Review Article

Overview of diagnosis, management and outcome of congenital hypothyroidism: A call for a national screening programme in Sudan

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ABSTRACT

Congenital hypothyroidism (CH) is the commonest preventable cause of mental retardation in children worldwide. It continued to be a major health problem amongst Sudanese children. The lack of a screening programme in Sudan may be the major factor of missing the diagnosis in newborns with such a condition that can present very subtle clinically, yet with poor neurodevelopmental consequences. The outcome is very good when the condition is noticed early (in the first 2 - 3 weeks of life). However, the prognosis is guarded when the diagnosis is delayed, with a squeal of different degrees of developmental delay depending on the severity of the condition. In this overview, we tried to highlight the important issues of screening, diagnosis and outcome with and without early management, worldwide. We thereby send a call out for all paediatricians and endocrine clinicians who work locally or outside Sudan to collaborate with the Sudanese Society of Paediatrician as well as other stakeholders in Sudan to help establishing a national screening programme for all common and preventable causes of childhood illnesses which has devastating consequences such as CH.

Key words:
Congenital hypothyroidism; Screening; Levothyroxine; Thyroid; Thyroxin; Sudan.

INTRODUCTION

Congenital hypothyroidism (CH) is the commonest preventable cause of mental retardation in children. Infants detected to have the condition through newborn

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screening programs and started on Levothyroxine (L-T4) in the first few weeks of life have a normal or near-normal neurodevelopment outcome [1]. In Sudan, no neonatal screening program for CH exists. Moreover, epidemiological studies addressing CH in the country are scanty and mostly unpublished in cited journals. The incidence of CH in Sudan is expected to be similar to that in other countries of the Region such as Saudi Arabia. The newborn screening for CH data from Saudi Arabia showed that the incidence is 1:3292 in the first one million of screened neonates [2]. The population of Sudan is 34,206,710 with an annual birth rate of 31.7 births/1,000 population [3]. Assuming that the incidence of CH in Sudan is not different from other countries in the region (1 in 3000-4000), accordingly, the expected number of neonates born with CH in Sudan will be around 250 to 350 per year. Implementation of CH screening program would potentially prevent mental retardation in this high number of neonates.

In most cases, the disorder is primary and permanent. It either results from anatomical abnormality in thyroid gland development or its location (dysgenesis, ectopia or agenesis) or a defect in thyroid hormone synthesis (dyshormonogenesis). Less commonly, the altered neonatal thyroid function is transient, due to maternal medication, maternal blocking antibodies, or iodine deficiency or excess transferred transplacentally to the foetus. In rare cases, CH may be secondary/tertiary hypothyroidism (central) resulting from a pituitary or hypothalamic abnormality (Table 1) [1].

The clinical diagnosis of CH is difficult as initial presentation is quite non specific in clinical features and also it can be masked by either having some residual thyroid function at birth or transplacental passage of maternal thyroid hormone (TH). This may result in temporary compensation in the affected infants. Approximately one third of maternal T4 crosses the placenta to the foetus at term [4]. The maternal T4, which has a half-life of 6 days, will be metabolized and excreted by 3 - 4 weeks of life. The symptoms and signs will, therefore, develop over the first weeks of life. However, the worsening unrecognized hypothyroxinemia will put a serious risk of poor neurodevelopmental outcome rendering the early detection of CH to be a matter of urgency.

Precise assays for measurement of thyroxin (T4) and/or thyroid stimulating hormone (TSH), or also called thyrotropin in a small volume of newborn blood was added to existed programmes of screening in the mid-1970s [5]. Recent advances in molecular and cell biology have led to improved understanding of normal thyroid physiology and of genes involved in thyroid gland development and disease [1]. In addition, the mechanism of thyroid hormone (TH) modulation of target gene expression has also been elucidated [6-9].

The incidence of CH increased worldwide in the last decades. For instance, it nearly doubled in USA from (1991-1994) to (2001-2004), from 1:3010 to 1:1660 [10]. This may be only partially explained by a lowering of screening test cut-offs, a change in birth population demographics, and an increase in preterm births [11]. Other causes possibly leading to this increase in CH incidence include a decrease in maternal iodine intake or involvement of environmental agents which are toxic to the thyroid gland [12,13].

Table 1 - Aetiology of congenital hypothyroidism

Primary CH
Thyroid dysgenesis
Aplasia
Hypoplasia
Ectopic gland
Thyroid dyshormonogenesis
Sodium-iodide symporter (trapping) defect
Thyroid peroxidase defect
Hydrogen peroxide generation or maturation defects
Thyroglobulin (Tg) defect
Deiodinase defect
Resistance to TSH binding or signalling
TSH receptor defect
G protein defect
Secondary (central) CH
Isolated TSH deficiency
Congenital hypopituitarism (multiple pituitary hormone deficiencies)
Peripheral CH
Thyroid hormone transport defect (monocarboxylase transporter 8)
Thyroid hormone metabolism defect (selenocysteine insertion sequence-binding protein 2)
Thyroid hormone resistance
Transient CH
Maternal or neonatal excess iodine exposure
Maternal or neonatal iodine deficiency
Maternal antithyroid drugs
Maternal TSH receptor Blocking Antibodies (TRB-Ab)
Heterozygous THOX2 or DUOXA2 mutations
Congenital hepatic haemangioma

CH - congenital hypothyroidism, Tg - thyroglobulin, TRB-Ab – thyroid stimulating hormone receptor blocking antibodies, TSH - thyroid stimulating antibodies.

DIAGNOSIS

Hypothyroidism is defined as low thyroid hormone (FT4) values. It is either due to a primary thyroid defect when associated with an elevated thyroid stimulating hormone (TSH), or when associated with low TSH it reflects a central defect. The screening and diagnostic methods used to facilitate early detection and management of CH will be discussed here.

The diagnostic tests used in assessing thyroid function can be classified into 2 categories:

- Tests to identify problems in thyroid function. These include:
  - Screening tests
  - Confirmatory serum thyroid function tests (TFT).
- Tests to identify the cause of this problem in function

or identify disturbed thyroid growth (anatomical problem). These include:

- Thyroid radionuclide scan
- Thyroid ultrasound scan (USS)
- Urinary iodine level
- Serum thyroglobulin (Tg) level
- Serum TSH receptor blocking antibodies (TRB-Ab) level

Many clinicians consider diagnostic tests to determine an underlying cause of CH as optional because the initial treatment decision is based primarily on thyroid function test (TFT) results. However, it is important for a cohort of infants to continue to perform these additional diagnostic studies to identify a specific aetiology [1]. These tests, especially genetic testing, may eventually lead to further improvement in the management and outcome of CH.

Screening methods

Thyroid screening tests are carried out on heel-prick blood sample taken from a newborn on special filter paper cards (known as Guthrie cards). The specimen routinely is collected between 2 and 5 days of age, although in preterm or acutely ill term babies it may be collected as early as 1 hour of age, upon admission to a neonatal intensive care unit [1]. If a peripheral blood was taken for screening in the first day of life, a repeat screening test should follow in the subsequent days. In Saudi Arabia, cord blood samples, with different cut-off values, are used in the screening programme which, similarly we presume, can be the most useful method to follow in Sudan. It is feasible and practical and will hopefully lead to a better coverage of the population. Though, reporting the positive results and starting the treatment is expected to be challenging in Sudan. Therefore, a rational system of easy reporting will be required to achieve an efficient and fully functioning screening service.

There are two screening strategies for the detection of CH in many countries including: a primary TSH/backup T4 method (Europe and Japan) and a primary T4/backup TSH method (USA) [14]. In addition, an increasing number of programs use a combined primary TSH plus T4 approach.

The main advantage of the primary T4 (and combined T4 and TSH) test is the ability to detect neonates with central hypothyroidism. Though, these patients are also at risk of developmental impairment. However, because central CH is rare and with increasing accuracy of TSH assays on small blood volumes, many programs worldwide have switched to an initial TSH/backup T4 test approach.

Each newborn screening program sets cut-off level for test results. Initially, most programs undertook an initial T4 test, with a backup TSH test on babies with a low T4. In cases with "intermediate results," e.g. low T4 but TSH below cut-off, a program may recommend that a repeat heel prick screening specimen be collected and sent for analysis [1].

Those programs of a routine second screening report that approximately 10% of CH cases are missed in the first test [15]. One group of the patients detected on the second specimen is infants with delayed TSH elevation. These patients have a low T4 but normal TSH level on the first screening, T4 remains low but the TSH level is elevated in the second screening. The infants prone to develop a delayed TSH elevation are usually the preterm or acutely ill term infants. The incidence of delayed TSH elevation is reported to be approximately 1:18,000 [16]. The cause of the delayed TSH elevation is still uncertain; a recent study showed that the majority of these patients with delayed elevation of TSH have transient hypothyroidism which reverts to normal without treatment [17]. Though we need to remember that the

purpose of early detection of CH is to prevent poor developmental outcome, a review of outcomes in the pre screening era concluded that only children with moderate or severe CH are likely to benefit from early detection and treatment and argues that detection of milder forms of CH is not cost effective [18]. Thus, whether newborn screening programs need to collect a routine or discretionary second specimen remains controversial [1].

Other Tests

Confirmatory thyroid function tests (TFT)

- The screening methods are not sufficient to establish a diagnosis of CH and this need confirmation by TFT (which include serum concentration of TSH, T4 and occasionally triiodothyronine (T3)). An infant with an elevated serum TSH level and a low free T4 (FT4) or total T4 is confirmed to have primary hypothyroidism. Because T4 and T3 are bound by more than 99% to serum proteins like thyroxin- binding globulin (TBG), some also measure binding proteins such as TBG and T3 resin uptake which their deficiency can be the primary problem. Assays that discriminate total from free hormones are available and in use. Instead of a direct measurement of FT4, the concentration of TBG can be determined and the total T4/TBG is used to assess the FT4 level [19].
- Serum TSH and T4 undergo dynamic changes in the first weeks of life [17]; and it is important to compare serum results to age-normal reference ranges [20].
- The finding of an elevated serum TSH but normal free T4 or total T4 is consistent with subclinical hypothyroidism when a clinical judgment is required to whether to start L-T4 or monitor TFT in cases of mild subclinical hypothyroidism. It may be reasonable to hold off treatment and recheck a serum TSH and free T4 in 1 week if the initial TSH is moderately high i.e between 10-20 mU/L. Though if the serum TSH has not normalized by 3-4 weeks of age many clinicians recommend treating which is also recommended if TSH is greater than 25mU/L or fails to trend towards normal [1].
- Most confirmatory serum testing is obtained around 1 to 2 weeks of age. Different laboratories have different cut-off levels for TSH depending on the assay method. Babies with TSH above the upper limit of normal should be started on thyroxin therapy. Infant with moderately high TSH (between 10-20mU/L) may have transient hypothyroidism, however most clinicians recommend treating these patients and giving the benefit of doubt. If transient hypothyroidism is suspected, treatment may be withheld at 3 years of age for 2 to 3 months and TFT repeated. If TSH fails to rise off treatment, the infant is declared to have transient hypothyroidism. Close follow up of TFT is required for infants with transient hypothyroidism [1,18,19].

Thyroid radionuclide and ultrasound scans (USS)

- Radionuclide uptake and scanning are the most accurate imaging tests to define the size and location of any thyroid tissue.
- Iodine-^{123} (I^{123}) or sodium pertechnetate 99m (Tc^{99m}) should be used in neonates; because I^{131} delivers too high dose of radioactivity to the thyroid and total body.
- Radionuclide uptake and scan may identify thyroid aplasia, hypoplasia (decreased uptake, small gland in a eutopic location), or an ectopic gland (small gland located somewhere between the foramen cecum and eutopic location over the thyroid cartilage). Absent uptake, typically diagnostic of thyroid aplasia, can also be seen with TSH gene mutations, TSH receptor-inactivating

mutations, iodide-trapping defects, and maternal TSH receptor blocking antibodies (TRB-Ab).

- Infants with absent uptake should be evaluated further by thyroid USS. Absent uptake but with a small-to-normal sized gland in a eutopic location determined by USS may be explained by TSH gene mutations, TSH receptor-inactivating mutations, iodide-trapping defects, and transplacental passage of maternal TRB-Ab. A large gland with increased uptake is compatible with one of the inborn errors of thyroid hormone production beyond trapping of iodide (dyshormonogenesis).
- Tc^{99m} test may be helpful in identification of defective oxidation and organification. If dyshormonogenesis is suspected, genetic tests to identify the specific defect may be undertaken.
- Doppler ultrasonography is reported to accurately identify up to 90% of ectopic glands [21].
- As with radionuclide scanning, a large gland is suggestive of one of the dyshormonogeneses.

Serum thyroglobulin (Tg) level

- If absent radionuclide uptake:
  - Low serum Tg level- thyroid aplasia
  - High serum Tg level - TSH receptor-inactivating mutations, iodide-trapping defects, or maternal TRB-Ab.
- If increased radionuclide uptake with a large gland: an elevated serum Tg level is suggestive of a Tg gene mutation.

Serum TSH receptor blocking antibodies (TRB-Ab) level

- The combination of absent radionuclide uptake and a small or normal eutopic gland in USS in an infant born to a mother with autoimmune thyroid disease is strongly suggestive of CH due to transplacental passage of maternal TRB-Ab.
- This can be confirmed by measurement of serum TRB-Ab in mother and/or infant.

Urinary iodine level

- Urinary iodine approximates iodine intake; the normal range in neonates is approximately 50 to 100g/24 h.
- Urinary iodine determination will confirm the diagnosis in case of a history of excess iodine ingestion in the mother or iodine exposure in the neonate, e.g. iodine-containing skin antiseptics.
- In an infant from an endemic area of iodine deficiency born with CH, measurement of urinary iodine will confirm low iodine levels.
- Other Studies to rule out associations
- All infants with CH should undergo screening hearing tests.
- The most common associated congenital defect is congenital heart disease which warrants a cardiac echocardiogram if any cardiac findings were revealed in clinical examination.

MANAGEMENT

- The goal of therapy is to normalize T4 within 2 weeks and TSH within 1 month. An optimal cognitive outcome depends on both the adequacy and timing of postnatal therapy. An initial dosage of 10 to 15 microgram/kg of L-T4 (depending on the severity of the initial hypothyroidism) has been recommended (Table 2 – [14]).
- So far, there is no evidence to suggest cognitive benefit from thyroid therapy for hypothyroxinemia of prematurity in the absence of a raised TSH [22-27].
- Although T3 is the more biologically active TH, most brain T3 is derived from local monodeiodination of T4, so T3 should not be used. The L-T4 pill should be crushed and suspended in a few millilitres of formula, breast milk, or water [14]. Most recently, T4 liquid formulation is not recommended for use anymore because of its unreliable dosage.

- • FT4 measurement at 1 week of therapy can confirm whether the serum concentration is increasing appropriately. The L-T4 dose should be adjusted according to the infant's clinical response and serum TFT results. During therapy, the serum total T4 or FT4 should be kept in the upper half of the reference range (target values depend on the assay method used [T4: 10–16 g/dL (130–206 nmol/L); FT4: 1.4 –2.3 ng/dL (18–30 pmol/L)] and TSH levels should be maintained between 0.5 and 2.0 mU/L, during the first 3 years of life with a low normal serum TSH [28]. The TSH response may sometimes be delayed because of relative pituitary resistance (hypothesized to result from in utero hypothyroidism, producing a resetting of the pituitary-thyroid feedback threshold) [14]. In such cases, the T4 value is used for titration of the dose of L-thyroxine.

FOLLOW UP

- Clinical examination, including assessment of growth and development, should be performed every few months during the first 3 years of life. Infants need to undergo frequent laboratory and clinical evaluations of thyroid function, growth, and development to ensure optimal T4 dosage and adherence to their therapy regimen (Table 2).
- Serum T4 and TSH measurements should be performed at more frequent intervals than the above recommendations when compliance is questioned, abnormal values are obtained, or dose or source of medication has been changed. FT4 and TSH measurements should be repeated 4 to 6 weeks after any change in L-T4 dosage.
- Noncompliance with the treatment is the most common cause of persistent TSH elevation and should be excluded. Other causes include: impaired T4 bioavailability. The latter may be caused by inhibition of T4 intestinal uptake by specific foods (soy, fibre) and medications (iron, calcium), malabsorption, or increased degradation (anticonvulsants; large haemangioma with high deiodinase activity). Those infants with low serum

Table 2 - Management of Congenital hypothyroidism (CH)

Medications
L-T4: 10–15 microgram/kg by mouth once daily
Monitoring
Recheck T4, TSH
2–4 weeks after initial treatment is begun
Every 1–2 months in the first 6 months
Every 3–4 months between 6 months and 3 years of age
Every 6–12 months from 3 years of age to end of growth
Goal of therapy
Normalize TSH and maintain T4 and FT4 in upper half of reference range
Assess permanence of CH
If initial thyroid scan shows ectopic/absent gland, CH is permanent
If initial TSH is 50 mU/L and there is no increase in TSH after newborn period,
then trial off therapy at 3 years of age
If TSH increases off therapy, consider permanent CH

CH - congenital hypothyroidism, T4 - thyroxin, FT4 - free thyroxin, L-T4 - levothyroxine, TSH - thyroid stimulating antibodies.

T4 values (below 10 g/dL [129 nmol/L]) and a TSH values greater than 15 mU/L during the first year of life have lower IQ than patients whose T4 concentrations were held constant at higher values [29].

- When attempting to achieve the optimal concentration of circulating FT4, clinicians should always bear in mind the adverse effects of excessive medication and thus be prepared to monitor blood concentrations of FT4 at close intervals. Prolonged hyperthyroidism has been associated with premature craniosynostosis [14].

OUTCOME

- The best outcome occurred when L-T4 was started by 2 weeks of age at 9.5 microgram/kg or more per day, compared with lower doses or later start of therapy [30].
- Growth rate and adult height are normal. There are minor differences in intelligence, school achievement, and neuropsychological tests in adults with CH that was treated early with L-T4 compared with control groups of classmates and siblings [31-35].
- Residual defects may include: impaired visuospatial processing and selective memory and sensorimotor defects. Whether these minor differences are preventable by further optimizing postnatal therapy remains controversial [14].
- Although more than 80% of infants who are treated before 3 months of age have an IQ greater than 85, 77% of these infants show some signs of minimal brain damage with learning and speech delay or impaired fine motor coordination in later life. Even in early-treated patients with CH, auditory brainstem evoked potentials can be impaired. The reason for this is not clear but might suggest inadequate protection for the developing brain by the prenatal maternal T4 [34, 36].
- Maternal hypothyroidism may also have persistent neurodevelopmental effects on the child [37-39].
- Thyroid hormone treatment regimens used today are more aggressive in targeting early correction of TSH than when the regimens used 10-20 years ago. Thus, newborn infants with CH today may have an even better intellectual and neurologic prognosis [14].

CONCLUSION

The aim of this overview on CH, its diagnosis, management and outcome is to shed a light on this important health problem with preventable devastating neurodevelopmental consequences. The promising outcome, when early detected and promptly treated, clearly highlights the importance of introducing a national screening programme in all countries including Sudan. Moreover, if we consider the cost of long term treatment of a child with neurodevelopmental delay, we will realize that preventing the sequel of CH, and promptly treating this condition in a time fashion, will be more cost effective, and will also guard against an expansion of disabled population in Sudan, in the long run.

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