

# Evaluation of thyroid status of infants in the intensive care setting

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## ABSTRACT

**Introduction:** Previous studies report the spectrum of thyroid function abnormalities in critically-ill neonates. In this study, we evaluated the thyroid status in critically-ill neonates, and determined whether thyroid function abnormalities are more common in sick neonatal infants.

**Methods:** In a prospective cohort study, 67 critically-ill infants from the Neonatal Intensive Care Unit (NICU), affiliated to Shiraz University of Medical Sciences, were entered into our study. Of all the included neonates, 33 were premature and seven were under 28 weeks of gestation. In addition to the routine thyroid-stimulating hormone (TSH)-screening (capillary specimen), serum free triiodothyronine (FT<sub>3</sub>), free thyroxine (FT<sub>4</sub>) and TSH were checked using radioimmunoassay kit twice (during critical illness and before discharge from the NICU).

**Results:** It was observed that abnormal TSH levels (screening test) were about 40-fold higher in critically-ill neonates compared with healthy neonates, while more than four-fifths of them were detected in the second sampling done after recovery. The mean FT<sub>3</sub> was significantly lower during the critical illness and it increased after recovery (2.537 and 3.232 pg/ml, respectively). Mean FT<sub>4</sub> and mean TSH during the illness and after recovery did not have any significant difference.

**Conclusion:** Thyroid function abnormalities are more common in infants under intensive care and most of them manifested as “euthyroid sick syndrome”; abnormal screening tests may be due to the transient elevation of TSH during recovery from illness. Therefore, only in cases in which TSH rises more than 15–20 mIU/L or TSH remains high for a month or longer, that treatment is needed, while other cases must be followed up by serial determination of TSH and

FT<sub>4</sub>. The levels of FT<sub>3</sub> and FT<sub>4</sub> during the illness were not affected by the duration and severity of the illness.

**Keywords:** euthyroid sick syndrome, neonatal intensive care unit, neonatal screening, thyroid function tests, thyroid status

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## INTRODUCTION

Considerable efforts are devoted worldwide to improve the neonatal health.<sup>(1)</sup> Advances in diagnostic techniques and therapeutic intervention are designed to enhance the overall outcome of the ever-increasing number of surviving premature and critically-ill infants. Thyroid function abnormalities are among the factors associated with poor neurodevelopmental outcome, especially in preterm and critically-ill infants.<sup>(2,3)</sup> Previous studies reported on the spectrum of thyroid function abnormalities in critically-ill neonates that include low thyroxine (T<sub>4</sub>) and normal free T<sub>4</sub> (FT<sub>4</sub>) that seem to be due to a decrease in the thyroid-binding globulin during the illness,<sup>(4)</sup> low T<sub>4</sub>, FT<sub>4</sub>, triiodothyronine (T<sub>3</sub>) and normal thyroid-stimulating hormone (TSH),<sup>(5-7)</sup> and transient primary hypothyroidism with a late rise of TSH.<sup>(8)</sup> In this study, we investigated thyroid function abnormalities in critically-ill neonates admitted in the intensive care unit of the hospitals affiliated to the Shiraz University of Medical Sciences.

## METHODS

Critically-ill infants admitted to the Neonatal Intensive Care Unit (NICU) of Shiraz University of Medical Sciences between October 2004 and March 2006 were considered as candidates for the study. Exclusion criteria were failure to obtain parental informed consent, admission due to extreme prematurity (birth weight [BW] < 1,000 g) alone, death during the hospital course, improvement before the third day of life, refusal of parents for second sampling, and inadequate samples. Information such as the age at the time of admission, gestational age, BW, Apgar score, diagnosis of illness, duration of illness, family history of thyroid disease, ventilator use, result of echocardiography, congenital anomalies and medications, were recorded.

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**Table I. Comparison of the thyroid function tests of patients with positive screening test with the normal range.**

Case	Body weight group	Period I			Period II		
		FT <sub>3</sub>	FT <sub>4</sub>	TSH	FT <sub>3</sub>	FT <sub>4</sub>	TSH
1	1	↓	NR	NR	NR	NR	↑
2	2	↓	↓	Borderline	↓	↓↓	↑
3	2	↓↓	NR	NR	↓	NR	↑
4	3	↓↓	↓	NR	↓	NR	↑
5	3	NR	NR	↑	NR	NR	↑
6	3	↓	NR	NR	NR	NR	↑

↓ : below normal range; NR: normal range; ↑: above normal range; borderline:  $5 < \text{TSH} < 10$  mIU/L

The infants were stratified by BW into three groups, viz. (1) very low BW (VLBW) i.e.  $\text{BW} < 1,500$  g; (2) low BW (LBW) i.e.  $1,500 \text{ g} \leq \text{BW} \leq 2,500$  g; and (3) normal BW (NBW) i.e.  $\text{BW} > 2,500$  g. Blood samples were obtained from infants on admission after the second day of life (during the critical illness) and also before discharge from the hospital (at the time of recovery from the illness), which were labelled I and II, respectively.

Screening of TSH was performed with a commercial enzyme immunoassay kit, Neo-TSH (Neonatal TSH ELIZA kit, IBL GmbH, Hamburg, Germany), an enzyme-linked immunosorbent assay (ELISA) method on dried blood spots on filter paper from the infant's heel. The generally-accepted cut-off value is 10 mIU/L: negative  $< 5$  mIU/L, borderline  $5$  to  $< 10$  mIU/L, positive  $\geq 10$  mIU/L. Free T<sub>3</sub> (FT<sub>3</sub>) and FT<sub>4</sub> were measured by a radioimmunoassay kit (RIA-gnost® FT<sub>3</sub> Sep 2005-Model 12 and RIA-gnost® FT<sub>4</sub> June 2005 model 14 [CIS Bio International, Gif-sur-Yvette Cedex, France]). These kits measured FT<sub>3</sub> and FT<sub>4</sub> by means of antibody-coated tubes and were carried out in two stages. The TSH was determined by a highly-sensitive immunoradiometric assay kit (TSH IRMA kit, Immunotech, Prague, Czech Republic). Screening of TSH was performed at School of Paramedical Sciences Laboratory, and other tests were performed at Endocrine Research Laboratory, Shiraz, Iran. Statistical analysis was performed with the Statistical Package for Social Sciences version 13.5 software (SPSS Inc, Chicago, IL, USA). Paired *t*-test and non-parametric tests (Mann-Whitney, Kruskal-Wallis, and Wilcoxon signed-rank tests) were used for statistical analysis where appropriate. A *p*-value  $< 0.05$  was regarded as statistically significant. The study was approved by the local ethics committee of the hospital.

## RESULTS

67 patients were enrolled in this study. The age of the patients during the illness was 1–25 days, so the first sampling was done at age  $14 \pm 11$  days. About half of the patients were three days of age and three-quarters were

**Table II. Comparison of changes of the thyroid function tests during critical illness in patients according to their birth weight.**

Birth weight group	p-value of differences in the mean between the two time periods, I & II		
	FT <sub>3</sub>	FT <sub>4</sub>	TSH
1	0.477	0.314	0.093
2	0.036	0.673	0.666
3	0.016	0.988	0.331

less than seven days of age during the first sampling, while after the recovery, they were  $27 \pm 20$  days of age. Of all the included neonates, nine were VLBW, 34 were LBW and 24 were NBW. 33 patients were premature and 34 were full-term. Among our patients, six patients had a positive screening test, five of whom were detected in the second sampling. Comparison of the results of the thyroid function tests of patients with positive TSH screening test with the normal range of these tests and their BWs are shown in Table I. The incidence of positive screening tests in healthy neonates in the province was 2.2 per 1,000. Positive screening tests between normal neonates and patients admitted in the NICU showed a significant difference ( $p < 0.001$ ). Positive tests by Neo-TSH test were compatible with a high TSH by radioimmunoassay method in all patients with a TSH level of 10–20 mIU/L.

The mean FT<sub>3</sub> during the critical illness (I) and at the time of recovery (II) was 2.537 and 2.232 pg/ml, respectively. The mean FT<sub>3</sub> was low during the critical illness and increased during recovery, and the difference was statistically significant ( $p < 0.001$ ). The mean FT<sub>4</sub> in the two samplings was 15.19 pg/ml during the illness and 15.83 pg/ml after recovery. The mean FT<sub>4</sub> was mildly lower during the critical illness, but the difference was not significant ( $p = 0.518$ ). The mean TSH (by immunoradiometric assay) during the two samplings was 7 and 5.9 mIU/L, respectively. The mean TSH was lower at the time of recovery, but the difference was not significant ( $p = 0.366$ ). The differences between the mean TSH, FT<sub>3</sub>, and FT<sub>4</sub> at the time of recovery (II) minus the

mean of these parameters at the time of admission were checked in each group. The p-values are shown in Table II. Only in Groups 2 and 3 (BW > 1,500 g) were the FT<sub>3</sub> at the time of admission significantly lower than that at the time of discharge from the NICU. The difference of the mean FT<sub>3</sub> during the two times (I and II) was significant in term and preterm neonates, but in term neonates it was more significant (p = 0.009 vs. p = 0.034).

In our study, ten patients had surgical problems. The difference of the mean FT<sub>3</sub>, FT<sub>4</sub> and TSH was compared during the two time periods (I and II) between the medical and surgical patients. In both groups, FT<sub>3</sub> was significantly lower during the critical illness, but in medical patients, the p-value was more significant (p = 0.003 for medical patients vs. p = 0.017 for surgical patients). FT<sub>4</sub> and TSH did not have any significant difference. Only 48 patients had a known Apgar score. The changes of the thyroid function tests were compared during the illness in patients with a good Apgar score (score ≥ 7, n = 32) and those with a low Apgar score (score < 7, n = 16). FT<sub>3</sub> was significantly lower during the critical illness in patients with a good Apgar score at the time of birth (p = 0.001), but in patients with a poor Apgar score, the difference was not significant (p = 0.472). In patients with a low Apgar score, the TSH was significantly lower during the critical illness (p = 0.028); however, in patients with a good Apgar score, the difference was not significant (p = 0.230).

The patients were assigned into three groups according to the duration of admission (< 7 days, 7–14 days, > 14 days) and the first FT<sub>3</sub>, FT<sub>4</sub> and TSH levels were compared, but the difference was not significant (p-values were 0.31, 0.13, 0.47, respectively). There were no significant differences between the first FT<sub>3</sub>, FT<sub>4</sub> and TSH levels of patients who needed a ventilator and those who did not (p-values were 0.93, 0.79, 0.32, respectively). 32 patients underwent echocardiography, while only eight of them had congenital heart disease (CHD) and 24 patients had normal echocardiography (patent ductus arteriosus in premature neonates was considered normal). There were no significant differences between the first FT<sub>3</sub>, FT<sub>4</sub> and TSH of patients with CHD and those with normal echocardiography (p-values = 0.18, 0.36, 0.53, respectively). Only one patient who had normal FT<sub>3</sub>, FT<sub>4</sub> and TSH in the first and second samples received dopamine, and no congenital anomaly, except for CHD, was detected.

## DISCUSSION

About six (9.0%) patients in the NICU had a positive screening test, more than four-fifths of whom were detected in the second sampling. Therefore, a significant

difference was observed between normal neonates and patients of the NICU (p < 0.001). FT<sub>3</sub>, FT<sub>4</sub> and TSH levels were evaluated in these patients (Table I), and the final diagnoses in these six patients were congenital hypothyroidism (CH) in one patient (Case 2), euthyroid sick syndrome in four (Cases 1, 3, 4 & 6) and high TSH with normal FT<sub>3</sub> and FT<sub>4</sub> (possible compensated CH) in one patient (Case 5). Previous studies reported on the spectrum of thyroid function abnormalities in critically-ill infants. In Franklin et al's study,<sup>(5)</sup> the infants developing respiratory distress syndrome had normal TSH, T<sub>3</sub>, T<sub>4</sub>, and FT<sub>4</sub> values at birth, but they had significantly low T<sub>3</sub>, T<sub>4</sub>, FT<sub>4</sub> values at the fifth day of age, while TSH values remained normal. Chen studied 31 critically-ill and 49 healthy control neonates, and reported lower T<sub>3</sub>, T<sub>4</sub> and FT<sub>4</sub> concentration in the sick neonates, but the serum TSH values were not significantly different between the sick and healthy neonates.<sup>(6)</sup> Reidel et al also reported low serum T<sub>4</sub> and FT<sub>4</sub> and normal TSH in preterm infants admitted to the NICU.<sup>(7)</sup>

Larson et al reported delayed TSH elevations in babies with congenital hypothyroidism in the NICU and recommended routine rescreening of patients admitted to the NICU, although they did not evaluate the type and cause of this problem.<sup>(8)</sup> Rapaport highlighted the importance of rescreening in NICU patients, especially those with congenital anomalies, CHD and patients receiving medications such as dopamine, steroid, amiodarone and exposure to iodine-containing drugs.<sup>(9)</sup> We had five patients with delayed TSH elevations, none of whom had CHD or congenital anomalies. As they did not receive dopamine and steroid during their critical illness, the most probable cause was transient elevation of TSH during recovery.

During recovery in patients with euthyroid sick syndrome, TSH may be transiently elevated (up to 15–20 mIU/L).<sup>(10-12)</sup> Elevation of TSH persists until FT<sub>3</sub> and FT<sub>4</sub> return to normal.<sup>(11-14)</sup> This pattern can be confusing if the elevated TSH level is associated with the still-reduced concentration of FT<sub>4</sub>.<sup>(15)</sup> Such patients meet all laboratory criteria for primary hypothyroidism with the exception of the clinical content. The follow-up generally reveals a normalisation of TSH and T<sub>4</sub> within 1–2 months. Treatment with thyroid hormones is not indicated in these patients.<sup>(15)</sup> Infants at risk should be monitored by serial determination of FT<sub>4</sub> and TSH, and thyroxine treatment should be initiated if the illness state is expected to persist and TSH remains elevated for one month or longer,<sup>(10)</sup> or if TSH rises to more than 20 mIU/L.<sup>(16)</sup>

Comparison of the mean thyroid function tests during the critical illness and after recovery in the NICU showed a significant reduction of FT<sub>3</sub> during the illness while it

increased after recovery. No significant change was seen in the FT<sub>4</sub> and TSH levels. Three-quarters of patients during the critical illness were less than seven days of age, and after recovery, all of them were more than seven days old. Therefore, the mean TSH, FT<sub>3</sub> and FT<sub>4</sub> in the first samples must be higher than those in the second samples, but the mean FT<sub>3</sub> and FT<sub>4</sub> in our patients were less in the first samples, especially the mean FT<sub>3</sub> that was significantly lower during the illness. This condition can be explained only with the euthyroid sick syndrome, similar to the results of Franklin et al's<sup>(5)</sup> and Riedel et al's<sup>(7)</sup> studies. In the euthyroid sick syndrome, the consistent finding is an abnormally-low serum T<sub>3</sub>, while T<sub>4</sub> and FT<sub>4</sub> levels may be low or normal and the TSH level is normal. This syndrome has been recognised in sick infants and children.<sup>(10)</sup> During recovery, TSH may be transiently elevated and this problem was seen in patients with a positive screening test. The mean TSH of all the NICU patients decreased at the time of recovery ( $p > 0.05$ ), which might be due to the effect of age on the TSH level; elevation of TSH was not observed in all patients with the euthyroid sick syndrome.

Low FT<sub>3</sub> (euthyroid sick syndrome) was seen only in neonates with a BW > 1,500 g. Reduction of FT<sub>3</sub> during illness occurs both in term and preterm neonates, but in term infants, it was more significant. The euthyroid sick syndrome is an adaptive response to decrease the metabolic rate in severely-ill patients.<sup>(10)</sup> This mechanism of adaptation may be less mature in preterm neonates, especially in LBW infants. In patients with a good Apgar score (score  $\geq 7$ ), FT<sub>3</sub> significantly decreased during the illness, but in patients with a low Apgar score (score < 7), this difference was not significant. TSH was significantly lower in patients with a low Apgar score, so the euthyroid sick syndrome is due to peripheral hormone metabolism that is seen during fasting and illness, and the central problem may affect the metabolism.<sup>(17)</sup> The euthyroid sick syndrome was seen both in medical and surgical patients. Some studies evaluated the association of FT<sub>3</sub> and FT<sub>4</sub> levels during an illness with the severity and duration of the disease;<sup>(18-20)</sup> however in our study, the levels of FT<sub>3</sub> and FT<sub>4</sub> during the illness was not affected by the duration of the illness, presence of CHD or the use of a ventilator.

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