Consequences of the Use of Low Blood-spot Thyroid-stimulating Hormone Cut-offs for the Neonatal Screening of Congenital Hypothyroidism

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Abstract

The consequences of using low blood-spot thyroid-stimulating hormone (b-TSH) cut-off values for newborn screening of congenital hypothyroidism (CH) are largely unknown. Therefore, the impact on CH epidemiology and classification generated by the introduction in our Italian region of a low b-TSH cut-off during 1999–2005 was retrospectively examined. This work was recently performed in collaboration with the Laboratory for Neonatal Screening and the Principal Follow-up Centre of the Lombardy region. The incidence of CH in this Italian population was 1:1,446 live births, with a predominance of functional over morphogenetic defects. The use of low b-TSH cut-offs allowed the detection of an unsuspected number of children with neonatal hypothyroidism, evolving to mild permanent thyroid dysfunction later in life. Premature birth was associated with a three- to five-fold increased risk of CH with gland *in situ*.

Keywords

Newborn screening, congenital hypothyroidism, thyroid-stimulating hormone, thyroid dyshormogenesis, thyroid dysgenesis, premature birth

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Congenital hypothyroidism (CH) is the most common congenital endocrine disease and avoidable cause of severe mental retardation. L-thyroxine supplementation started by two to three weeks of age can prevent severe neurological damage. Thus, in economically advanced countries, neonatal screening programmes have been instituted to allow early CH detection and initiation of therapy.

In the mid-1970s, a newborn screening programme for CH was started in Quebec and rapidly developed in other countries.[1–4] Two principal screening strategies have been followed: a primary thyroid-stimulating hormone (TSH) method, more common in Europe, Japan and Oceania, and a primary T4 method, more common in North America. The use of these strategies has allowed the early detection of a larger number of CH cases, with a currently reported incidence of 1:3,000–4,000 newborns.[1–4] A recent European survey on about 6 million newborns, mostly screened using a primary TSH method, reported an overall incidence of 1:2,709.[5] In 1987–2003, the Italian CH Registry reported a national incidence of 1:2,500 out of about 7,520,000 live newborns.[6]

The current understanding of CH indicates that morphogenetic defects (athyreosis, ectopy, hemiagenesis or hypoplasia) account for about 75% of total cases. The remainder have a thyroid gland *in situ* (GIS) that may be associated with either transient or permanent functional defects.[1–8] This classification is based on the experience with screening programmes using primary T4 determination or TSH cut-off values of 20–40mU/l in the dry blood-spot. These strategies have been followed mainly in order to avoid excessive recall rates and limit costs, and were justified by the general assumption that milder CH forms are devoid of neurological consequences. However, definitive proof for this hypothesis is lacking.

Considerable advances in the analytical performance of TSH measurements have been made during recent years, and highly sensitive TSH assays are now largely employed as the first-line test for thyroid function.[9] As a direct consequence of such analytical improvements, lowering of the upper limit of normal range for TSH determination has been recommended.[9,10] Thus, all of these considerations justify studies aimed at investigating the impact that more sensitive screening strategies may have on the incidence and clinical classification of the disease.

The screening centre in the Lombardy region uses a primary TSH method for the screening of about 89,000 newborns per year. This reference centre chose to shift the blood-spot TSH (b-TSH) cut-off level from 20mU/l down to 12mU/l in 1999 and to 10mU/l in 2002. The thyroid function parameters and clinical features at birth of all children born over a seven-year period in Lombardy were retrospectively analysed with the aim of verifying the impact of lower b-TSH cut-off values on the epidemiology and clinical classification of CH.[11]

Results and Discussion

During 1999–2005, in Lombardy 629,042 newborns were screened for CH using low b-TSH cut-offs (12/10mU/l). The main results are illustrated in *Table 1* and *Figure 1*. We found a CH incidence of 1:1,446 live newborns, which is at least double that currently reported in textbooks.[1–8] Indeed, using the virtual cut-off values of

Table 1: Overall Results of the Newborn Screening Programme for Congenital Hypothyroidism in Lombardy Between 1999 and 2005

b-TSH Cut-off (mU/l)	Positive Cases Detected by Screening	Positive Cases with Transient/ Permanent hyperTSH	Positive CH Cases on L-T4 Therapy	CH Incidence
12–10	1,013	578	435	1:1,446
20 (virtual)	280	45	237	1:2,654

The total number of screened newborns was 629,042. Blood-spot thyroid-stimulating hormone (b-TSH) cut-off values for the first determination on blood-spot were 12mU/l in the period 1999–2002 and 10mU/l in the period 2003–2005. A total of 435/1,013 candidate newborns (43%) were found to be hypothyroid and started 3,5,3,5-tetraiodo-L-thyronine (L-T4) treatment (true congenital hypothyroidism [CH]). The category of positive newborns with hyperthyrotropinemia (hyperTSH) includes the cases positive at the second TSH determination in whom L-T4 treatment was not started because hypothyroidism was not confirmed by the follow-up centres. The results of the screening that would had been obtained in the same period (1999–2005) with the virtual cut-off of 20mU/l are reported in the bottom row for comparison.

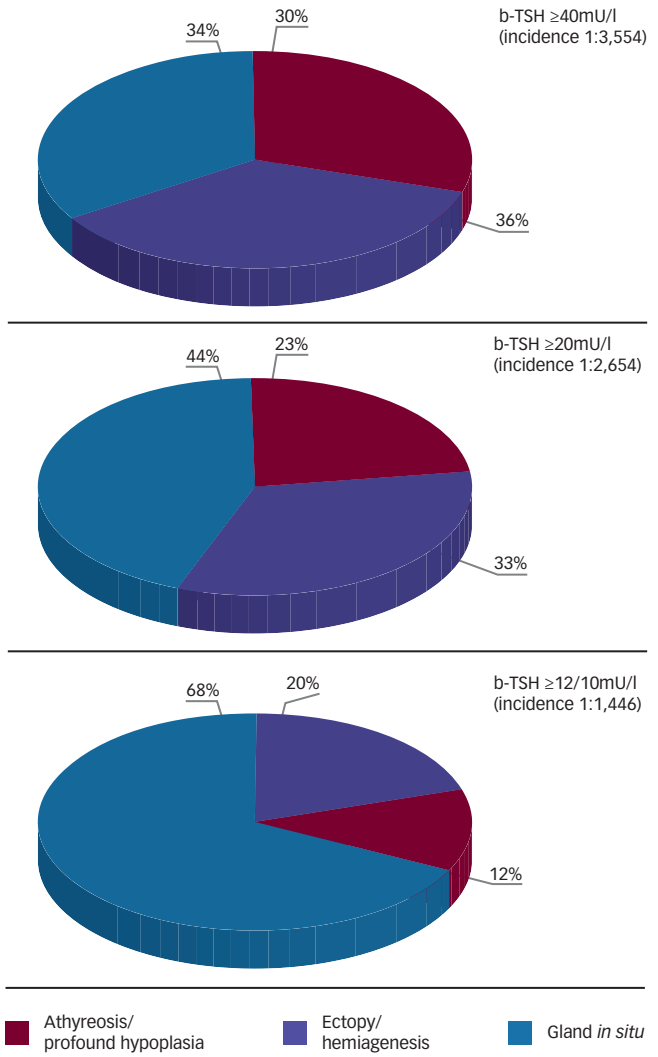
20 or 40mU/l, the CH incidence was 1:2,654 and 1:3,554 newborns, respectively. Importantly, 45% of CH newborns in this series, including a considerable number of cases with thyroid ectopy or hemiagenesis (8.5% of all dysgenesis), would have been missed using the virtual cut-off of 20mU/l. The illustrated approach dramatically raises the sensitivity for the detection of hypothyroid newborns with GIS, who accounted for about two-thirds of the examined CH population (see *Figure 1*).

In order to confirm the diagnosis of CH, TSH and free thyroxin index (FT4) were measured in serum at a median age of 10 days of post-natal life. Serum biochemical data indicated that the use of low b-TSH cut-offs led to the early detection of a true CH population with neonatal hypothyroidism.[11] Indeed, only 25% of the CH cases with GIS had serum FT4 within the normal range (>1.5ng/dl). Therefore, the large majority of positive cases had serum parameters of thyroid function in the hypothyroid range in the early post-natal period, when higher thyroid activity is required for adaptation to extrauterine life and growth and for neurological development.

Since defective neurological development is the main consequence of untreated congenital hypothyroidism,[3,12] L-thyroxine was cautiously given to all confirmed hypothyroid infants. The indication to give treatment as early as possible to these positive infants is emphasised by the observations of impaired psycho-neurological outcome and subtle cognitive deficits in the treated CH population compared with unaffected siblings[13–17] and by the impaired intellectual development described in transient neonatal hypothyroidism and hyperthyrotropinaemia.[18,19] On this basis, it is conceivable that a significant number of behavioural/neurological disorders (e.g. attention-deficit disorder) nowadays recognised later in life might be due to missed forms of neonatal CH. In support of this hypothesis is the recent report of a patient with a defect in the *DEHAL1* gene who presented mental retardation due to the missed neonatal diagnosis of CH with a b-TSH value of 15mU/l at the newborn screening.[20]

Re-evaluation of a representative consecutive cohort of 59 GIS patients at three to five years of age revealed that 78% had a permanent thyroid defect.[11] These findings are consistent with the surprisingly elevated prevalence of innate disorders of thyroid function and with recent data describing the presence of genetic defects in several CH cases evolving in milder forms of permanent non-autoimmune thyroid dysfunction later in life.[7,8,21–24] Among these, of particular relevance is the high frequency of iodide organification defects (IODs). Indeed, if these mild thyroid defects remain unrecognised, they may generate other morbidities later in life, i.e. goitre, abnormalities of lipid metabolism, heart function and linear growth, as well as potentially causing maternal hypothyroidism during pregnancy, which could hamper the neurological development of the offspring.[25]

Figure 1: Classification of Congenital Hypothyroidism According to Different Blood-spot Thyroid-stimulating Hormone Cut-off Values



Observe the prevalence of dysgenetic congenital hypothyroidism (CH) if the virtual blood-spot thyroid-stimulating hormone (b-TSH) cut-offs of 20 and 40mU/l were used and the shift towards a higher incidence of confirmed CH and a higher prevalence of gland in situ *(GIS) defects in the same newborn population by lowering the b-TSH cut-off (12mU/l in 1999–2002 and 10mU/l in 2003–2005).*

The lower threshold for screening led to an impressive modification of CH epidemiology[11] (see *Figure 1*). It is likely that environmental factors may contribute to the elevated incidence of functional defects by uncovering mild forms of thyroid hormonogenesis in predisposed individuals. Iodide deficiency is the environmental factor

most widely associated with an increased prevalence of CH. Analysis of the prevalence of b-TSH values above 5mU/l unexpectedly revealed that Lombardy, one of the richest regions in Europe, is still characterised by a borderline mild iodide deficiency over the last 10 years (5.4–6.3%; optimal iodide supply <3%).[26,27]

Besides low iodine intake, other mechanisms possibly contributing to the high incidence of functional defects include thyroid-disrupting chemicals and premature birth. Very recently, higher neonatal TSH values were reported in babies born in Lombardy from mothers exposed 25 years previously to dioxin contamination during the famous Seveso accident in 1976,[28,29] suggesting that contaminants may have contributed to our findings. In addition, our data revealed the frequent association of CH with premature birth, which represents a condition with a three- to five-fold increased risk of CH with GIS.[11] Children born prematurely were reported to be predisposed to non-autoimmune thyroid dysfunction as a likely consequence of the defective maturation of the hypothalamic–pituitary–thyroid axis.[30] Therefore, hypothyroidism should be included among the frequent consequences of premature birth and may contribute to the developmental defects affecting children born prematurely.[31–33] The number of premature children has grown rapidly in recent years and survival of very pre-term infants is nowadays increased.[32,33] For these reasons, an appropriate strategy of blood sampling with a default second determination of TSH during the third week of post-natal life is highly recommended for CH screening purposes in premature babies. This allowed the possible drawback of delayed TSH rise to be overcome in most premature babies and the initiation of treatment within the fourth week in positive cases.

Children born prematurely were reported to be predisposed to non-autoimmune thyroid dysfunction as a likely consequence of the defective maturation of the hypothalamic–pituitary–thyroid axis.

To our knowledge, our findings[11] are the first to give support to the indication by the National Academy of Clinical Biochemistry (NACB) for the use of lower TSH cut-offs for CH screening.[9,34] The implementation of the NACB recommendations has been hampered mainly by the fear of an unjustified increase in the costs of screening programmes. Nevertheless, we estimated that the reduction of the b-TSH cut-off in 1999–2005 caused an increment of 22% in the number of tests per neonate/year.[11] This increment was the only relevant additional cost raised by the new screening strategy. We believe that this effort may be justified since a previously unsuspected number of newborns with neonatal hypothyroidism were detected at birth. In our experience, the possibility of obtaining a more careful determination of thyroid status in neonates at moderate risk of CH was well-received by most parents.

Low b-TSH cut-offs (<20mU/l) are nowadays used in most European countries[6] and in most screening laboratories in Italy.[11] However, this is accompanied by extremely varied recall rates and CH incidences.[5] Such differences are difficult to explain and we believe that the decision to lower the screening threshold should be taken only after a careful consideration of the quality performances of the laboratories and of the specific territorial characteristics.

In conclusion, we found that the use of a low b-TSH cut-off for neonatal screening is associated with about double the CH incidence previously thought.[11] This is mainly due to the detection of hypothyroid newborns with GIS, later evolving into permanent mild thyroid dysfunction. Premature birth represents a high-risk condition for this type of CH. In contrast to what is currently known, inborn functional defects were noticeably more common than dysgenetic forms in this CH population. Further studies are needed to define the appropriate treatment and follow-up strategy for the large group of CH children who evolve towards mild thyroid dysfunction later in life. ■

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