Neonatal Screening for Congenital Hypothyroidism: What It Has Taught us About Thyroid and Brain Development

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4.1 Premises

Congenital hypothyroidism (CH) is a relatively common disorder with a prevalence of 1 in 2,500 live births [1]. CH is characterized by a significant deficiency of thyroid hormones starting in the perinatal period, which can lead to severe intellectual disabilities if left untreated but which was only recognized clinically at a median age of 9 months [2]. Therefore, biochemical screening for CH is now routinely performed at 2 days of life, enabling the initiation of thyroid hormone therapy during the second week of life, if required. The implementation, since the 1970s [3], of a universal newborn screening (NBS) for CH has prevented severe intellectual disability in numerous patients [4, 5]. This tremendous success might suggest that the "problem of CH has been solved" and that it now suffices to refine the screening procedure to "diagnose" all possible cases, even the most benign. This belief leads to the following misperceptions:

1. CH is mainly an alteration of thyroid function, and if confirmed, additional diagnostic procedures (e.g., thyroid scintigraphy or genetic analysis) are seen as superfluous.

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2. Consequently, the management of CH is based on restoring thyroid function to normal, but to know the cause of CH is not necessary [6].
3. To diagnose all cases of CH, the solution is to increase the sensitivity of the NBS.

Taken together, these misperceptions combine themselves into a vicious circle:

1. CH is defined on the basis of a blood test cutoff value on NBS, confirmed by a second blood test value at diagnosis.
2. Specificity of the NBS is often evaluated afterward (2–3 years later), with another blood test, the result of which will determine whether to stop or to continue T4 therapy; in the latter case, CH is defined as permanent.
3. Permanent CH is seen as serious (worthy of treatment), regardless of its severity or cause, and therefore, the goal of NBS for CH is to identify the maximal number of cases of "permanent CH."

Given that the initial screening and intermediary and final diagnoses are mainly based on a blood test, this closed system leads to self-validation and self-correlation. Moreover, at each step, the cutoff may vary widely, and ultimately sensitivity and specificity of the NBS also vary depending on the definition used to label a CH case as permanent; this self-fulfilling prophecy is also refractory to any test and refutation. This has led to a steady increase in the incidence of CH (defined again with a blood test alone) in the USA [7]. Even though this increased incidence was essentially due to an increased incidence of benign cases, failure to identify the underlying cause of CH through imaging complicates our understanding of the significance of this phenomenon.

This situation illustrates the need for

1. A clear diagnosis with the use of thyroid scintigraphy [8], thyroid echography, or both [9]
2. An assessment of maternal thyroid function and thyroid autoantibodies
3. A molecular diagnosis in either syndromic cases (e.g., Brain-Lung-Thyroid Syndrome [10, 11]) or in cases of familial hyperthyrotropinemia (e.g., TSH-receptor mutations [12, 13])

Thus, even if the benefit of NBS of CH is unquestionable, a thorough diagnostic procedure will help by avoiding CH overdiagnosis due to liberal NBS cutoffs by providing valuable feedback on the performance of NBS. With these premises in mind and considering the recently published guidelines [14], we will discuss in this chapter the epidemiology of CH based on screening, the continuous health burden of CH [15], the initial diagnostic procedure and follow-up, and the emergence of molecular diagnosis and personalized medicine for patients with CH.

4.2 Newborn Screening and Epidemiology of CH

Early detection and treatment of CH through NBS prevents the severe intellectual disability which was frequently observed in the prescreening era, when 8–27 % of CH patients had IQ of less than 70 and the mean IQ was ~85, 15–20 points below the

Table 4.1 Breakdown of CH incidence stratified for diagnostic subgroups in different jurisdictions

CH incidence	Québec, Canada	Milan, Italy	Albert, NZ[a]	Castanet, France		
Period	1990–2009		1993–2010	1980–1998		
TSH threshold (mU/L)	15- 15	15–5	20	12–10	15	Variable over time
Global	1: 2,900	1: 2,450	1: 2,654	1: 1,446	1: 3,850	1: 3,560
Dysgenesis	1: 4,200	1: 4,510	1: 4,740	1: 4,520	1: 6,250*[1]	1: 5,000
Dyshormonogeneis	1: 29,300	1: 37,800	NA	NA	1: 17,000	NA
Normal gland *in situ*	1: 22,250	1: 9,850	NA	NA	NA	NA

[a]Incidence among Caucasians only

population mean [4]. Because primary hypothyroidism is at least 10-fold more common than central hypothyroidism and because only 19 % of cases of central hypothyroidism have T4 below the cutoff [16], primary TSH screening is the most sensitive test [14]. In practice, many jurisdictions use a combination of TSH and T4 strategies with various TSH and T4 cutoffs [1, 17], which explains the differences observed in the reported global incidence. Furthermore, CH is a heterogeneous condition with multiple causes (see chapter BONA_CH etiology) (see reviews [18, 19]). NOSTRO

Therefore, to better compare different NBS screening strategies, firstly the etiological category (established through thyroid scintigraphy) is extremely helpful, and secondly the ethnic composition of the screened population has to be considered, given that thyroid dysgenesis is common in Caucasians but rarely observed in Blacks [20] and that thyroid dyshormonogenesis might be enriched in certain ethnic groups [21] or in ethnic groups with a high rate of consanguinity [22]. Of note, when ethnic background is taken into account, the incidences of thyroid dysgenesis and dyshormonogenesis (i.e., the severe forms of CH) are almost similar across countries (Table 4.1), whereas the incidence of functional CH as defined above varies greatly even within the same jurisdiction using different screening procedures over time [1, 23]. This explains why estimates of global CH incidence vary greatly (1:1,600 to 1:3,500) across the world, whereas the incidence of thyroid dysgenesis (~1:5,000) remains stable within an ethnic group over time [24]. Contrasting with the stable incidence of thyroid dysgenesis [24], that of functional CH may be affected by toxic contaminants such as dioxin. Indeed, slightly increased TSH values have been observed in neonates born to mothers contaminated in 1976 after the Seveso accident [25]. Altogether, to better assess and compare NBS programs, a diagnostic evaluation as complete as possible should follow a positive screening result. Appropriate treatment of confirmed cases is crucial, but follow-up data on health and developmental outcomes should also be collected prospectively.

4.3 Initial Diagnostic Procedure and Follow-Up

NBS is only the start of a process that should lead to diagnosis, management, and outcome evaluation of CH [14]. First, the detection of a high TSH concentration on screening should be communicated quickly to the parents, and the newborn should

be referred to experienced physicians to confirm the diagnosis and to start the treatment as early as possible [26]. Initial work-up should include (1) assessment of venous TSH and free T4, (2) an X-ray of the knee to assess the severity of intrauterine hypothyroidism by the presence or absence of femoral and tibial epiphyses, and (3) either thyroid scintigraphy or echography (or both) to establish the anatomical diagnosis (i.e., ectopy, athyreosis, normal gland, or goiter). Nowadays, it is possible to perform all these diagnostic procedures on the same day to avoid any delay in the initiation of the treatment.

A thorough diagnostic procedure will serve both the patient and the population. First, a clear diagnosis with explanation based on imaging will increase adherence to treatment [27], a point which is not negligible given the high proportion of poorly compliant CH patients, a proportion which may reach as much as 38 % after 36 months of treatment [28]. Second, an accurate diagnosis allows a better assessment of NBS performance and a better assessment of the possible causes of incidence variations [1, 21, 23, 24]. This said, even if advantages of thyroid imaging for the diagnosis of CH are obvious, the diagnosis of all cases of thyroid dysgenesis (even the subclinical cases of thyroid ectopy or hemiagenesis) should not become the new goal of NBS for CH. Indeed, one should keep in mind that some patients with ectopic thyroid maintain normal serum thyroxine throughout life [29] and may not need LT4 treatment. Therefore, it is acceptable that some cases with thyroid ectopy are missed by CH [1]. Immediately after the diagnostic procedures, LT4 should be started. An optimal treatment of CH is essential for neurodevelopment, so reliable L-T4 preparations are crucial [30]. The treatment should be started no later than 2 weeks after birth and an initial dose of L-T4 of 10-15 μg/kg per day is recommended [14]. This practice of early and high dose treatment is based on observational studies [26, 31] and only one randomized controlled trial [32]. However, calls for additional RCTs on this question [33] raise ethical issues. Considering the controversies regarding the reliability of generic L-T4 [34, 35], brand rather than generic L-T4 tablets should be used [14] and switching brands (with inherent variable bioequivalence) should be avoided, as it requires additional blood draws to measure TSH levels [30]. The first follow-up visit should take place 2–3 weeks after initiation of L-T4 treatment, at which time the TSH level should be normalized. The patients should then, be followed every 1 to 3 months until 1 yr of age, and every 2 to 4 months until 3 yrs of age; during these visits, assessment of global development is important, and we suggest that infants with severe CH should be referred to the audiologist given the high proportion of hearing impairment in CH patients (see paragraph below) [36]. Thereafter, evaluations should be carried out every 6 to 12 months until growth is completed.

4.4 Continuous Health Burden of CH

Since the 1970s, NBS for CH followed by appropriate treatment allows most affected children to attain their full intellectual potential, with one tablet of thyroid hormone daily. However, intellectual disability may still be observed, especially in

severely affected children, and this is reflected, in some cohorts, in a mean loss of 10 IQ points compared to controls drawn from the general population [37]. Although milder than in the prescreening era, such mean loss of intellectual potential has significant social and economic impact when aggregated across hundreds of individuals [15, 38, 39]: given that (1) thyroid ectopy and athyreosis account for 60 % of CH cases and that (2) each IQ point raises worker productivity by 1.7 to 2.3 % (for a lifetime earning of 700,000$), we estimate (for a country of 35 million inhabitants such as Canada) a global economic benefit of 1–1.3 million $ per year for each IQ point gained in patients suffering from severe CH, i.e., thyroid ectopy and athyreosis [38]. Even early high-dose thyroxine treatment cannot fully prevent neurocognitive deficit in the most severe cases [40]. Moreover, a fourfold increase of hearing impairment is observed in the French national cohort of CH patients [36, 39]. Consistent with the neurocognitive deficit reported in the Swiss cohort [37, 40], Leger et al. reported that male patients with athyreosis and with low socioeconomic background have an increased likelihood of not graduating from high school [39]. Of note, even if CH prognosis has improved considerably over time, some patients diagnosed in the early years of screening displayed comorbidity and mortality due to various neurodevelopmental disorders and associated malformations [41]. Finally, lower fertility has recently been reported in women (but not in men) suffering from the most severe form of CH [36].

All these data should remind us that, 40 years after the first implementation of routine screening, the health burden of CH has not disappeared, perhaps because the cause of the severe forms of CH (i.e., mainly thyroid ectopy and athyreosis) remains mostly unknown. This represents a critical barrier to further improving the outcome of CH. It is therefore important to consider the role of possible genetic markers in making an even earlier diagnosis of these most severe forms of CH.

4.5 New Persepctives: Emergence of Molecular Diagnosis and Personalized Medicine for Patients with CH?

The genetic causes of dyshormonogenetic goiters are well described, and these conditions follow classical Mendelian models of inheritance (reviewed in [19]). Those of functional CH are being unraveled and have significant clinical implications: the demonstration of a heterozygous mutation in TSHR may justify stopping treatment with thyroxine, on the basis that the persistent hyperthyrotropinemia overcomes the TSH resistance [13]. The finding of mono- or even biallelic inactivation of *DUOX2* also justifies testing treatment withdrawal, since CH may be transient [42].

On the other hand, the majority of cases of thyroid dysgenesis (thyroid ectopy and athyreosis being the most frequent and severe) have no identified genetic cause. Underscoring the lack of clear genetic determinants is the fact that thyroid dysgenesis is predominantly not inherited (98 % of cases are sporadic [43]); thyroid dysgenesis also has a high discordance rate (92 %) between monozygotic (MZ) twins and a female and ethnic (Caucasian) predominance [20, 44]. Germline mutations in the thyroid-related transcription factors NKX2.1, NKX2.5, FOXE1, and PAX-8

have been identified by candidate gene screening in at most 3 % of patients with sporadic thyroid dysgenesis [19, 45]. Linkage analysis has excluded these genes in rare multiplex families with thyroid dysgenesis [46]. Moreover, evidence of non-penetrance of mutations in genes such as *NKX2.5* in close relatives of patients [47] suggests that modifiers, possibly additional germline mutations such as copy number variants (CNVs) and/or somatic mutations, are associated with thyroid dysgenesis. Indeed, a higher rate of CNVs is expected in congenital disorders [48], and Thorwarth et al. found a high rate of CNVs in thyroid dysgenesis but exclusively in athyreosis and thyroid hypoplasia [49]. Even though this study did not find recurrent CNVs and did not show any functional analyses, it provides the "proof of concept" that differences in gene copy number could account for the small heritable component of thyroid dysgenesis and shows that it is reasonable to use a higher-resolution platform to screen for CNVs and single-nucleotide variants (SNVs) in thyroid dysgenesis. Given the unprecedented high sensitivity of these "omics" methods, functional studies are now necessary to assess the pathogenicity of the genetic variants identified, and in this respect, the zebrafish model has proven its utility [50, 51].

Conclusion

Intellectual disability, health impairment, and increased mortality may still be observed in a subset of patients with CH despite the universal NBS and early treatment of this condition [36, 37, 39, 41]. To better treat children with thyroid dysgenesis, we need to (1) diagnose them even earlier, (2) better predict the severity and extent of potential neurocognitive deficits as well as the presence of additional developmental abnormalities unrelated to CH *per se*, and (3) propose even better treatment avoiding under- and overtreatment [52]. It is therefore crucial to better understand the cause of thyroid dysgenesis that future studies focus on the biological mechanisms responsible for thyroid dysgenesis (i.e., the severe forms of CH for which data clearly show that early treatment provides neurodevelopmental benefits) and for which NBS was originally implemented. Hopefully, this will generate novel therapeutic modalities for children affected with severe CH.

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