Endemic cretinism in Thailand: a multidisciplinary survey

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Abstract

Endemic cretinism has been classified into neurological and myxedematous types. Profound mental deficiency, deaf-mutism and cerebral diplegia are predominantly found in the former. The latter have been described as less mentally retarded but with severe growth retardation and myxedematous features. The pathogenesis of different clinical types of endemic cretinism is still unclear. Recently, a unifying hypothesis suggested that iodine deficiency, severe enough to cause maternal and fetal hypothyroxinemia, results in neurological defects in all cretins.

We conducted the present study in northern Thailand to determine the validity of this hypothesis in another geographical area. The study consisted of a multidisciplinary survey on 112 endemic cretins aged 2–66 years in Nan. They were categorized clinically into three types of endemic cretins, neurological (n = 57), myxedematous (n = 19) and mixed form (n = 36). The subjects were generally short and the majority had severe mental retardation (mean intellectual quotient (I.Q.) 30.8 ± 8.8), psychomotor defect and profound sensorineural hearing loss. The I.Q. score and proportion of cretins with sensorineural hearing loss and psychomotor defect were similar among the three types of cretins. The most frequent neurological abnormalities were spasticity, hyper-reflexia, the presence of primitive reflexes and gait disturbance. These abnormalities were distributed equally among the three types of endemic cretins. Delayed skeletal maturation and abnormal epiphysis were also present in all types of cretins. However, myxedematous cretins were shorter (P < 0.01), having more myxedematous features (P < 0.05 to P < 0.001) and less sexual maturation (P < 0.05). Thyroid volume was lower in cretins with hypothyroidism (P < 0.01).

In conclusion, our findings support the hypothesis that neurological features are present in all types of cretins, and are the consequence of maternal and fetal hypothyroxinemia due to severe iodine deficiency. The clinical manifestations of the cretins were subsequently modified by the length and severity of postnatal iodine deficiency and hypothyroidism.

Introduction

Endemic cretinism is the most severe result of iodine deficiency. It has been classified into two clinical types, neurological and myxedematous cretinism (1). Neurological cretins are characterized by profound mental deficiency, deaf-mutism, cerebral diplegia but clinical euthyroidism. In contrast, myxedematous cretins are traditionally described as less mentally retarded but with severe growth retardation and other signs of hypothyroidism. The prevalence of different types of endemic cretinism also varies geographically. Myxedematous cretins are primarily found endemic in Nepal, central Africa and western China (2–4) while neurological cretins are more ubiquitous.

There is controversy about the pathophysiology of the different types of endemic cretinism and also about their different geographical distribution (5), and it has been claimed that a single theory cannot explain all the abnormalities observed. Recently, Boyages & Halpern (6) have proposed a unifying hypothesis for the pathophysicsiology of endemic cretinism based on their extensive study of endemic cretinism in western China (7). They found that, contrary to common belief, the degree of mental retardation and the frequency of neurological abnormalities are found in both types of endemic cretinism. They suggested that all neurological abnormalities occurred in utero due to both maternal and fetal hypothyroxinemia secondary to severe iodine deficiency. Postnataally, the persistence of hypothyroidism, either from continuing iodine deficiency or other mechanisms causing thyroid failure, entails the development of myxedematous cretinism.

Endemic cretinism is present in northern Thailand. We conducted a multidisciplinary survey, namely clinical, biochemical, audiological, psychological and radiological examination of endemic cretinism, in the Nan province. Our purpose was to determine the validity of the unifying hypothesis of endemic cretinism proposed by Boyages & Halpern (6).
Subjects and methods

Study area

Nan province is situated in the northern mountainous area of Thailand. The total goiter rate in Nan was 36.4% and the total number of cretins was 456. The prevalence of cretinism was as high as 0.1% in one district (8). The study was performed in three districts, Pua, Toongchang and Santisuk.

Classification of cretins

One hundred and twelve cretins were recruited by local health officers. They were then examined by local physicians who classified them into three classical types, neurological, myxedematous and mixed types, by a standard guideline based on the definition of endemic cretinism proposed by the Pan American Health Organization (9). The demographic data of the cretins in this study is shown in Table 1.

Multidisciplinary examination

A research team from the Ramathibodi Hospital comprised of adult and pediatric endocrinologists, neurologists, an otolaryngologist, psychologists and a radiologist examined the cretins without prior knowledge of their classification.

General physical and endocrinological examinations were extensively performed, including goiter palpation and assessment of testicular size in men by orchidometry. Full neurological and detailed otolaryngologic examinations were also performed. Hearing ability (air and bone conduction threshold (frequencies 250–8000 Hz) was measured by a portable clinical pure tone audiometer (Maico, USA) which had been calibrated per Ansi standard, USA of 1969, ISO 1978, and 1981.

Intellectual quotient (I.Q.) was assessed by the Arthur point scale of performance test (10) and visual-perceptive neuromuscular ability was assessed by the Bender Gestalt Test (11).

Radiological examinations included plain X-rays for lateral skull, hips and left hands. The degree of bone maturation was assessed by the criteria of Greulich & Pyle (12). Goiter volume was determined by ultrasonography using a portable ultrasonography machine (Hitachi EUB 200) with a 5 MHz transducer. Calculation of goiter volume was based on Brunn’s equation (13).

Blood was collected from all cretins and sera were kept frozen for the determination of thyroxine (T4), free T4 and thyrotropin (TSH) concentrations. Serum T4 was measured by the Amerlex-M T4 kit from Johnson & Johnson Clinical Diagnostics Inc., USA. Serum-free T4, T3 and TSH concentrations were measured by chemiluminescent assays (Johnson & Johnson Clinical Diagnostics Inc.) Serum anti-TPO and anti-Tg antibodies were determined by RIA (RSR Ltd, UK). The cut-off level for positive anti-TPO and anti-Tg antibodies was 0.3 U/ml.

Statistical analyses

Comparisons between groups were evaluated by Student’s t-test for normal distribution data or Mann–Whitney rank sum test for skewed data. ANOVA was

Table 1 Demographic data of endemic cretins in this study. Values are means ± s.d. with the range in parentheses.

<table>
<thead>
<tr>
<th>Types of endemic cretins</th>
<th>Neurological (n = 57)</th>
<th>Myxedematous (n = 19)</th>
<th>Mixed (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.2 ± 12.6</td>
<td>39.6 ± 17.8</td>
<td>33.6 ± 9.5</td>
</tr>
<tr>
<td>(13–66)</td>
<td>(2–64)</td>
<td>(13–50)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>149.0 ± 8.6</td>
<td>131.5 ± 22.4</td>
<td>144.4 ± 9.6</td>
</tr>
<tr>
<td>(110–163.5)</td>
<td>(79–153)</td>
<td>(121–160.7)</td>
<td></td>
</tr>
<tr>
<td>Sitting height (cm)</td>
<td>79.5 ± 4.5a</td>
<td>70.4 ± 10.6b</td>
<td>78.5 ± 5.1</td>
</tr>
<tr>
<td>(62–87.5)</td>
<td>(49–81)</td>
<td>(61.5–87)</td>
<td></td>
</tr>
<tr>
<td>Arm span (cm)</td>
<td>152.2 ± 9.6</td>
<td>132.4 ± 23.9</td>
<td>149.9 ± 11.8</td>
</tr>
<tr>
<td>(111–169)</td>
<td>(73.5–158)</td>
<td>(121–172)</td>
<td></td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>54.5 ± 6.4</td>
<td>52.9 ± 2.1</td>
<td>54.2 ± 2.0</td>
</tr>
<tr>
<td>(46–89)</td>
<td>(47–55.2)</td>
<td>(46.5–58)</td>
<td></td>
</tr>
</tbody>
</table>

a P < 0.01 compared with myxedematous cretins; b P < 0.01 compared with mixed cretins.

Table 2 I.Q. scores and proportion of endemic cretins with psychomotor defects. Data are means ± s.d.; the numbers in parentheses are ranges.

<table>
<thead>
<tr>
<th>Types of endemic cretins</th>
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<th>Myxedematous (n = 19)</th>
<th>Mixed (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.Q.</td>
<td>32.3 ± 9.38</td>
<td>30.6 ± 8.3</td>
<td>28.6 ± 7.8</td>
</tr>
<tr>
<td>(14–61)</td>
<td>(13–43)</td>
<td>(10–55)</td>
<td></td>
</tr>
<tr>
<td>Proportion of cretins with psychomotor defect (%)</td>
<td>22.8</td>
<td>5.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Borderline</td>
<td>75.4</td>
<td>94.7</td>
<td>88.9</td>
</tr>
<tr>
<td>Defective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear Sensoneural hearing loss (%)</td>
<td>8.8</td>
<td>5.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Mild–moderate</td>
<td>12.3</td>
<td>26.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Moderate–severe</td>
<td>73.7</td>
<td>57.9</td>
<td>72.0</td>
</tr>
<tr>
<td>Profound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conductive hearing loss (%) –</td>
<td>–</td>
<td>5.3</td>
<td>–</td>
</tr>
<tr>
<td>Left ear Sensoneural hearing loss (%)</td>
<td>12.3</td>
<td>5.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Mild–moderate</td>
<td>22.8</td>
<td>47.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Moderate–severe</td>
<td>59.6</td>
<td>42.1</td>
<td>63.9</td>
</tr>
<tr>
<td>Profound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conductive hearing loss (%) –</td>
<td>–</td>
<td>5.3</td>
<td>–</td>
</tr>
</tbody>
</table>
used for comparison between subgroups. Differences between two proportions were evaluated by chi-square analysis. All statistical calculations were done by computer using the Statistical Package for the Social Sciences Program.

Results

General physical appearances and endocrine manifestations

All three types of cretins were shorter than age-matched normal Thai subjects (14). However, myxedematous cretins were shortest (Table 1).

Myxedematous features were found more in myxedematous cretins as demonstrated in Fig. 1. Also, less sexual maturation as indicated by a smaller testicular volume was observed in myxedematous cretins (Fig. 2).

Psychological examination

The majority of cretins had severe mental retardation with a mean I.Q. score of 30.8 ± 8.8. The I.Q. score and proportion of cretins with a psychomotor defect were similar among the three types of cretins as demonstrated in Table 2.

Otology-audiology examination

The proportion of cretins with bilateral sensorineural hearing loss was similar among the three types of cretins. This was also the case with conductive hearing losses (Table 2).

Neurological examination

Different types of neurological abnormalities were observed in all three types of cretins. Notably, defects in extrapyramidal tract and primitive reflexes were most frequently present. The details of neurological abnormalities are provided in Table 3. The proportion of cretins with abnormal neurological signs were not different among the three types of cretins. However, the number of cretins with motor abnormalities (weakness and spasticity) was greater in mixed cretins (Fig. 3).

Biochemical findings

Data on serum $T_4$, free $T_4$, $T_3$ and TSH concentrations and thyroid autoantibodies are demonstrated in Table 4. Myxedematous cretins had lower serum $T_4$ and free $T_4$ levels than neurological cretins, and lower serum $T_3$ levels than mixed cretins. Myxedematous cretins also had the highest levels of serum TSH. The percentage of
cretins with detectable circulating thyroid autoantibodies was similar among the three types of cretins.

**X-rays findings and ultrasonography**

The number of cretins with abnormal X-rays was not different among the three types (18%, 44%, and 32% in neurological, myxedematous and mixed cretins respectively). The abnormalities included coxa vara, coxa valga, stripped epiphyses, enlarged sella turcica and delayed bone age.

Cretins were classified into two groups according to their thyroid function test. The euthyroid group consisted of 95 cretins and the hypothyroid group 17 cretins. The mean serum \( T_4 \) and TSH levels in the euthyroid cretins were \( 94 \pm 21 \, \text{S.D.} \, \text{nmol/l} \) and \( 1.3 \pm 0.7 \, \text{mU/l} \) respectively and the levels in the

<table>
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<th>Myxedematous ((n = 19))</th>
<th>Mixed ((n = 36))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_4 ) (nmol/l)</td>
<td>101 ± 40</td>
<td>75 ± 31</td>
<td>96 ± 27</td>
</tr>
<tr>
<td></td>
<td>(52–338)</td>
<td>(13–115)</td>
<td>(22–150)</td>
</tr>
<tr>
<td>Free ( T_4 ) (pmol/l)</td>
<td>21.2 ± 11.6(^a)</td>
<td>15.5 ± 6.5</td>
<td>19.3 ± 7.7</td>
</tr>
<tr>
<td></td>
<td>(10.3–101.9)</td>
<td>(0.7–21.9)</td>
<td>(2.6–51.6)</td>
</tr>
<tr>
<td>( T_3 ) (nmol/l)</td>
<td>2.3 ± 1.4</td>
<td>1.8 ± 0.6(^a)</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>(1.1–12.0)</td>
<td>(UD 2.6)</td>
<td>(1.2–4.5)</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>2.1 ± 0.7</td>
<td>41.8 ± 118.0</td>
<td>2.6 ± 22.6</td>
</tr>
<tr>
<td></td>
<td>(UD 29.7)</td>
<td>(0.6–499)</td>
<td>(UD 22.6)</td>
</tr>
<tr>
<td>Anti-TPO antibody (%)*</td>
<td>7.0</td>
<td>10.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Anti-Tg antibody (%)*</td>
<td>10.5</td>
<td>10.5</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*Numbers of cretins with circulating thyroid autoantibodies above normal; anti-TPO and anti-Tg antibodies >0.3 U/ml were considered positive. UD = undetectable (TSH < 0.04 mU/l). \( \text{a} P < 0.05 \) compared with myxedematous cretins; \( \text{b} P < 0.05 \) compared with mixed cretins.
hypothyroid cretins were 67 ± 39 nmol/l and 67.8 ± 137.2 mU/l respectively. The thyroid volume of hypothyroid cretins as assessed by ultrasonography was significantly less than their euthyroid counterparts (9.9 ± 8.4 ml vs 23.8 ± 18.9 ml, P < 0.01) (Fig. 4).

Discussion
The essential finding of this study was a similar frequency of low intelligence, defects in visual-perceptive neuromanual ability, sensorineural hearing loss and neurological defects in all three types of endemic cretinism. However, growth retardation, myxedematous features and sexual immaturity were found at a much greater frequency in myxedematous cretins. Our conclusion concurred with an earlier study of similar design performed by Boyages et al. in China (7) and two recent studies from Italy (15, 16). In addition, neurological abnormalities frequently found in cretins (gait disorder, spasticity, hyper-reflexia, primitive reflexes) were similar to those reported earlier (3, 7, 15, 16).

The similar frequency of intelligence and neurological deficiency in all types of cretins pointed to a primary pathophysiologic event, which probably occurred in utero. Many studies have indicated that the critical period of the adverse effect of iodine deficiency on brain development is during early gestation. The classic study by Pharoah et al. (17) in Papua, New Guinea clearly demonstrated that iodine must be given before conception rather than during pregnancy to be effective in the prevention of endemic cretinism. A recent study in western China documented that iodine must be given to the pregnant mother in the second trimester to prevent neurological damage (18). Treatment later in pregnancy or after delivery may improve brain growth and developmental achievement slightly, but it does not improve neurologic status (18). These data indicate that thyroid hormones are essential for brain development in utero during early pregnancy before the onset of fetal thyroid function, which commences at week 12 of gestation (19).

Both T₄ and T₃ have been detected in rat embryo (20) and fetal rat brain (21) before the onset of fetal thyroid function. Morreale de Escobar et al. (22) demonstrated that maternal hypothyroxinemia due to iodine deficiency resulted in lack of thyroid hormone in fetal tissues during early pregnancy, even before the onset of fetal thyroid function. In addition, specific T₃ receptors have been found in rat (23) and human fetal brain early in gestation (24). More recently, Contempre et al. (25) have demonstrated the presence of thyroid hormone in human embryonic cavities as early as the second month of pregnancy. Thus it seems that T₄ can be transferred through the placenta throughout gestation at least to some degree. This view is emphasized by a recent report of severe clinical hypothyroidism in a neonate born with fetomaternal hypothyroxinemia due to Pit-1 deficiency (28). It is well documented that neonates born with sporadic congenital hypothyroidism appear normal at birth, only 5% will be detected clinically (29). In addition, neurological damage is rarely evident in sporadic congenital hypothyroidism. This indicates that, unlike in endemic cretinism, maternal T₄ has helped to alleviate fetal hypothyroidism in utero.

Postnatally, persistent hypothyroidism, either from iodine deficiency or from other causes of thyroid gland failure, results in myxedematous manifestations of endemic cretinism. In contrast, restoration of thyroid function occurs postnatally in neurological cretins (6). The etiology of thyroid failure in myxedematous cretins remains speculative. The possibilities include thiocynate toxicity (30) and selenium deficiency (31). Some investigators (32, 33) but not others (34) have provided evidence of immunological mechanisms causing destruction of the thyroid. The mechanism of the lack of adequate thyroid compensation in myxedematous cretins in Thailand is not known. The number of cretins with circulating thyroid autoantibodies were also similar among the three types.

Selenium deficiency has received much attention lately. Glutathione peroxidase of the thyroid gland, helping to neutralize hydrogen peroxide radicals, is a selenoenzyme (35). Lack of selenium results in both decreased thyroid peroxidase activity, allowing peroxide radicals to accumulate, as well as in induced thyroid cell...
fibrosis (36). Selenium is also a component of the type I deiodinase enzyme which converts T₄ to T₃ (37). A decrease in the activity of this enzyme in selenium deficiency in combination with iodine deficiency may help in restoring T₃ levels to the brain, thus protecting it from further neurological damage (38). Glutathione peroxidase activity was found to be decreased in selenium-deficient areas in Zaire, and the enzyme activity in cretins was half the level in normal subjects (38). Combined iodine and selenium deficiency could thus explain the large predominance of the myxedematous cretin as typically seen in Zaire. However, neurological cretinism was predominantly found in endemic areas of both iodine and selenium deficiency in China (39). In addition, our study, which indicated similar degrees of mental and neurological abnormality in both traditional types of cretins, does not support the contention that selenium deficiency protects against the neurological damage of iodine deficiency in some manner. Other environmental factors may therefore be responsible for thyroid atrophy in such patients. In this context, two independent investigators have demonstrated that reversibility of severe hypothyroidism with iodine supplement could be accomplished only before 4 years of life in patients with endemic cretinism (40, 41). This age-dependent reversibility of severe hypothyroidism with iodine supplementation supports the hypothesis that a progressive loss of functional capacity of the thyroid occurs in patients with myxedematous cretinism.

Our study therefore supports the hypothesis that neurological defects, common to all types of cretins, are the result of the combination of maternal and fetal hypothyroxinemia secondary to iodine deficiency, whereas the degree of myxedematous features is due to the length and severity of postnatal hypothyroidism (6). Our study also indicates that the pathogenesis of endemic cretinism is universal and similar in different geographical areas of the world.

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