Evaluation of thyroid status of infants in the intensive care setting

Hemmati F, Pishva N

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 (FT₃), free thyroxine (FT₄) 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 FT₃ was significantly lower during the critical illness and it increased after recovery (2.537 and 3.232 pg/ml, respectively). Mean FT₄ 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 FT₄. The levels of FT₃ and FT₄ 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

INTRODUCTION
Considerable efforts are devoted worldwide to improve the neonatal health. 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. Previous studies reported on the spectrum of thyroid function abnormalities in critically-ill neonates that include low thyroxine (T₄) and normal free T₄ (FT₄) that seem to be due to a decrease in the thyroid-bonding globulin during the illness, low Ts, FT₄, triiodothyronine (T₃) and normal thyroid-stimulating hormone (TSH), and transient primary hypothyroidism with a late rise of TSH. 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.
The infants were stratified by BW into three groups, viz. (1) very low BW (VLBW) i.e. BW < 1,500 g; (2) low BW (LBW) i.e. 1,500 g ≤ BW ≤ 2,500 g; and (3) normal BW (NBW) i.e. 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 ≥ 10 mIU/L. Free T3 (FT3) and FT4 were measured by a radioimmunoassay kit (RIA-gnost® FT3 Sep 2005-Model 12 and RIA-gnost® FT4 June 2005 model 14 [CIS Bio International, Gif-sur-Yvette Cedex, France]). These kits measured FT3 and FT4 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 ± 11 days. About half of the patients were three days of age and three-quarters were less than seven days of age during the first sampling, while after the recovery, they were 27 ± 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.

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↓: below normal range; NR: normal range; ↑: above normal range; borderline: 5 < TSH < 10 mIU/L

The incidence of positive screening tests in healthy neonates in the province was 2.2 per 1,000. 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 FT3 during the critical illness (I) and at the time of recovery (II) was 2.537 and 2.232 pg/ml, respectively. The mean FT4 was low during the critical illness and increased during recovery, and the difference was statistically significant (p < 0.001). The mean FT4 in the two samplings was 15.19 pg/ml during the illness and 15.83 pg/ml after recovery. The mean FT4 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, FT3, and FT4 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 FT₄ at the time of admission significantly lower than that at the time of discharge from the NICU. The difference of the mean FT₄ 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 FT₄, FT₃ and TSH was compared during the two time periods (I and II) between the medical and surgical patients. In both groups, FT₄ 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). FT₃ 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). FT₄ 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 FT₄, FT₃ 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 FT₄, FT₃ 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 FT₄, FT₃ 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 FT₄, FT₃ 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). FT₄, FT₃ 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 II), euthyroid sick syndrome in four (Cases 1, 3, 4 & 6) and high TSH with normal FT₄ and FT₃ (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, the infants developing respiratory distress syndrome had normal TSH, T₄, T₃, and FT₄ values at birth, but they had significantly low T₃, T₄, FT₃ 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 T₃, T₄ and FT₃ concentration in the sick neonates, but the serum TSH values were not significantly different between the sick and healthy neonates. Reidel et al also reported low serum T₄ and FT₃, and normal TSH in preterm infants admitted to the NICU.

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. 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. 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). Elelevation of TSH persists until FT₄ and FT₃ return to normal. This pattern can be confusing if the elevated TSH level is associated with the still-reduced concentration of FT₃. 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 T₃ within 1–2 months. Treatment with thyroid hormones is not indicated in these patients. Infants at risk should be monitored by serial determination of FT₄ 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, or if TSH rises to more than 20 mIU/L.

Comparison of the mean thyroid function tests during the critical illness and after recovery in the NICU showed a significant reduction of FT₃ during the illness while it
increased after recovery. No significant change was seen in the FT₃ 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, FT₃ and FT₄ in the first samples must be higher than those in the second samples, but the mean FT₃ and FT₄ in our patients were less in the first samples, especially the mean FT₃ 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 (5) and Riedel et al.'s (7) studies. In the euthyroid sick syndrome, the consistent finding is an abnormally-low serum T₃, while T₄ and FT₄ levels may be low or normal and the TSH level is normal. This syndrome has been recognised in sick infants and children. 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 FT₃ (euthyroid sick syndrome) was seen only in neonates with a BW > 1,500 g. Reduction of FT₃ 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. This mechanism of adaptation may be less mature in preterm neonates, especially in LBW infants. In patients with a good Apgar score (score ≥ 7), FT₃ 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. The euthyroid sick syndrome was seen both in medical and surgical patients. Some studies evaluated the association of FT₃ and FT₄ levels during an illness with the severity and duration of the disease; however, in our study, the levels of FT₃ and FT₄ during the illness was not affected by the duration of the illness, presence of CHD or the use of a ventilator.

ACKNOWLEDGEMENTS

The authors would like to thank the Office of Vice Chancellor of Research of Shiraz University of Medical Sciences for financial support of this study, and Dr Davood Mehrabani and Mrs Nasreen Shokrpour at Center for Development of Clinical Research of Nemazeed Hospital for their editorial assistance.

REFERENCES