York state program found the incidence nearly double in twin births (1:876) as compared to singletons (1:1765), and even higher with multiple births (1:575). Older mothers (> 39 years) had a higher incidence (1:1,328) compared to younger mothers (< 20 years, 1:1,703). The incidence was higher in preterm vs. term infants.[5]

Table-1: Incidence of congenital hypothyroidism: Selected demographics from New York State (2000-2003)

Demographic Incidence	
Overall	1:1681
Gender	
Male	1:1763
Female	1:1601
Ethnicity	
White	1:1815
Black	1:1902
Asian	1:1016
Hispanic	1:1559
Birth weight	
< 1500 g	1:1396
1500 - 2500 g	1:851
> 2500 g	1:1843
Single vs. multiple births	
Single	1:1765
Twin	1:876
Multiple	1:575
Mother's age	
< 20 years	1:1703
20-29 years	1:1608
30-39 years	1:1677
> 39 years	1:1328

Etiology:

Permanent congenital hypothyroidism may be due to primary or secondary (central) causes. Primary causes include defects of thyroid gland development, deficiencies in thyroid hormone production, and hypothyroidism resulting from defects of TSH binding or signal transduction. Peripheral hypothyroidism results from defects in thyroid hormone transport, metabolism, or resistance to thyroid hormone action. Secondary or central causes include defects of thyrotropin releasing hormone (TRH) formation or binding and TSH production.

Transient hypothyroidism may be caused by maternal or neonatal factors. Maternal factors include anti-thyroid medications, trans-placental thyrotropin receptor

blocking antibodies and exposure to iodine deficiency or excess. The insights into the pathogenesis of congenital hypothyroidism have revealed that genetic causes are detectable not only in patients with dyshormonogenesis, but also in individual patients with developmental defects of the thyroid, which were previously regarded to have a non-inherited sporadic disorder.[23]

However, although molecular genetic testing can clarify the cause of dyshormonogenesis in the majority of patients, the molecular basis of congenital hypothyroidism in those with thyroid dysgenesis remains predominantly unknown. Only few familial cases of thyroid dysgenesis have been reported to date and discordance is found even between monozygotic twins.[24,25] Nevertheless, in single cases of thyroid dysgenesis, inactivating mutations in transcription-factor-encoding genes expressed during thyroid organogenesis have been identified.[23]

In addition, congenital hypothyroidism with normal localization of the thyroid gland or a goiter can reflect a recessively inherited defect of thyroid hormone synthesis. These rare mutations have clinical relevance, as they enable clinicians to provide genetic counseling, as well as adequate treatment and follow-up, for example because affected patients with thyroid dysgenesis can manifest with more complex comorbidities. Nevertheless, in some patients with well-defined genetic defects, such as Down syndrome[26] or Williams–Beuren syndrome[27] the molecular basis of the usually mild forms of congenital hypothyroidism or hyperthyrotropinemia remains to be identified.

Classification and etiology of congenital hypothyroidism

1	Primary hypothyroidism
1a	Thyroid dysgenesis: hypo-thyroidism due to a developmental anomaly
	(Thyroid ectopia, athyreosis, hypoplasia, hemiagenesis)
	Associated mutations: (these account for only 2% of thyroid dysgenesis cases; 98% unknown)
	TTF-2, NKX2.1, NKX2.5, PAX-9
1b	Thyroid dyshormonogenesis: hypothyroidism due to impaired hormone production
	Associated mutations:
	Sodium-iodide symporter (NIS) defect, Thyroid peroxidise (TPO) defects
	Hydrogen peroxide generation defects (DUOX2, DUOXA2 gene mutations)
	Pendrin defect (Pendred syndrome), Thyroglobulin defect
	Iodotyrosine deiodinase defect (DEHAL1, SECISBP2 gene mutations)
1c	Resistance to TSH binding or signalling
	Associated mutations: TSH receptor defect, G -protein mutation: pseudohypoparathyroidism type 1a

2	Central hypothyroidism (syn: Secondary hypothyroidism)
2a	Isolated TSH deficiency (TSH b subunit gene mutation)
2b	Thyrotropin-releasing hormone (TRH) deficiency
	Isolated, pituitary stalk interruption syndrome (PSIS), hypothalamic lesion, e.g. hamartoma
2c	Thyrotropin-releasing hormone(TRH) resistance
	TRH receptor gene mutation
2d	Hypothyroidism due to deficient transcription factors involved in pituitary development or function
	HESX1, LHX3, LHX4, PIT1, PROP1 gene mutations

3	Peripheral hypothyroidism
3a	Resistance to thyroid hormone, Thyroid receptor b mutation
3b	Abnormalities of thyroid hormone transport- Allan-Herndon-Dudley syndrome (monocarboxylase transporter 8 [MCT8] gene mutation)

4	Syndromic hypothyroidism
4a	Pendred syndrome - (hypothyroidism- deafness - goiter) Pendrin mutation
4b	Bamforth-Lazarus syndrome - (hypothyroidism - cleft palate - spiky hair) TTF-2 mutation
4c	Ectodermal dysplasia - (hypohidrotic - hypothyroidism - ciliary dyskinesia)
4d	Hypothyroidism - (dysmorphism - postaxial polydactyly - intellectual deficit)
4e	Kocher - Deber - Semilange syndrome - (muscular pseudohypertrophy- hypothyroidism)
4f	Benign chorea – hypothyroidism
4g	Choreoathetosis - (hypothyroidism - neonatal respiratory distress) NKX2.1 /TTF-1 mutation
4h	Obesity - colitis - (hypothyroidism - cardiac hypertrophy - developmental delay)

5	Transient congenital hypothyroidism
5a	Maternal intake of anti-thyroid drugs
5b	Trans-placental passage of maternal TSH receptor blocking antibodies
5c	Maternal and neonatal iodine deficiency or excess
5d	Heterozygous mutations of THOX2 or DUOXA2
5e	Congenital hepatic hemangioma/hemangio-endo-thelioma

Mutations Causing Thyroid Dysgenesis:

Due to the low frequency of mutations in patients with thyroid dysgenesis,[28,29] genetic testing should be initiated only in those patients with either a suggestive clinical manifestation (*FOXE1*, *NKX2−1* and *NKX2−5* gene mutations) or with a familial occurrence of thyroid dysgenesis (*PAX8* and *TSHR* gene mutations).

FOXE1

At birth, the clinical diagnosis of a child with congenital hypothyroidism and thyroid dysgenesis associated with cleft palate and striking spiky hairs should suggest the diagnosis of the Bamforth–Lazarus syndrome,[30] which is caused by a mutation in the transcription-factor-encoding gene *FOXE1*.[31,32] These children have an un-favourable cognitive outcome despite adequate treatment of congenital hypothyroidism owing to the additional role of FOXE1 in the development of the central nervous system (CNS). This prognosis, as well as the autosomal recessive mode of inheritance, should be addressed in genetic counselling.

NKX2−1

The majority of patients with mutations of the *NKX2−1* gene present with either mild or severe congenital hypothyroidism in association with variable pulmonary symptoms, as well as neurological alterations, such as severe choreo-athetosis, ataxia and other movement disorders.[33,34] This particular association of symptoms results from the multiple roles of the NKX2−1 transcription factor in the development and function of different organ systems, that is, the CNS, lung and thyroid. Genetic counselling is based on the autosomal dominant inheritance; however, the relevance of counselling is very limited due to the variable penetrance of *NKX2−1* gene mutations within the three affected organ systems.

NKX2−5

A very rare variant of congenital hypothyroidism due to mutations in the *NKX2−5* gene was described in four patients, of whom one was affected by an associated heart defect. Although heart defects account for 50% of all associated malformations in congenital hypothyroidism, only this one *NKX2−5* mutation has been reported to date.[35]

PAX8

Another example of a thyroid transcription factor defect that affects thyroid function and development is the *PAX8* gene mutation. This defect in thyroid dysgenesis leads to a variable and potentially asymmetric hypoplasia of the thyroid gland. Hypothyroidism can be mild, and some patients manifest an elevation of TSH levels only later during childhood, thereby escaping the diagnosis by neonatal screening.[36] In addition to thyroid dysgenesis, *PAX8* gene mutations can also lead to unilateral kidney agenesis. Patients with a *PAX8* mutation should, therefore, undergo renal ultrasound investigation to detect renal anomalies.[37] Although PAX8 is also expressed in the brain and the ear anlage, no further defect or clinical symptom of the CNS has been described in PAX8-deficient patients.[38]

TSHR

Even before the description of thyroid dysgenesis caused by transcription factor defects, inactivating mutations of the TSH receptor were found to result in congenital hypothyroidism and thyroid dysgenesis with autosomal recessive inheritance.[39] Because the encoding gene, *TSHR*, is expressed only late during foetal development, homozygous or compound heterozygous inactivating mutations lead to hypoplasia and not to an ectopic gland or agenesis of the gland. A less severe inactivation of the TSH receptor can also result in mildly elevated TSH levels with normal T4 levels.[40]

Mutations causing thyroid dyshormonogenesis

Each step of the complex process of thyroid hormone synthesis, including iodine transport into the thyroid follicle (via the sodium-iodide symporter NIS and the sodium-independent chloride/iodide transporter pendrin[41] and iodine incorporation into the nascent thyroid hormone (via the enzymes thyroid peroxidase [TPO,][42] dual oxidases [DUOX][43] and the matrix protein thyroglobulin can be affected.[44]

TPO and TG

Since the first description of an inactivating mutation in the *TPO* gene in 1992,[45] it was shown that in most children with thyroid dyshormogenesis, a molecular inherited defect of thyroid hormone synthesis can be diagnosed. The partial or complete loss of activity of TPO or thyroglobulin (encoded by the *TG* gene) leads to severe hypothyroidism with a large goiter.

SLC26A4

The *SLC26A4* gene encodes pendrin, a protein expressed in follicular cells and in cells of the inner ear that transports iodine into the thyroid follicle. In children with mutations in this gene, an associated hearing loss can be present and might help to focus the molecular genetic diagnosis.[46]

DUOX

In contrast to the effects of insufficient or absent TPO or thyroglobulin activity, defects in the H2O2-generating oxidase system (DUOX2, DUOX2a) are more subtle and can appear as a transient, mild TSH elevation, possibly due to the redundancy of different proteins in the oxidase system.[47]

GNAS

Combined central and primary congenital hypothyroidism can result from mutations in the *GNAS* gene, which cause

pseudo-hypoparathyroidism type 1a.[48] The underlying gene defect affects the function of the G−protein α, which is crucial for TRH as well as TSH receptor signaling, leading to only mildly elevated TSH levels.[49] Features that are clinically suggestive of this form of congenital hyperthyroidism are the associated findings of short digits and short stature and mental retardation despite adequate levothyroxine treatment.

Clinical Diagnosis:

Clinical symptoms of congenital hypothyroidism detected by screening in neonates are usually subtle and nonspecific. They include long-term jaundice, feeding difficulty, lethargy, constipation, macroglossia, hypothermia, edema, wide posterior fontanel, umbilical hernia and the so-called typical 'hypothyroid facial appearance'. If congenital hypo-thyroidism remains untreated, the clinical symptoms become evident in the second half of the first year of life, with growth retardation and a delay in motor development. In addition to the delay in the development of motor skills, intellectual disability is the most important and devastating clinical symptom of congenital hypothyroidism, as it is not reversible.

Almost 10% of neonates with congenital hypothyroidism are affected by additional congenital malformations.[50] Congenital heart defects are the most common, affecting 50% of patients. Congenital hypothyroidism can also occur as one obligatory feature of rare genetic syndromes, such as the Bamforth–Lazarus syndrome, and is more frequent in children with Down syndrome[51] and pseudo-hypoparathyroidism type 1a.[52] Clinical symptoms of an underlying syndrome can precede the diagnosis of congenital hypothyroidism, especially in patients with the Bamforth–Lazarus syndrome, in whom cleft palate and spiky hairs are present at birth. Mild congenital hypothyroidism or elevated TSH levels are more frequent in patients with Williams–Beuren syndrome and in those with pseudohypoparathyroidism type 1a.

Variants of congenital hypothyroidism that are characterized by an inappropriate low TSH level, such as central and preterm congenital hypothyroidism, cannot be diagnosed with TSH-based screening strategies. Because free T4 measurement in dried blood spots has not been established with sufficient sensitivity and specificity so far, indirect strategies were developed to diagnose these disease variants. In the Netherlands, an elaborated approach combines the screening of total T4 with measurement of TSH and thyroxine-binding globulin as a surrogate for the free T4 fraction.[53] The results of this program clearly show that, in addition to primary congenital hypothyroidism, almost all cases of central congenital hypothyroidism can be detected, with an incidence rate of 1 in 21,000, which is close to the rate of 1 in 19,000 calculated based on the clinical diagnosis of central congenital hypothyroidism.[54]

Confirmatory Diagnosis:

Biochemical measurements

Once a child has a conspicuous result in the neonatal screening, the definite diagnosis of congenital hypothyroidism depends on a so-called 'confirmatory diagnosis. To avoid misdiagnosis owing to a transient TSH surge or a sample error, serum measurement of TSH, T4 either total or free T4 and T3 is necessary before treatment can be initiated. In neonates with elevated serum TSH and low thyroid hormone levels, the diagnosis of congenital hypothyroidism is considered to be confirmed; thyroid imaging and testing for maternal thyroid antibodies is then recommended to more precisely define subgroups of congenital hypothyroidism.[55,56]

In patients with confirmed severe congenital hypothyroidism, serum levels of TSH >50 mU/l and low T4 or free T4 levels are present, whereas T3 values are in the lower normal range in most cases. It is difficult to interpret the values that reflect mild congenital hypothyroidism, with TSH

levels <50 mU/l and normal or borderline T4 (or free T4) concentration. Because signs and symptoms of congenital hypothyroidism are related to decreased thyroid hormone levels and not to elevated TSH levels, it is necessary to assess whether a child is deprived of thyroid hormone or not. Inter-individual T4 levels vary enormously, and the normal range of T4 and free T4 can differ by 100%.[57] In addition, neonatal T4 levels change rapidly in the first days of life, and the almost twofold higher levels in the first week of life need to be considered in the assessment.[57]

A stable, elevated TSH level with normal T4 concentration is present in at least 3% of the 'healthy' child population, given that the upper normal TSH level is defined by statistical means of +2 SD when measuring normal control populations. Longitudinal measurements in large cohorts revealed that a TSH level <7.5 mU/l will not further increase over time.[58] This 'normal', elevated TSH level, therefore, probably reflects an inborn variant of the individual set-point of the hypothalamus–pituitary–thyroid axis and does not represent imminent pathology.

Imaging:

As part of the confirmatory diagnosis, imaging can be employed in neonates with biochemically proven congenital hypothyroidism to define the subgroup of hypothyroid pathology (thyroid dysgenesis versus dyshormonogenesis). The techniques used for imaging differs between centres and depends mostly on local experience and availability. The non invasive ultrasonography technique is sufficient to separate a structural defect from a normal or enlarged gland, whereas only the more invasive scintigraphy either with radioactive iodine or technetium, performed when TSH concentration is still high enables an exact localization of an ectopic, ie. lingual thyroid gland.[59]

To further increase the specificity in discerning subgroups of congenital hypothyroidism, thyroglobulin can be measured as a thyroid-tissue-specific marker. The discrimination of goiter versus athyrosis (lack of the thyroid gland) can easily be achieved in children by combining measurement of thyroglobulin levels and ultrasonography. However, the more subtle differentiation of apparent athyrosis from an ectopic thyroid gland although possible in most cases of complete absence of thyroglobulin remains difficult in some children, owing to the individual overlap of thyroglobulin levels in these conditions.[60] Nevertheless, as the demonstration of an ectopic gland versus athyrosis does not change the indication for or dose of levothyroxine, several paediatric centres regard ultrasonography combined with measurement of thyroglobulin levels to be sufficient and do not perform scintigraphy.

Thyroid antibodies and iodine

In children with confirmed biochemical hypothyroidism and a normal thyroid gland on imaging, a further diagnostic step should be performed to exclude either a maternal thyroid autoimmune disease or an iodine overload as a potential cause of transient congenital hypothyroidism. Typically, maternal antibodies that can cause foetal hypothyroidism block the TSH receptor and after clearance from the infant's circulation at an age of 6 months, thyroid function normalizes.[61,62] The same transient course can be expected in those rare cases of iodine overload that can result from maternal use of disinfectent with povidone iodine before or during delivery or from a direct application of this substance to the neonate during preoperative disinfection. The transdermal resorption of high amounts of iodine leads to an inactivation of the neonatal thyroid gland (Wolff–Chaikoff effect) and sometimes causes severe but short-lasting hypothyroidism.[63,64] Treatment of the child is still necessary for several weeks until normal thyroid function is restored.

Treatment

In principle, successful treatment is achieved by taking a single oral levothyroxine dose in the morning. The choice of levothyroxine rather than liothyronine or a combination of the two is reasonable, because the biologically active liothyronine is generated by local expression of deiodinases, especially in the brain and other target tissues.[65] In addition, studies have shown that treatment with liothyronine is not superior in terms of final cognitive outcome.[66] In most countries, levothyroxine for oral application is only licensed as a tablet. In Europe, liquid preparations with a concentration of 5 µg per drop are available, which allows smaller intervals of dose adjustment.[67]

Dose and start of treatment

The initial doses for neonates in the first screening programs were chosen on the basis of practicability (availability of tablet preparations of levothyroxine for adults: 25.0 µg, 50.0 µg or 37.5 µg as half of a 75.0 µg tablet) and individual clinician's experience. Irrespective of the dose, the initial results were encouraging, given that a beneficial effect, with normal growth, motor development and IQ, was found in almost all treated children.[68,69]

However, in two studies of young adult patients diagnosed in the first screening programs in Canada and Norway, who were treated with an initial dose of 25 µg per day, the final full-scale IQ was in the normal range, albeit consistently 6–8 points lower than that of an appropriate sibling control group.[70,71] This gap was argued to potentially result from an insufficient effect of the 25 µg levothyroxine dose.[72]

Newer, retrospective comparisons and prospective, but nonrandomized, observations revealed an improved cognitive outcome with an increased dose of levothyroxine >10 µg/kg body weight daily.[72-74] In addition, a randomized study comparing 37.5 µg and 50.0 µg of levothyroxine revealed a better full-scale IQ in the high-dose group compared with the low-dose group at an age of 2-8 years.[75] Together, these data clearly favour high levothyroxine doses (>10 µg/kg per day) to improve IQ outcome in children with congenital hypothyroidism. However, in a cohort from Switzerland, a high dose of 14.9 µg/kg body weight still resulted in a 9–points-lower full-scale IQ compared with that of a matched control group.[76]

Closely linked with the effect of a high versus low initial treatment dose is the question whether an early start of treatment can further improve the IQ in patients with congenital hypothyroidism. Several studies compared an early versus late start of treatment, that is, 10 days versus 16 days[77] and <15 days versus >21 days after birth,[78] which revealed a consistently better IQ in the early-treatment group. Whether an even earlier start of treatment, before the age of 10 days, will close the gap of full-scale IQ points remains to be investigated. Based on currently available outcome data, which do not reach a high level of evidence, most guidelines now recommend a high dose of levothyroxine of 10–15 µg/kg body weight with the aim to start treatment within the first 2 weeks of life.[79]

Mild forms of congenital hypothyroidism

A current topic of discussion concerns the diagnosis and necessity for treatment of mild forms of congenital hypothyroidism in children also referred as hyperthyropinemia. Several groups have now reported their experience with low TSH cut-off levels of 10 mU/l and even 6 mU/l.[77,78] This increase was accompanied by a more than 10-fold higher rate of screening TSH re-investigations, for example, a recall rate that is in the range of 0.1–0.3% of all screened neonates when the TSH cut-off level is 15 mU/l. The majority of children with supposed congenital hypothyroidism were shown to have permanent elevated TSH levels (>5 mU/l) at 2–3 years of age,[77] which was argued to be proof of congenital hypothyroidism and support the need for continued treatment with levothyroxine.

However, these children—who had hyperthyrotropinemia rather than 'true' congenital hypothyroidism were treated without any evidence of a clinically significant benefit of treatment for their cognitive development. Nevertheless, given the devastating effect of hypothyroidism on the neonatal development of the CNS and because individual patients with mild TSH elevation might have borderline T_4 values, the tendency to over treat is easily comprehensible. Therefore, outcome studies that include a substantial number of untreated children with mild congenital hypothyroidism are urgently needed to better judge this particular treatment indication.

European Society for Paediatric Endocrinology recently published guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism in 2014.[80] They recommended worldwide screening for primary CH with TSH testing. In preterm neonates; low-birth weight (LBW) and very low-birth weight (VLBW) neonates; ill and preterm newborns admitted to neonatal intensive care units, second screening should also be considered. If capillary TSH concentration from blood obtained on neonatal screening is >40 mU/L treatment should be started immediately. Regarding venous TFT results, the society recommends that if venous free T4 (FT4) concentration is below norms for age, treatment should be started immediately. If venous TSH concentration is >20 mU/L, treatment should be started, even if FT4 concentration is normal. If venous TSH concentration is > 6 to 20 mU/l beyond 21 days in a well baby with normal FT4 concentration it is suggested to consider either initiating thyroxin supplementation immediately and retesting, off treatment, at a later stage; or not giving any treatment but retesting two weeks later.

CONCLUSION:

Congenital hypothyroidism is a very important clinical entity which may lead to permanent neurological, cognitive deficit and milestone developmental delay. It needs high index of suspicion for timely diagnosis and appropriate management to avoid these permanent disabilities. The key in successful management and avoidance of serious complications lies in timely starting of proper doses of thyroxin therapy.

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