Ultrasonographic Findings in Neonates Screened for Congenital Hypothyroidism

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Abstract. Ninety-seven newborn infants, who were referred because of positive TSH results at screening for congenital hypothyroidism (CH), underwent ultrasonography (US) of the thyroid. US findings were classified into four groups: A) undetectable thyroid (n=7, 7.2%), B) significantly enlarged thyroid (n=5, 5.2%), C) unilaterally small thyroid (n=2, 2.1%), and D) normal thyroid (n=83, 85.5%). All 12 cases in groups A and B had TSH levels higher than 30 $\mu\text{U}/\text{ml}$ at the screening, and 11 of them had elevated confirmatory TSH levels exceeding 50 $\mu\text{U}/\text{ml}$. In one patient in group A and both patients in group C, the serum TSH levels remained mildly elevated. Thus, all infants with abnormal US findings showed persisting abnormal TSH levels, although some showed only mild elevation. By contrast, among the 7 infants in group D with high TSH levels ($>30 \mu\text{U}/\text{ml}$) at the screening, 4 of them subsequently showed transient elevation of serum TSH levels. In conclusion, abnormal US findings of the thyroid were associated with abnormal thyroid function and a subsequent requirement of therapy. Thyroid US provides useful information for the management of infants screened for CH.

Key words: congenital hypothyroidism, ultrasonography, etiology

Introduction

Nationwide neonatal screening for congenital hypothyroidism (CH) has been implemented in Japan since 1979. Infants with dried blood TSH levels on filter paper $>10 \mu\text{U}/\text{ml}$ at the screening, are referred for further examination (1). In general, replacement therapy is started without obtaining etiologic information by scintigraphy to avoid delay in treatment. An etiologic diagnosis is commonly performed later at several years of age

(1). Although thyroid ultrasonography is safer, less expensive, and more convenient than scintigraphy, and may provide additional objective information about thyroid anatomy, its reliability is questioned when compared with scintigraphy (2-7). In this study, we performed thyroid US on all infants with a positive test at the screening for CH in a 2 year period and assessed US findings in relation to TSH levels at the screening, confirmatory serum TSH (i.e. serum TSH measured at the first hospital visit), TSH during follow-up, and treatment status.

Subjects and Methods

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Fig. 1 Distribution of thyroid volume in 97 infants. The distribution is compatible with normal distribution (mean $\pm$ SD = 3.50 ± 2.02 [ml]) and we defined a thyroid larger than +2 SD (7.55 ml) as a significantly enlarged thyroid.

newborns underwent screening for CH in Miyagi Prefecture, Japan. During that period, 111 infants had positive TSH, and 97 were referred to Tohoku University Hospital. Nineteen were referred immediately after their first results because the dried blood TSH level on filter paper were $>30 \mu\text{U/ml}$, while the remainder were referred after obtaining a second abnormal result ($>10 \mu\text{U/ml}$).

We performed thyroid US on all 97 infants on their first visit (11–39 days old). A real-time mechanical sector scanner (Ultrasound Scanner EUB-8000, Hitachi, Tokyo, Japan) with a digital beam-former system and a 10 MHz probe was used for the thyroid scan. We examined first if the thyroid was clearly visible at its normal location, then if the thyroid was normally shaped, and finally, we measured the gland volume; the latter was estimated from the thickness of each lobe by Ueda's simplified method (8). US findings were classified into four groups as follows: A) undetectable thyroid suggesting athyreosis, severe hypoplasia, or ectopic thyroid; B) significantly enlarged thyroid, suggesting dyshormonogenesis; C) unilaterally small thyroid, indicating thyroid hemi-hypoplasia; and D) normal thyroid in size,

shape, and location. The distribution of thyroid volume among 97 infants is shown in Fig. 1. The distribution is compatible with normal distribution by the Kolmogorov-Smirnov test, and a thyroid larger than +2 SD (7.55 ml) was defined as a significantly enlarged thyroid. Typical US images in each group are demonstrated in Fig. 2.

TSH for the screening was measured using dried blood samples collected on filter paper. At our hospital, serum TSH was measured with a sandwich EIA (AxSYM TSH, Dainabot, Tokyo, Japan) with the results available on the same day. The normal range of adult serum TSH is 0.49–4.67 $\mu\text{U/ml}$ with this assay.

Treatment with L-T4 was started based mainly on the serum TSH values and also on serum free-T4 values. We recommended to the parents starting treatment if the serum TSH was $>15 \mu\text{U/ml}$ on the first visit, $>10 \mu\text{U/ml}$ at 1 month old, $>7 \mu\text{U/ml}$ at 2 months, and $>6 \mu\text{U/ml}$ after 3 months. When the recommendation was accepted, we initiated L-T4 therapy. Serum TSH levels at start of treatment of all treated infants and those of the infants followed without treatment are shown in Fig. 3.

Results

Ninety-seven infants were allocated into the four groups described above. Seven (7.2%) were classified into group A, 5 (5.2%) into group B, 2 (2.1%) into group C, and 83 (85.5%) into group D.

Nineteen infants had TSH level $>30 \mu\text{U/ml}$ at first screening, and these were immediately referred. All 12 infants in groups A and B had an initial screening TSH $>30 \mu\text{U/ml}$ and a confirmatory TSH $>50 \mu\text{U/ml}$ in all but one. In the 2 patients with hemi-hypoplastic thyroid, the first screening TSH levels were 13.1, 11.3 $\mu\text{U/ml}$ and the confirmatory TSH levels were 9.91, 8.97 $\mu\text{U/ml}$ respectively. Seven of the 83 infants with normal thyroid by US had high TSH levels ($>30 \mu\text{U/ml}$) at the first screening. Among them, 5 had lowered serum confirmatory TSH levels (0.92–14.84 $\mu\text{U/ml}$).

Fig. 2 Typical ultrasonographic images for: A: Group A, undetectable thyroid. B: Group B, significantly enlarged thyroid. C: Group C, unilaterally small thyroid. D: Group D, normal thyroid. The scale is the same in all 4 figures.

Table 1. TSH values at first screening

Group	First screening TSH ($\mu\text{U/ml}$)		Total
	> 30	10-30	
A	7	0	7
B	5	0	5
C	0	2	2
D	7	76	83
Total	19	78	97

Table 2. Treatment status

Group	Initiation of L-T4 replacement			Total
	Yes	No	Failed to follow	
A	7	0	0	7
B	5	0	0	5
C	2	0	0	2
D	24	54	5	83
Total	38	54	5	97

L-T4 replacement was initiated in 38 of 97 subjects (Table 2). Eleven of the 14 infants (78.5%) with abnormal US findings (groups A, B, and C) were immediately treated. One patient in group A had a mildly elevated TSH ($11.85 \mu\text{U/ml}$) at first visit, but the TSH level increased at 1 month old ($18.15 \mu\text{U/ml}$) and was eventually treated. Two

patients in group C retained slightly elevated TSH ($10.06 \mu\text{U/ml}$ at 1 month and $6.07 \mu\text{U/ml}$ at 3 months), indicating mild hypothyroidism, and treatment was subsequently started. In 24 infants in group D, replacement therapy was begun according to the criteria described above. Serum TSH at the onset of therapy in these 24 patients

Fig. 3 Serum TSH levels of the infants. The symbols (×: Group A, Δ: Group B, □: Group C, ●: Group D) show TSH levels of the infants at the time of start of treatment. The lines show serum TSH levels of the untreated infants during follow-up.

ranged from 5.5 to 17.4 $\mu\text{U/ml}$ (Fig. 3).

Discussion

We performed thyroid US in 97 infants screened for congenital hypothyroidism (CH). Nearly 80% of those with abnormal thyroid images had extremely high screening and confirmatory TSH values, suggesting a severe functional defect of the thyroid, and all were treated immediately. The remaining subjects with abnormal US findings had only slightly elevated TSH levels at first, but the values did not normalize, and eventually treatment was started. On the other hand, 5 of the

7 infants with normal thyroid image had lowered confirmatory serum TSH levels despite a high TSH ($>30 \mu\text{U/ml}$) at first screening, and in 4 of them serum TSH levels soon normalized.

To determine the etiology of CH, thyroid scintigraphy has been widely used. Thyroid US can also provide objective anatomic information. Compared with scintigraphy, however, the utility of US has been controversial. In some studies, US findings were not concordant with scintigraphy (4, 7). However, the quality of the imaging equipment and the interpretive skill of the physician influence the reliability of US. Some studies reported that US was reliable in delineating thyroid anatomy, although there were limits to diagnosing an ectopic thyroid (2, 5, 6). The US also possesses merits superior to scintigraphy: it is free from irradiation, less expensive, and more convenient. In this study, US was performed using a digital ultrasound scanner equipped with a 10 MHz transducer, and the thyroid was clearly visible as shown in Fig. 2. Obviously, the results of US should be confirmed by later scintigraphy.

The infants in group A were categorized as thyroid dysgenesis including athyreosis, severe thyroid hypoplasia, or ectopic thyroid. Hypothyroidism due to thyroid dysgenesis is permanent and generally severe, and long-term intellectual outcome is poor, particularly in the athyreotic group (9, 10). Since a recent study has shown that early high-dose treatment, even in the severest patients, may restore intellectual outcome (11), an etiologic classification before the onset of replacement treatment is important. Although US provides a rough etiologic classification of dysgenesis or dysmorphogenesis, it would be useful for the initial management of these patients.

The infants in group B would be diagnosed as goitrous cretinism due to dysmorphogenesis. However, permanent hypothyroidism in these infants should be confirmed later to rule out the possible transient form unless TSH levels increase during therapy.

The infants in group C were considered to

have thyroid hemi-hypoplasia. An association between hemi-hypoplasia and CH has not been previously defined. Shabana et al. (12) reported that the prevalence of thyroid hemi-agenesis was 0.2% in normal school children without apparent thyroid disease. In adults, however, thyroid hemi-agenesis is associated with thyroid diseases such as adenocarcinoma, hyperthyroidism, hypothyroidism, benign adenoma, goiter, and chronic thyroiditis (13). Although it is uncertain whether mild hypothyroidism in these infants should be treated, we believe that it is best to follow them on replacement therapy with careful later observation.

Several infants in group D had normal thyroid hormone levels but persistent mildly elevated TSH levels. It is controversial whether to treat such infants, however, considering the safety of replacement and the possible developmental sequelae in children, we prefer treating them with L-T4 for a year or two.

In conclusion, abnormal US findings of the thyroid were associated with abnormal thyroid function and subsequent requirement of therapy. US in infants screened for CH provides valuable information for determining the diagnosis and follow-up schedule.

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