Iodine deficiency and neonatal hypothyroidism*

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The incidence of neonatal hypothyroidism, as reflected in cord-blood thyroxine and thyrotropin levels, varied from 0.6% to 13.3% in iodine-deficient and normal regions of India (selected districts of Uttar Pradesh and Kerala and the city of Delhi), depending on the degree of environmental iodine deficiency. In populations with a high incidence of neonatal hypothyroidism, an increased prevalence of nerve deafness and a shift to the left in the distribution of IQ scores (towards lower scores) have been demonstrated. These indications of mild brain damage suggest that nutritional iodine deficiency can present in other ways than goitre or cretinism. Determination of the incidence of neonatal hypothyroidism using dried cord-blood spot screening appears to be the most useful and reliable method to assess the risk of brain damage in iodine-deficient areas.

The reported incidence of neonatal hypothyroidism in developed countries without iodine deficiency or endemic goitre varies from 1 in 3000 to 1 in 12 000 births (1–3). Recently, we reported a 4% incidence in the Gonda district of Uttar Pradesh, which lies in the sub-Himalayan endemic goitre belt (4–6), and found significantly lower mean thyroxine (T4) values and elevated mean thyrotropin (TSH) values in apparently normal newborns (5, 6). These studies have now been extended to several other areas of India which have varying degrees of iodine deficiency and goitre prevalence. Although screening for neonatal hypothyroidism has not been adopted as a measure to prevent mental retardation in any of the developing countries, we also investigated the intelligence quotients (IQ) of schoolchildren and the prevalence of nerve deafness in the population of two severely iodine-deficient villages in areas with a very high incidence of neonatal hypothyroidism. The results of these studies are described below.

MATERIALS AND METHODS

Screening for neonatal hypothyroidism by randomized sampling was organized in the Gonda, Deoria and Gorakhpur districts of Uttar Pradesh in north India, in the city of Delhi, and in the Aleppey and Quilon districts of Kerala in south India. The districts of Gonda, Deoria and Gorakhpur are situated in the classical sub-Himalayan endemic goitre belt described many years ago by Ramalingaswami et al. (7); endemic goitre and cretinism are still prevalent in these districts (8). Although the city of Delhi is now reported to have pockets of endemic goitre (9), endemic cretinism is not prevalent there. Endemic goitre is not prevalent in the coastal strips of Aleppey and Quilon districts (10).
Assessment of iodine deficiency and prevalence of goitre andcretinism

Goitre prevalence was determined by school and village surveys, using the methods and definitions given by Stanbury (11). Endemic cretinism, as defined by Querido et al. (12), was looked for in the study area during the goitre survey and its prevalence assessed.

The severity of iodine deficiency in a given area was assessed by determining the pattern of urinary iodide excretion (micrograms of iodine per gram of creatinine) in the population, using the criteria defined by Pollis (13). Random urine samples were collected in tightly stoppered wide-mouthed polythene jars, in which toluene was added as preservative. Urinary iodine was estimated by the alkali ash method described by Barker et al. (14) with minor modifications. Creatinine was estimated by the alkaline picrate method.

Organization of screening

The unit of health care delivery at the district level in India is the primary health centre (PHC) which operates through 10 subcentres, each providing a population of 10,000 with mainly maternity and child health services. Screening for neonatal hypothyroidism was organized in the district hospitals, primary health centres, and in the community (subcentres and village level) with the cooperation of auxiliary nurse-midwives and traditional birth attendants who were attached to the subcentres of each PHC. In Delhi the screening was hospital-based.

A randomized sampling method was adopted for the screening, 25% of the PHCs in each district being randomly selected; from these, 25% of the subcentres were selected at random to initiate the screening. As there are on average 16 PHCs in a district, a total of 10 subcentres from the 4 PHCs were incorporated in the screening programme. The total population covered by these 10 subcentres was about 100,000. The annual crude birth rate in the three districts of Uttar Pradesh has been estimated to be 40 per thousand; the total number of births in the 100,000 population under the screening programme, in each district, would therefore be expected to be 4000/year.

Our previous experience shows that serious iodine deficiency (defined as more than 50% prevalence of goitre and of endemic cretinism in the population) is associated with at least a 4% incidence of neonatal hypothyroidism (6). Based on this and the assumption of a 95% confidence interval and 25% relative error, the number of newborns to be screened to assess serious iodine deficiency in a given district can be computed to be roughly 600 to 1200 per year. Thus, 15-30% coverage of the newborns in the 10 subcentres (randomly selected from each district) would be sufficient to make a definitive diagnosis of serious iodine deficiency based on a high incidence of neonatal hypothyroidism in the district.

Using the above guidelines on community-based screening, and also by organizing hospital-based screening wherever feasible, a representative cross-section of newborns were screened in the different study areas. The method of sample collection and techniques of cord-blood hormone assays, including their cost-effectiveness, as well as the criteria for diagnosis of neonatal hypothyroidism in the screening programme, have already been reported (6, 16).

Assessment of intelligence quotient and prevalence of nerve deafness

The impact of iodine-deficiency related neonatal hypothyroidism on brain development in non-cretinous populations was assessed by determining the intelligence quotient (IQ) and the prevalence of nerve deafness among children in two villages with a high incidence of neonatal hypothyroidism. The IQs of primary-school children in the village of K.S. (within the purview of Colonojganj PHC in Gonda district) were assessed using Bhatia's battery of performance tests, Malin's intelligence scale, and the Bender visual motor gestalt tests (15). These tests, which have been adapted for use in Indian villages and are recognized to be culture-free, were carried out in the village school by a trained psychomtrist using the children's own language.

The audiommetric studies were done on 93 subjects (representative cross-section of the population) in a quiet mud hut in the village of Randham (Deoria district) in two stages using a portable, battery-operated, pure-tone audiometer. In stage I, auditory screening was done at 5 dB more than the threshold obtained for the reference subject; tones were presented only once at the predetermined level. In stage II, threshold testing was done with the same instrument, in the same environment, in those subjects who were not able to hear in any of the frequencies used. A standard procedure was employed for threshold tests by air and bone conduction.

RESULTS

The overall prevalence of goitre in the district of Deoria was 80%; while 3-5% cretinism was observed in the seriously goitrous flood-prone villages of this

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Table 1. Assessment of iodine deficiency and incidence of neonatal hypothyroidism in the study areas

<table>
<thead>
<tr>
<th>District or area</th>
<th>Prevalence of goitre (%)</th>
<th>Prevalence of cretinism (%)</th>
<th>Urinary iodine excretion (Follis' group)</th>
<th>Incidence of neonatal hypothyroidism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoria</td>
<td>80</td>
<td>3–5</td>
<td>V</td>
<td>13.3</td>
</tr>
<tr>
<td>Gorakhpur</td>
<td>60–70</td>
<td>0–4</td>
<td>V</td>
<td>8.5</td>
</tr>
<tr>
<td>Gonda</td>
<td>60</td>
<td>0–4</td>
<td>V</td>
<td>7.5</td>
</tr>
<tr>
<td>Delhi</td>
<td>29</td>
<td>0</td>
<td>II &amp; III</td>
<td>0.6</td>
</tr>
<tr>
<td>Kerala</td>
<td>1.3</td>
<td>0</td>
<td>Not studied</td>
<td>0.12</td>
</tr>
</tbody>
</table>

district, the goitre prevalence was less severe and cretinism was rare in some villages that had not been exposed to floods. The urinary iodine excretion pattern observed in this study area was in group V of Follis’ classification. In 1983–84 a total of 1092 newborns were screened from this district (mostly from the Padrauna hospital for women in the Kuberwath PHC); the incidence of neonatal hypothyroidism here was 13.3% (Table 1).

Goitre prevalences of 60–70% were observed in the Gorakhpur and Gonda districts; cretinism was present in several flood-affected villages but there were also a few villages with a lower goitre prevalence and no obvious cretinism. The urinary iodine excretion pattern observed in these two districts was again in Follis’ group V. A total of 1935 newborns from Gonda and 774 newborns from Gorakhpur were screened for neonatal hypothyroidism and the observed incidence was 7.3% and 8.5%, respectively (Table 1).

The overall goitre prevalence in Delhi as reported by the National Goitre Control Programme is 29%; the pattern of urinary iodide excretion observed by us in Delhi was in Follis’ group II and III in different regions. A total of 1024 newborns were screened from Delhi during the period of the study; the overall incidence of neonatal hypothyroidism was 0.6% (Table 1).

The mean goitre prevalence in the coastal strips of Alleppey and Quilon in Kerala was 1.3%. More than half of these swellings were solitary nodules, histologically identifiable as follicular adenoma (10), and no syndrome resembling endemic cretinism was observed. The urinary iodine excretion pattern could not be studied, but the absence of endemic goitre practically excluded environmental iodine deficiency in this region. A total of 1440 newborns were screened for neonatal hypothyroidism; the overall incidence observed was 0.12%.

**IQ evaluation and audiometry**

Table 2 gives the results of IQ evaluation in the primary-school children of village K.S. (Gonda district) where the incidence of neonatal hypothyroidism was 15%. The IQ scores observed indicate a clear shift to the left (lower IQs) in both age groups, more than 23% of the children studied having scores below 70 and a third with scores ranging from 70 to 79. Our findings indicate borderline mental subnormality in

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of children studied</th>
<th>≤69</th>
<th>70–79</th>
<th>80–89</th>
<th>90–109</th>
<th>110–119</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–10</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>11–16</td>
<td>50</td>
<td>12</td>
<td>17</td>
<td>11</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>14</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Percentage in study population</td>
<td></td>
<td>23.3</td>
<td>33.3</td>
<td>25</td>
<td>16.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Percentage in normal populationa</td>
<td></td>
<td>2.2</td>
<td>6.7</td>
<td>16.1</td>
<td>50.0</td>
<td>16.1</td>
</tr>
</tbody>
</table>

a Age-matched from normal (not iodine-deficient) Indian villages
more than half the schoolchildren in the study population.

The results of audiometry in the village of Ramdhani in Deoria district (with a goitre prevalence of 95%) showed that 18 of the 93 subjects had a sensorineural hearing loss and only one had conductive loss. This 20% prevalence of nerve deafness is striking because the main type of deafness in Indian villages is conductive and due to middle ear disease (Dr S. K. Kakkar, personal communication, 1985).

DISCUSSION

Our results permit the following conclusions:

(a) the incidence of neonatal hypothyroidism, as reflected in cord-blood thyroxine and thyrotropin levels, is significantly higher in regions with iodine deficiency and endemic goitre;

(b) the incidence of neonatal hypothyroidism varied from 0.6% to 13% depending on the severity of iodine deficiency, as assessed by the pattern of urinary iodide excretion, as well as the prevalence of goitre and cretinism in the affected population;

(c) in areas with a high incidence of neonatal hypothyroidism due to iodine deficiency, cretinism may be present but milder degrees of neurological damage will affect a substantial proportion of the population.

High incidence of neonatal hypothyroidism in iodine-deficient areas with endemic goitre and/or cretinism have been reported from other countries. Thilly et al. (17) reported 10% incidence in Zaire, as reflected in cord-blood hormone levels at birth; a good proportion (10–20%) of these children remained hypothyroid in the post-weaning period and ended up as myxoedematous cretins. According to these authors, the continued hypothyroidism through childhood and adolescence was due to cassava consumption by these patients which aggravated the iodine-deficient state.

Sava et al. examined the cord blood from 180 newborns from a region of Sicily with endemic goitre and cretinism and reported 9.3% incidence of neonatal hypothyroidism at birth. On following up these children for a period of 6 weeks to 10 months, they found transient hypothyroidism which lasted for more than 12 weeks in a significant proportion.

The question of transient hypothyroidism is important in assessing the degree and extent of hypothyroidism in an iodine-deficient environment. The actual proportion of the detected newborns with hypothyroidism, who are likely to fall in the category of transient hypothyroidism in a given environment, has to be evaluated by careful follow-up of these infants without treatment. However, this was neither feasible in the present study nor was it considered ethical by us. We invariably provided thyroxine for treatment, free of cost, to all detected newborns as soon as we could make this available to them.

The following observations indicate that the detected newborns with hypothyroidism may continue long enough postnatally to end up with significant neurological damage: (a) the severe degree of hypothyroxaemia observed in our study; (b) the severity of iodine deficiency in the study areas and the demonstrated low iodine content in the breast milk of the mothers in these areas (Kochupillai, unpublished observations); and (c) the evidence of significant mild brain damage in a striking proportion of children in areas with a high incidence of neonatal hypothyroidism. Nerve deafness and mental subnormality are well recognized features of neurological damage caused by iodine deficiency. These facts, when taken together, can be interpreted to mean that environmental iodine deficiency is causing much more brain damage than is evident by overt cretinism in the millions of people living in the sub-Himalayan endemic goitre belt.

In our experience, determination of the incidence of neonatal hypothyroidism by measuring the cord-blood thyroxine levels at birth is the most useful and reliable method to assess the risk of brain damage to infants and children growing up in an iodine-deficient environment. We have also shown that this method can be adopted successfully and cost-effectively in developing countries (6, 16); it should therefore be an important component of programmes to control iodine-deficiency disorders in these countries.

RÉSUMÉ

CARENCE IODÉE ET HYPOTHYROÏDIE NÉONATALE

L'incidence de l'hypothyroïdie néonatale a été évaluée, d'après les taux de thyroxine et de thyrotrophine dans le sang du cordon, dans différentes régions de l'Inde avec ou sans carence iodée d'origine environnementale. Les échan-
Follis (1964) d’après l’excrétion urinaire d’iode dans la population. Dans deux villages où la carence iodée est forte et où l’incidence de l’hypothyroïdie néonatale est élevée, on a évalué les troubles neurologiques liés à la carence iodée en prenant comme critères la prévalence de la surdité de perception et le quotient intellectuel (QI) des écoliers.

Nos résultats montrent: a) une incidence de l’hypothyroïdie néonatale allant de 0,6% à 13,3%, selon la gravité de la carence iodée dans la région; et b) une prévalence de 20% de la surdité de perception chez les villageois ainsi qu’un très net déplacement vers la gauche (vers des valeurs plus faibles) de la distribution des QI parmi les écoliers des villages à forte incidence d’hypothyroïdie néonatale.

Ces résultats tendent à montrer que la carence iodée d’origine environnementale constitue un problème de santé publique beaucoup plus grave que ne l’indique l’incidence du goitre ou du cétotisme et qu’elle peut gravement compromettre les ressources humaines de pays en développement où vivent des millions de personnes. Le dépistage de l’hypothyroïdie néonatale est réalisable et pourrait être appliqué avec profit dans ces pays dans le but d’évaluer le risque de lésions cérébrales dans les environnements pauvres en iodé.

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