Neonatal thyroid screening as a monitoring tool for the control of iodine deficiency

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In conditions of iodine deficiency, the frequency distribution of neonatal thyroid-stimulating hormone (TSH) is shifted towards elevated values. Elevated serum TSH in the neonate indicates insufficient supply of thyroid hormones to the developing brain, and therefore constitutes the only indicator that allows prediction of brain damage, which is the main complication of iodine deficiency. This paper reviews studies on neonatal thyroid function in iodine deficiency and confirms the former statement by WHO/UNICEF/ICCIDD that the frequency of neonatal TSH above 5 mU/L blood is below 3% in conditions of normal iodine supply, that a frequency of 3–19.9% indicates mild iodine deficiency and that frequencies of 20–39.9% and above 40% indicate moderate to severe iodine deficiency, respectively. Neonatal thyroid screening appears as a particularly sensitive index in the monitoring of iodine supply at a population level.

Systematic screening for congenital hypothyroidism in the neonate allows the early detection and therapy of infants affected by sporadic, permanent hypothyroidism and, consequently, prevents the development of severe mental retardation (1). In addition, primary thyroid-stimulating hormone (TSH) screening also detects transient disorders of the thyroid function, such as transient hyperthyrotropinemia and transient primary hypothyroidism (2). Both conditions can result in brain damage (3). Their main cause is iodine deficiency (4). Elevated serum TSH in the neonate indicates an insufficient supply of thyroid hormones to the developing brain, and therefore constitutes the only indicator that allows prediction of possible impairment of mental development at the population level, which is the main consequence of iodine deficiency.

This paper discusses the use of neonatal thyroid screening based on primary TSH determination as an indicator of the presence and severity of iodine deficiency and as a monitoring tool in programs of iodine supplementation at a population level.

Neonatal thyroid screening in severe iodine deficiency

In some parts of the world, severe iodine deficiency (iodine intake below 25 μg/d) results in the occurrence not only of endemic goiter but also of a high prevalence of defectives with a clinical and biochemical picture of thyroid failure which is almost entirely similar to the one observed in the past in unrecognized sporadic congenital hypothyroidism (5).

This syndrome has been extensively studied in the central part of Africa (6–8). In this area, the population is submitted to the combined actions of severe iodine and selenium deficiencies and of thiocyanate (SCN) overload. Exposure to SCN results from the chronic consumption of poorly detoxified cassava rich in linamarin, a cyanogenic glucoside whose detoxification in the organism results in the release of thiocyanate, a powerful goitrogenic agent (8). The prevalence of goiter before the implementation of iodine prophylaxis was 76.8%. In addition, 4.3% of the population and up to 10–12% in certain hyperendemic pockets, exhibited a caricatural picture of hypothyroidism with severe retardation in growth, mental and sexual development, puffy features, myxedema, dry and scaly skin and hair. These defectives also had a marked retardation in bone maturation with epiphyseal dysgenesis suggesting that hypothyroidism was already present around or even before birth (7, 8).

Pilot studies including measurements of the serum levels of TSH and thyroid hormones on cord blood confirmed this hypothesis by showing that as many as 1 in 10 neonates had a cord serum TSH above 100 mU/L and a cord T4 below 3 μg/dL (38 nmol/L) (8, 9). These observations suggested that the occurrence of severe hypothyroidism during the critical period of brain development can be predicted and optimally prevented.
thanks to a systematic evaluation of thyroid function at birth. These findings also constituted the starting point of an approach to systematic screening for congenital hypothyroidism in the neonate by our group (10). Other severe endemic goiter areas, complicated by cretinism, also exhibited similar anomalies on cord blood; for example India and, to a lesser extent, Peru (5).

The role played by iodine deficiency in the alterations of neonatal thyroid function and subsequent overt hypothyroidism was demonstrated by the systematic prevention of both anomalies following the implementation of programs of iodine supplementation of the affected populations and especially of the pregnant women (9).

Neonatal thyroid screening in mild and moderate iodine deficiency

It was then reported that similar, although much less important anomalies of thyroid function, and especially of transient elevation of serum TSH at the time of screening for CH, could be found in areas with a less severe degree of iodine deficiency. These studies are reported in detail elsewhere (2, 4, 11). One of the particular aspects of these studies is that the degree of impairment of thyroid function in the neonate was systematically more important than in adults of the same areas. It thus appeared that neonates are more susceptible than adults to the effects of iodine deficiency. One of the reasons for this hypersensitivity is the existence of a particularly small pool of intra-thyroidal iodine in the neonate, whose turnover rate is increased by factors of about 60 and 120 in mild and severe iodine deficiency, respectively (12).

Use of neonatal thyroid screening as a monitoring tool in IDD control

Based on the data available in the literature, the proposal was made to use neonatal thyroid screening programs using primary TSH as a monitoring tool in the evaluation of the degree of iodine deficiency and of the effectiveness of programs of iodine supplementation (13).

In a first step, attention was focused on the use of the recall rate of neonates under suspicion of CH as an index of iodine intake of the population: based on a survey of the data available in Europe in 1986, it could be demonstrated that there was an inverse relationship in populations of newborns between the median urinary iodine used as an index of their iodine intake and the frequency of serum TSH at screening above 50 mU/L blood (20–25 mU/L whole blood spotted on filter paper), i.e. the recall rate under suspicion of CH: the recall rate was below 0.1% when the urinary iodine was above 100 μg/L, indicating iodine repletion. It started to increase when this concentration reached a critical threshold of about 40–50 μg/L and was as high as 10% when this concentration was below 30 μg/L, indicating severe iodine deficiency (14).

Subsequently, the global shift of the frequency distribution of neonatal TSH towards elevated values

<table>
<thead>
<tr>
<th>Country</th>
<th>Frequency (%) of neonatal TSH &gt; 5 mU/L</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Adequate iodine nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia NS Wales</td>
<td>&lt;3</td>
<td>Idem</td>
</tr>
<tr>
<td>Spain Basque region</td>
<td>3.7</td>
<td>Dehera et al. Unpublished</td>
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<tr>
<td>Bulgaria Russe</td>
<td>3.4</td>
<td>Stoeva et al. Exp Clin Endocrinol Diabetes 1997; 107 Suppl 4: 51 (20)</td>
</tr>
<tr>
<td>II. Mild IDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>4.5</td>
<td>Delange. Thyroid 1998; 8: 1185 (12)</td>
</tr>
<tr>
<td>Italy Calabria</td>
<td>14.4</td>
<td>Costante et al. J Endocrinol Invest 1997; 20: 251 (21)</td>
</tr>
<tr>
<td>Spain Aragon</td>
<td>19.5</td>
<td>Dea es et al. Unpublished</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>55?</td>
<td>Kung Clin Endocrinol 1997; 46: 315 (22)</td>
</tr>
<tr>
<td>III. Moderate IDD</td>
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<td></td>
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<td>IV. Severe IDD</td>
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<td>China Guizhou province</td>
<td>39</td>
<td>Shi et al. IDD Newsletter 1998; 14: 36 (24)</td>
</tr>
<tr>
<td>Thailand Chiangmai</td>
<td>59</td>
<td>Rajatanavir et al. Thyroid 1997; 7: 599 (19)</td>
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<td>Georgia</td>
<td>63</td>
<td>Cruse. Unpublished</td>
</tr>
<tr>
<td>Pakistan Peshawar</td>
<td>80</td>
<td>Idem</td>
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</table>

* Based on the WHO/UNICEF/ICCIDD criteria 1994 for prevalence of goiter and urinary iodine (13).
was considered. This curve was frequently represented by cumulative frequencies of neonatal TSH (15, 16). Attention was focused on the frequency of values above a cut-off point of 5 mU/L whole blood, which is approximately the lower limit of detection of TSH from whole blood collected on filter paper when using traditional, relatively insensitive, TSH assays. This cut-off of 5 mU/L is much lower than the one used as criterion for recalling neonates under suspicion of CH.

Table 1 reviews the data from the literature on the frequency of neonatal TSH above the cut-off point of 5 mU/L in conditions of adequate iodine intake (above 100 µg/d), and in conditions of mild (50–100 µg/d), moderate (25–50 µg/d) and severe (less than 25 µg/d) iodine deficiency. In normal conditions, this frequency is below or around 3%. The frequency varies from 4.5% to 19.5% in mild IDD, except for the outlier value of 55% reported from Hong Kong. This frequency is 25–32% in moderate IDD and varies from 39% to 80% in conditions of severe iodine deficiency.

These different data confirm the validity of the proposal made by WHO/UNICEF/ICCIDD in 1994 to include neonatal TSH as an additional indicator of a significant health problem of iodine deficiency (13) (Table 2). The proposal was made that in conditions of adequate iodine nutrition the frequency of neonatal TSH above 5 mU/L should be below 3%. A frequency between 3% and 19.9% would indicate mild IDD. A frequency between 20% and 39.9% would indicate moderate IDD and a frequency above 80% suggests severe IDD.

Increasing information becomes available on the use of neonatal thyroid screening for monitoring the efficiency and sustainability of programs of iodine supplementation at a population level. An elegant example is Poland, where the implementation of a program of iodine supplementation resulted in a shift of the distribution curve of neonatal TSH towards lower values, reaching progressively the type of curve observed in iodine sufficient areas (17, 18).

Another interesting experience is Thailand: Rajatanavanin et al. (19) measured neonatal TSH in many districts of an endemic province in the Northern part of the country. In addition to the frequency distribution curves of neonatal TSH, they also calculated the odds ratios of having neonatal TSH greater than the 95th percentile value of neonatal TSH obtained in Bangkok used as a control area. All values in the province were higher than 1, indicating a shift to the right of the frequency distribution of TSH. They showed that there was a direct correlation between the odds ratios and the prevalence of goiter. They made the additional interesting observation that only some 200 individual values of neonatal TSH are sufficient when the measurements are done sequentially in a given area to see a significant difference at odd ratios of 2. This contribution is particularly interesting from a public health point of view. They showed that as the prevalence of goiter decreased following iodine supplementation, the odds ratios also decreased.

Conclusions

1. Primary thyroid screening for congenital hypothyroidism is a particularly sensitive index in the evaluation of degree of iodine deficiency.
2. Neonatal TSH has the major advantage of being the single indicator allowing prediction of possible impairment of mental development at a population level.
3. Neonatal thyroid screening is also an excellent monitoring tool in the evaluation of the impact of programs of iodine supplementation.
4. However, the implementation of a thyroid screening program raises serious technical and financial problems. Urinary iodine remains the most universal and recommended indicator for the degree and correction of IDD.

References

6. Bastenie PA, Erman AM, Thys O, Beckers C, Schrieck HGVD,
12. Delange F. Screening for congenital hypothyroidism used as an indicator of the degree of IDD and its control. Thyroid 1998; 8: 1185–92