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[Tc]-99m Thyroid Scintigraphy in Congenital Hypothyroidism Screening Program

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Summary

The aetiology of congenital hypothyroidism (CH) may be important in determining disease severity, outcome and treatment schedules because athyroid patients need higher treatment doses and close monitoring particularly early in life. The aim of this study was to evaluate thyroid scintigraphy (TS) findings in infants with CH and to determine the relationship of serum TSH and T4 values with thyroid agenesia, in an attempt to identify factors that may detect thyroid agenesia before treatment. Since August 2002 to April 2005, screening program for CH was carried out in the Isfahan University of Medical Sciences and Health Services, Isfahan, Iran. Screening was performed by measuring both the serums T4 and TSH concentration at day 3–7 of birth. Full-term newborns were recalled based on a serum TSH >20 mIU/l or serum T4 <6.5 μg/dl and premature newborns based on T4 level by weight and TSH level by age. After repeating the laboratory test and clinical evaluation, Tc-99m TS was recommended for all infants with suspected CH before thyroxin replacement therapy. On the basis of Tc-99m TS, the thyroid gland was classified as normal scan, ectopic, goiter and athyrosis. TS results were compared with serum T4 and TSH levels. Of 93 381 newborns screened over a period of nearly 3 years, 262 neonates were found to have CH. The overall incidence of CH was 1 : 357 live births with a female/male ratio (F/M) of 1.4/1. Thyroid scan was performed on 116 (54%) of the infants with CH; of them, 33 cases (28.4%) were athyrotic (F/M = 0.8/1) while seven infants (6%) had ectopic thyroid (F/M = 1.3/1) and 76 cases (65.6%) had a normal thyroid scan (F/M = 1.5/1). Infants with the absence of thyroid in TS had significantly higher TSH value in comparison with those with ectopic or normal TS (116.3 ± 109.64 vs. 108.10 ± 62.92 or 55.35 ± 48.26 mIU/l, respectively, $P < 0.0001$). Although not statistically different, the mean T4 level was higher in normal TS group than in ectopic and athyrotic groups (8.03 ± 3.48 vs. 6.36 ± 5.57 or 5.04 ± 3 μg/dl, respectively, $P = 0.09$). We conclude that Tc-99m TS is a useful diagnostic tool for the initial investigation of suspected CH and considering the correlation of TS results with blood TSH levels, proper management and close monitoring of hypothyroid infants with severe hormonal alterations is necessary for the detection of thyroid agenesia.

Key words: congenital hypothyroidism, Tc-99m thyroid scintigraphy, thyroid agenesia, screening.

Introduction

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder and it is well-documented that without thyroxin replacement from early life, it causes irreversible neurodevelopment impairment [1, 2]. The prevalence of CH is occurring in approximately one in 3000–4000 live births in North America and Europe [3]. Whereas in Iran, it is detected at a rate of 1 : 914 live births in Tehran, 1 : 1423 live births in Fars province and 1 : 370 live births in Isfahan [4]. CH is most commonly caused by developmental defects of thyroid gland (85%); which in turn consists of either thyroid agenesia (40% of all cases) or incomplete or aberrant migration (40%), or hypoplasia of a eutopic gland [1]. Thyroid dysgenesis is commonly sporadic with unknown mechanisms. However, recent studies estimate that approximately 2% of the cases with thyroid dysgenesis are familial [1]. The remaining 10–20% of the infants with CH have dyshormonogenesis that is transmitted by an

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autosomal recessive mode of inheritance [5]. There are gender and ethnic variations in CH. Overall, there is a 2/1 female/male ratio and higher prevalence in Caucasians and Hispanics than in White infants [6]. Although neonatal thyroid screening programs have been extremely successful in the prevention of neurodevelopmental deficit, some studies have reported subtle neuropsychological disturbance in severely affected infants despite early detection and treatment [7–9]. The aetiology of CH may be important in determining the disease severity, outcome and treatment schedules. Patients with athyrosis have shown the greatest hormonal alteration and they need higher treatment doses and close monitoring particularly early in life [10–11].

Thyroid imaging with technetium TC-99 m provide information about the size and the location of thyroid gland [12]. Thyroid Scintigraphy (TS) is not routinely used to determine different forms of CH prior to the thyroxin replacement therapy [13]. Patients with a non-visualized gland or with images suggesting dyshormonogenesis should be re-evaluated at 3–4 years of age, after withdrawal of levothyroxin therapy [14].

Considering the high prevalence of CH in our country (Iran) and the importance of its proper treatment in preventing developmental and intellectual impairment, this study was conducted to evaluate the TS findings in infants with CH and to determine the relationships of serum TSH and T4 values with thyroid agenesia, in an attempt to identify factors that may detect thyroid agenesia.

Material and Methods

Since August 2002 to April 2005, the screening program for CH was carried out in the Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences and Health Services, Isfahan, Iran. All neonates were born in 17 maternity hospitals of Isfahan and were referred for screening. The neonates' sex, weight, height, head circumferences, maternal age and parents' consanguinity were recorded. Venous blood samples were obtained on the day of referral (3rd–7th day of birth) by trained nurses, from the cubital vein, and serum T4 and TSH levels were measured. Serum T4 and TSH were measured by radioimmunoassay (RIA) and immunoradiometric assay (IRMA) methods, respectively, using Iran Kavoshyar Co. kits (Tehran, Iran) and by gamma counter of Isfahan Endocrine and Metabolism Research Center (Berthold LB 2111-12). The sensitivity of T4 and TSH tests were 0.38 μg/dl and 0.05 mIU/l, respectively. A 99m-pertechnetate scintigraphy of thyroid was performed by using a gamma camera equipped with a parallel hole collimeter.

A pediatric endocrinologist and a general practitioner evaluated the results of laboratory tests to determine neonates who needed to be recalled. Recalls were implemented based on the level of T4 and TSH. In the case of $T4 < 6.5$ μg/dl or TSH >20 mIU/l on 3rd–7th days after birth, and $T4 < 6.5$ μg/dl or TSH >10 mIU/l after the 7th day of birth, the neonates were recalled. Immature neonates with low level of T4 for their weight or with high TSH levels for their age were recalled, as well [15].

Considering the first TSH values (3rd–7th day of birth), the proper approach was selected. If TSH level was between 20 and 39 mIU/l, T4 and TSH measurements were repeated, but if TSH level was >40 mIU/l, then treatment was initiated as well as repeating lab test. If the result of the second test was within the normal limits, the neonate was considered to have transient CH, in which the treatment was halted and the neonate was excluded from the study; otherwise, the treatment was continued.

All recalled neonates were examined clinically by a pediatric endocrinologist. According to the results of secondary measurements (on 7th–28th days of birth), neonates were considered as hypothyroid when having TSH > 10 mIU/l and $T4 < 6.5$ μg/dl. In both premature and full-term neonates whose T4 measurements were low according to their weight, complimentary tests including T3 resin uptake (T3RU) and free T4 index (FTI) were performed and treatment was started if these results were abnormal.

In order to determine the aetiology of CH, all infants were recommended to perform TS before treatment. A 99m-pertechnetate scintigraphy of thyroid was performed. On the basis of Tc-99m TS, the thyroid gland was classified as normal scan, ectopic, goiter and athyrosis. Athyrosis was diagnosed in infants whose thyroid scans did not show any radionuclide uptake. According to our screening strategy, CH newborns with normal thyroid scan and dyshormonogenesis had to be re-evaluated on their 3rd–4th years of age, after interruption of treatment for at least 4 week. The serum T4 & TSH values (first measurement) in confirmed hypothyroid patients were compared between athyrotic, ectopic and normal thyroid scan groups.

Statistical analyses

Data were recorded on questionnaires and transferred to coding sheets in a computer database. Data analyses were performed using SPSS version 10.5 (Chicago Inc., USA). Frequency, mean and SD for demographic data, T4 and TSH levels in neonates are presented. We compared the mean T4 and TSH values between the athyrotic, ectopic and normal scan groups by one-way analysis of variance (ANOVA) and *post hoc* Tukey test. Gender and consanguinity differences between groups were analyzed by chi-square test. Statistical significance was considered to be at the 5% probability level.

Results

Of the 93 381 newborns who were screened over a period of nearly 3 years, 262 neonates were found with CH. The overall incidence of CH was 1 : 357. Among hypothyroid neonates, 110 (42%) were males and 152 (58%) were females leading to a female : male ratio of 1.4 : 1. There was no parental consanguinity among 158 (61%) hypothyroid neonates, whereas the parents of 74 (28%) of them had first-cousin consanguinity and 27 (11%) had second-degree consanguinity.

The mean ± SD serum T4 and TSH levels of hypothyroid newborns were 6.58 ± 3.47 μg/dl and 48.79 ± 62.93 mIU/l, respectively.

Of the 262 infants with CH, TC-99m TS was performed on 116 (54%) infants and the parents of the remainder neonates accepted to perform TS on the third year of age. TS revealed ectopia in 7 (6%), thyroid agenesia in 33 (28.4%) and normal TS in 76 (65.5%) cases.

The demographic data and TS results in infants with CH are summarized in Table 1. Normal scan was predominated in females than males (60.5 vs. 39.5%, respectively), and athyroid gland was more frequent in males than females (54.5 vs. 45.5%, respectively), but no statistical gender difference was found between the two groups ($P = 0.4$). There was no difference in the prevalence of parental consanguinity among athyrotic, ectopic and normal TS infants ($P = 0.3$).

The mean T4 and TSH values in hypothyroid neonates based on TS results are shown in Table 2. There was no difference between normal scan, athyroid and ectopic groups in the mean T4 values ($P = 0.09$), but significant difference was found in the mean TSH values between the three groups ($P = 0.002$). Athyroid infants had significantly higher TSH values compared with those with normal TS (116 ± 109.64 vs. 55.35 ± 48.26 mIU/l, respectively, $P < 0.0001$).

Discussion

This study revealed the incidence of CH in Isfahan, Iran, to be one case per 357 newborns which is about 10 times higher than that reported from America and Europe [3]. The prevalence of CH in other regions of Iran (Tehran, Fars province) have been lower than our area [4], but are ~3–4 times more than that reported from some Western countries [2]. Indeed, the prevalence of permanent CH has to be determined by the exclusion of transient hypothyroid cases after withdrawal of L-T4 therapy at 3–4 years of age.

The main cause of compensated or transient primary hypothyroidism is iodine deficiency [16], however, from many years ago, this problem has been solved in Iran [17]. A previous study in Isfahan has shown that urinary iodine excretion was in the optimal range in neonates and their mothers [18]. The other causes of transient hypothyroidism are transfer of blocking antibodies or antithyroid drugs and iodine exposure [19–22]. Despite of our suggestion to gynecologists and delivery room nurses about not using povidone iodine for delivery, we are not sure about their compliance, so this may be a cause of high CH found in our area. None of the mothers of neonates with CH had a history of antithyroid drug intake but blocking antibodies were not measured, this was a limitation in our study. Other variables such as environmental, genetic, ethnic variation and familial factors are involved in increased prevalence rate of CH in some population [23, 24]. We suggested that these factors may be the cause of high CH in our community that should be evaluated within the next years. One study from Saudi Arabia performed on 147 infants with CH detected a prevalence of 21.8% athyrosis, 42.2% ectopic gland and 36% eutopic gland [25]. Another trial in Chile showed that neonates with CH had 47% ectopic, 29.1% eutopic and 24.3% athyrotic gland [26]. The result of our study was nearly similar to these studies. In our study, the high percentage of normal TS before treatment may be due to transient hypothyroidism or dyshormonogenesis. Consequently, as recommended, definite diagnosis has to be confirmed at third to fourth years of age, after the interruption of replacement therapy for at least 4 weeks [14].

When the diagnosis of CH is confirmed, some clinicians do not recommend routine thyroid imaging prior to starting levothyroxin therapy, because they believe that the imaging results would not alter their management [27]. Subtype of primary CH has shown different degrees of impairment of thyroid

TABLE 1
Demographic characteristics and thyroid scan results in infants with congenital hypothyroidism

	n (%)	Sex		Parents' consanguinity		
		Male *n* (%)	Female *n* (%)	Yes		No
				1st degree *n* (%)	2nd degree *n* (%)	*n* (%)
Normal scan	76 (65.5%)	30 (39.5%)	46 (60.5%)	26 (34.2%)	9 (11.9%)	44 (53.9%)
Ectopic gland	7 (6.1%)	3 (42.9%)	4 (57.1%)	3 (42.8%)	1 (14.3%)	3 (42.9%)
Athyrosis	33 (28.4)	18 (54.5%)	15 (45.5%)	10 (30.3%)	1 (3%)	22 (66.7%)

TABLE 2
The mean T4 and TSH values in hypothyroid neonates based on TS results

	TSH[a] (mIU/l) Mean (SD), Range	T4[b] (μg/dl) Mean (SD), Range
Normal scan, $n=76$	55.35 (48.26), 8–240	8.03 (3.48), 0.60–13.20
Ectopic gland, $n=7$	108.10 (62.92), 34.80–224	6.36 (5.57), 1.30–15.30
Athyrosis, $n=33$	116.3 (109.64), 10.20–492	5.04 (3.9), 0.60–11.50

[a]The normal range in serum TSH is considered to be 0.6–20 mIU/l and 0.6–10 mIU/l on the 3rd–7th days and 8th–28th days of birth, respectively [15].
[b]The normal range in serum T4 is considered to be 6.5–15.0 μg/dl in term neonates [15].

function [28]. There are limited data available on patterns of hormonal concentration for T4 and TSH in children with different etiologies of CH. A previous study, in which the disease severity was related to etiological category, reported that despite rapid normalization of mean T4 levels in different etiologies category of CH, the mean TSH level at screening and during the first 6 months of follow-up were consistently higher in those with athyrosis than in those with dysgenetic or dyshormonogenetic etiologies. The percentage of patients who required a dose increase in the first 6 months was significantly higher in athyrotic group than in other groups [11]. In our study, the mean TSH level was significantly higher in the athyrotic group. Accumulating data from this and other studies provide strong support for the view that the aetiology should be considered as an important determinant of severity of disease and treatment schedules in patients with CH. The follow-up schedules for CH may differ in the three aetiological categories (athyrosis, dysgenesis, dyshormonogenesis) based on the different hormonal patterns and responses to therapy [11]. Generally, CH children with most severe and prolonged disease at diagnosis have the worst outcome [29]. It is established that the outcome is better in infants with severe hypothyroidism if thyroxin replacement therapy would be started on a high dosage due to the reduced period of postnatal hypothyroidism. However, the efficacy of a high dosage for milder forms of CH is yet to be confirmed [30]. Thus, the Tc-99m TS can add useful information in the clinical evaluation of infants with CH for choosing the better treatment strategies especially in patients with athyrosis. We suggest that performing TS, as soon as possible before starting replacement therapy would be useful. Due to higher mean screening TSH levels in infants with athyrosis than in the other two groups, TS especially in CH patients with severe hormonal alteration can determine the athyrotic group for the beginning of higher dose of L-T4 as well as closer monitoring. If the thyroid gland is present in the normal position in TS, later discontinuation of treatment is more probable, but in athyrotic or ectopic patients, lifelong therapy with higher dose might be needed. Therefore, TS also provide useful prognostic information for counseling with parents of CH patients and their follow-up program.

According to the results of the present study, in infants with athyrosis, the mean TSH level was significantly higher than the normal scan group. No statistical differences were found between ectopic and athyrotic patients or ectopic and normal TS groups in the mean TSH values, but athyrotic patients when compared with ectopic and ectopic when compared with normal scan group had an increasing TSH level. However, no statistical difference was detected between the groups in the mean T4 levels, but the mean T4 values in athyrotic patients were lower than in other groups. Some studies also showed that newborns with normal TS had less hormonal alterations than those with athyrosis [11, 26, 28]. Our findings were consistent with the study of Hanukoglu *et al.* [11], who examined the patterns of TSH and T4 in the three groups based on their thyroid scans (athyrosis, dysgenesis and dyshormonogenesis). They reported that the mean TSH levels at screening and during the first 6 months of follow-up were consistently higher in those with athyrosis than in those with dysgenesis or dyshormonogenesis aetiologies. The athyrotic group also had lowest total T4 levels at diagnosis and at 3 months of age. They concluded that CH patients without thyroid gland (agenesia) need close monitoring and prompt treatment particularly early in life. Contrary to the findings of these studies [11, 26, 28], in our patients with athyrosis, T4 levels were not lower than in the other two groups but with a larger sample size there is a probability to find a statistical difference. Conversely, one study showed that the initial T4 levels correlated with the degree of skeletal maturation and aetiology, but initial TSH level could not predict the nature of CH [31]. Further confirming studies, with large sample size and longer period are necessary to prove definite relationship of hormonal alteration and aetiology in CH.

We found that the mean TSH level was significantly higher in those with athyrosis than in patients with ectopic and normal scans. This implies that due to the need for close monitoring and higher dose of L-T4 replacement in CH patients with athyrosis, an aetiological diagnosis is advisable before treatment. This is especially important in patients with high level of TSH with impression of athyrosis. Tc-99m TS is a useful diagnostic tool for the initial investigation of suspected CH and due to correlation of TS results with serum TSH levels, proper management and close monitoring of hypothyroid infants with severe hormonal alterations is necessary with considering probability of thyroid agenesis.

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