Evaluation of Congenital Hypothyroidism in Fars Province, Iran

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Abstract

Objective: In Iran thyroid-stimulating hormone (TSH) based neonatal screening program is included in health care services from 2005 for detection of patients with primary congenital hypothyroidism (CH). This study was performed for a critical evaluation of the screening program primary congenital hypothyroidism in Fars province, Iran.

Methods: From November 2006 to September 2007, TSH serum concentrations of 63031 newborns, 3 to 5 days old born in Fars province, were measured by heel prick. The newborns with TSH ≥5mIU/L were recalled for measurement of serumT4 and TSH in venous blood samples

Findings: Of 127 recalled subjects, 43 were confirmed to be hypothyroid, showing a prevalence of 1:1465 with F:M ratio of 1.05:1. The most common clinical and radiological findings were prolonged jaundice (73%), large anterior fontanel (56%), wide posterior fontanel (55%), absence of distal femoral epiphysis (20%), and umbilical hernia (11%). Scintigraphy of the thyroid with 99mTC revealed eutopia (67.4%), hypoplasia (23.3%), agenesis (4.7%) and ectopia (2.3%).

Conclusion: It is concluded that a cut off value of TSH≥5mIU/L overestimates recalling the number of patients with CH. The most common cause of congenital hypothyroidism is not dysgenesis of the gland and perhaps dyshormonogenesis in Iran is more common than what is reported in other countries.

Key Words: Congenital Hypothyroidism; Thyroxin; Thyroglobulin; Thyroid Dysgenesis; Fars province

Introduction

Thyroid hormone is important for normal development of the nervous system [1]. The critical period for the central nervous system to be dependant on thyroid hormone is known to extend from fetal life until at least the first two years after birth [2]. Congenital hypothyroidism (CH) of any cause is difficult to be recognized in neonatal period because of normal gross appearance [3]. The delayed diagnosis made only on the basis of clinical findings may result in irreversible complications such as mental retardation and deafness [4,5]. The difficulty in recognizing congenital hypothyroidism and the serious consequences of delayed therapy have led to the introduction of screening programs for hypothyroidism in newborns by measuring (thyroxine) (T4) or thyroid-stimulating hormone (TSH or thyrotropin) in spots of blood collected
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Subjects and Methods

In Iran, neonatal CH screening method is primarily based on TSH measurement in filter paper blood spots. Between November 2006 and September 2007, all of the neonates born in Fars province were screened for CH between 3-5 days, and those who had TSH ≥5 mIU/L were referred to pediatric endocrine and metabolic clinic of Shiraz University of Medical Sciences for further evaluation.

Using a questionnaire, the neonates’ sex, weight, height, head circumference, family history, gestational age, parent’s consanguinity, history and length of icterus or exchange transfusion were recorded. Neonate had a complete physical examination by a pediatric endocrinologist and they were specifically checked for the presence of icterus, umbilical hernia and size of anterior and posterior fontanels. Venous blood samples were obtained on the day of referral by trained nurses, from the cubital vein and serum T₄ and TSH were measured. Normal range for serum TSH between 1-3 were 1.7-9.1 mIU/L and T₄= 7-12µg/dL.

A pediatric endocrinologist evaluated the laboratory results and then the neonates who had TSH ≥10 mIU/L were recalled for further evaluation. On recall, serum free T₄, thyroglobulin (ELISA, ORGENTEC, Germany), Normal range, 2-5ng/dL, intra-assay CV = 1.9 – 3.2 % & interassay CV=1.1-1.7%, T₃RU (ELISA, Monobind, Germany), Normal range 25-38%, intra-assay CV=0.73–1.37% & interassay CV=1.1-1.6%, and maternal urinary iodine concentration was measured. Knee X-Ray of the neonate for the presence of distal femoral epiphyses and 99mTC thyroid scanning was also performed and thyroid ultrasonography was performed when scintigraphy did not show any uptake. Thyroid scan with 131I was performed if thyroid scan was normal in 99m TC scan to evaluate organification defect.

Treatment was started if serum TSH was ≥10mIU/L or serumT₄ ≤ 7µg/dL with a single dose of levothyroxin (10-15 µg/kg/d).

Patients were followed weekly for the first two weeks and then monthly with serum T₄ and TSH. Clinical examination for developmental and physical indices including weight, height and head circumference were performed in each visit.

Statistical analysis was performed by SPSS software (version 14).

Findings

Between November 2006 and September 2007, 63031 neonates were screened in Fars province. In total, 127 neonates (one out of every 500 screened neonates) with an abnormal screening test result were referred. In 43 neonates, CH was diagnosed. The prevalence of CH was one in 1465 neonates (1:1465).

There were 22 (51%) female and 21 (49%) male infants who had CH. In this study there was no statistically significant difference between males and females ($P=0.525$)

In CH patients, the mean TSH levels were 31.4±2.5 SD. All but one of the patients had serum free T₄ <0.5ng/dL (0.27± 0.13 SD). Serum thyroglobulin was between 0-479 ng/dL with a median of 13.9, and the mean level of T₃RU was 26.1 ± 4 SD (Table 1).

In CH cases 32% had heel stick TSH <10mIU/L, 18% TSH=10-14.910mIU/L and 50% TSH ≥15-10mIU/L.

The most common clinical and radiological findings were prolonged jaundice (73.1%), large anterior fontanel (65%), wide posterior fontanel (55%), absence of distal femoral epiphysis (20.9%) and umbilical hernia (11.6%)(Table 2).
**Table 1:** Mean serum levels of T₄, TSH, free T₄, Tg and T₃RU in congenital hypothyroidism neonates

<table>
<thead>
<tr>
<th></th>
<th>Serum T₄</th>
<th>Serum TSH</th>
<th>Serum free T₄</th>
<th>Serum Tg</th>
<th>T₃RU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>3.551</td>
<td>31.407</td>
<td>0.272</td>
<td>42.591</td>
<td>26.147</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>0.1</td>
<td>8.5</td>
<td>0.1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>11.6</td>
<td>100</td>
<td>0.8</td>
<td>476</td>
<td>36.4</td>
</tr>
<tr>
<td><strong>Std Deviation</strong></td>
<td>2.51</td>
<td>20.367</td>
<td>0.131</td>
<td>99.887</td>
<td>4.046</td>
</tr>
</tbody>
</table>

T₄: thyroxine; TSH: thyroid-stimulating hormone; Tg: Thyroglobulin; T₃RU: triiodothyronine resin uptake

Scintigraphy was done in all patients. Of 13 (30.3%) dysgenetic cases, 2 had agenesis, one had ectopia and 10 had hypoplasia of thyroid gland. Eutopic thyroid gland was present in 30 neonates (in one neonate with goiter). These patients underwent ¹³¹I scan (for diagnosis of organification defect), 10 (23.3%) cases showed no uptake of ¹³¹I, that were proposed to have organification defect (the most common cause of dyshormonogenesis). One neonate had normal thyroid scan, but no detectable thyroglobulin (Tg) level, suggestive of the defect in Tg synthesis.

Parental consanguinity was found in 15 (34%) of CH patients and 2 (4%) patients had gestational age ≤36 weeks.

None of the mothers of the CH patients had iodine deficiency according to the measurement of their urinary iodine concentration. The most associated illness was glucose-6-phosphatase dehydrogenase (G6PD) deficiency in 4 neonates.

**Discussion**

In the present study, 63031 newborns from different parts of Fars province were screened for CH, and 127 of them had abnormal test results. Among this population 43 (35%) had a definite diagnosis of CH. The prevalence of CH was estimated to be 1:1465. This varies in different parts of the world. It has been reported to be 1:1300 in Netherland [10], 1:2326 in Turkey [11], 1:1823 in Lebanon [12], 1:1800 in Greek Cypriot population [13] and 1:3136 in Northeast Thailand [14].

The results of one study which was performed in Tehran and Damavand between 1997 and 2001 by Ordookhani et al [15] showed a prevalence of 1:914, although it was reported to be 1:1433 in the study of Amirhakimi et al [16] from Shiraz in 1990 and 1:370 by Hashemipour et al from Isfahan [17].

Iodine deficiency has been known to be one of the causes of neonatal hypothyroidism [18-20]; however, this problem has been solved in Iran [21] and in this study urinary iodine excretion was in the optimal range in mothers of CH neonates.

The female:male ratio in Japan (Osaka) assessment was reported to be 1.2:1 [22], 2:1 in Bosnia [23] and 1.8:1 in Saudi Arabia [24]. In the present study, this ratio was 1.05:1. The recall rate in our study is 2%, however in other reports from Turkey it is 1.6 % [11].

In some studies, the prevalence of CH in premature neonates has been twice as high as that in full term ones [25]. In our study the frequency of prematurity was 4% for healthy and CH neonates and there was no statistically significant difference between them.

In the present study, the most common clinical and radiological findings were prolonged jaundice, large anterior fontanel, wide posterior fontanel, absence of distal femoral epiphysis and umbilical hernia, in other study in Iran, prolonged jaundice

**Table 2:** Clinical and radiological findings in patients with congenital hypothyroidism

<table>
<thead>
<tr>
<th>Prolonged jaundice</th>
<th>Umbilical hernia</th>
<th>Large anterior fontanel</th>
<th>Wide posterior fontanel</th>
<th>Distal femoral epiphysys</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>31</td>
<td>24</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>-</td>
<td>12</td>
<td>19</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>
was more common than other symptoms [26], but in Greece the most common findings were umbilical hernia, widened anterior fontanel, and palpebral edema [13]. This difference may be due to ethnic variation in presenting symptoms of CH.

All patients with definite diagnosis of CH were studied by radioisotope (99mTC) scanning. Interestingly compared with previous studies, thyroid dysgenesis had no statistical difference with dyshormonogenesis (P=0.1) (95% confidence interval of dysgenesis=16.5–44% and dyshormogenesis=10.6–35.9%). However, in Germany 70% of CH neonates had dysgenesis [27] and in Thailand dysgenesis of thyroid was the most common cause of CH[14]. The difference may be due to the high prevalence of consanguinity in our region which may itself result in higher proportion of CH cases caused by dyshormonogenesis.

In another study by Ordookhani et al in Iran, dysgenesis was the cause of 50% of CH neonates [15], By counting our program, dyshormonogenesis is expected to be present in more than 10-15% (23.3 %) of CH cases reported elsewhere.

Serum T4 <4 µg/dL was found in 4 patients with absent distal femoral epiphysis, showing that primary serum T4 level is related to the degree of skeletal maturation.

In another study in Iran, anti Tg antibody was found in 4 of 6 patients with transient CH[28]. According to the present study, this antibody was detected in 7 out of 43 patients. More investigation is needed for finding the relationship between CH and this protein.

In the present study all newborns were screened between the 3rd to 5th day of life but nearly two thirds of those with suspicious screening test results, were referred between 15th and 28th day of life. These findings show the importance of early screening of newborns for CH, and early recalling of these patients is important for immediate initiation of treatment and prevention of neurological damage. To reach these goals, training health care personnel and physicians for immediate referral of patients is very important.

Whole blood TSH ≥5mIU/L was considered as a cutoff point for recalling the patients. From 84 neonates who did not have CH due to further studies, 86% had whole blood TSH ≤5 to <15 and 14% had TSH ≥15. According to this study most of the neonates with 5≤TSH<15 were diagnosed normal. But on the other hand, 50% of neonates with CH diagnosis had 5≤TSH<15. According to these findings whole blood TSH≥15mIU/L seems to be a more reliable and cost effective cutoff point for recalling patients in screening programs of CH. In Bosnia and Herzegovina, the TSH cutoff value for recall was ≥20mIU/L in whole blood [23], ≥15mIU/L in Mexico [29] and ≥25mIU/L in Thailand [14].

Raising cutoff point from 5 to 15 will certainly reduce recalling rate considerably and therefore reduces the number of false negative cases (86% in our study). On the other hand 50% (23 cases) of approved CH had 5≤TSH<15. So further evaluation is needed to design a more accurate cut off point to reduce false negative diagnosis and also prevent missing CH cases. We had the limitation to evaluate all causes of hypothyroidism and the titer of TRBA, and also perchlorate discharge test was not available at that period of time, therefore, we evaluated only organification defect with 131I scanning.

Conclusion

Due to the importance of early diagnosis and treatment of CH, screening programs must be included in primary health care policies. At the present time, there is a good policy and appropriate methods are available for screening of CH in Iran, but it seems that the cut-off point for TSH ≥5mIU/L in whole blood overestimates the real number of patients. Considering TSH ≥5mIU/L as a cut-off point for recalling neonates and low (33%) positive predictive value of this point shows that more investigation and research is needed for establishing accurate level of TSH as a criterion for recalling patients.

The most common cause of CH in our study was neither dysgenesis of thyroid nor dyshormonogenesis. Interestingly dyshormonogenesis was more common than expected. This may be because of higher rates of consanguinity in our country.

In addition, considering the fact that most neonates were recalled after second week of life based on primary screening test results, and
importance of early definite diagnosis and initiation of therapy, there would be need for a more efficient study.

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Conflict of Interest: None

References


