

EVALUATION OF THYROID FUNCTIONS IN CRITICALLY ILL INFANTS

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ABSTRACT

The degree to which thyroid functions are affected by non-thyroid illness and an assessment of its correlation with mortality was evaluated. Thirty infants (20 M, 10 F) with a mean age of 433±3.28 months (±1 SD), with severe acute systemic illness and 30 healthy controls, age and sex matched, were studied for total serum T3, T4 and TSH levels at admission and recovery or before death. Serum thyroid hormones were measured using standard techniques.

There was no significant change in thyroid indices with age, sex, nutritional status, serum protein and C-reactive protein. Serum T3 levels in infants were significantly lower (0.62 ± 0.63 ng/ml) than the controls (1.90 ± 0.62) ($p < 0.001$), with normal T4 and TSH levels at admission. Both serum T3 and T4 levels increased with recovery. Out of 30 infants studied, 14 died whereas 16 were discharged. It was noticed that T3 and T4 values were significantly reduced at or near death when compared with the admission levels ($p < 0.001$). Prognosis could not be determined at the time of admission, as thyroid indices at admission of patients who died, when compared to infants who were discharged, showed no significant difference in T3, T4 or TSH levels.

The above mentioned changes in thyroid indices probably occur as a temporary adaptive mechanism to limit catabolism in states of stress such as infection. Hence, it is suggested that thyroid function tests be interpreted with caution in patients with non-thyroid illness.

Key words: *Thyroid function, Systemic illness, Prognosis.*

Malnutrition and illness influence every aspect of thyroid hormone economy, from the control of secretion to the delivery, metabolism and ultimate action. This has led to the terminology known as "Sick Euthyroid Syndrome" which is characterized by significant decrease in serum tri-iodothyronine (T3) slight decrease in serum thyroxin (T4) increase in reverse T3 level and no significant change in thyroid stimulating hormone (TSH) level(1-5). During the past two decades, considerable progress has been made in the understanding of the peripheral metabolism of thyroid hormones in diseases that do not primarily affect thyroid gland. Interestingly, all the conditions in which sick euthyroid syndrome has been documented have nothing more in common than catabolic state. Hence, it has been suggested that the decrease in thyroid hormone level may be a protective phenomenon to limit protein catabolism and lower energy requirements in non-thyroidal illness (NTI)(6).

The degree to which thyroid functions are affected by NTI is related to the severity of the illness and can serve as a useful, if relatively non-specific, prognostic indicator(7). In adults, in different studies significant correlation of serum T3 and T4 levels and patient's prognosis has been shown and mortality is significantly higher in patients of NTI with low T4 and progressively declining T3 levels. However, in children and especially in infants no definite correlation has yet been found(7-10). If the correlation

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can be established, children with a poor prognosis (low T3 T4 levels) could be identified earlier and this may allow for closer observation and therapeutic intervention.

Material and Methods

The study was conducted at the Department of Pediatrics in collaboration with the Department of Nuclear Medicine, Safdarjang Hospital, New Delhi. Study subjects comprised of 30 children in age group 1 month to 12 months (20 M, 10 F) suffering from acute severe systemic illness requiring intensive therapy. Bronchopneumonia was the commonest illness, others being septicemia, meningitis, gastroenteritis, bronchiolitis and severe spasmodic bronchitis. All the infants were examined and relevant investigations and treatment for their disease were instituted and the progress monitored. Equal number of age (1-12 mo) and sex matched healthy infants (mostly siblings of patients) were taken as controls. All infants with maternal history of thyroid dysfunction, children with clinical evidence of endocrine abnormality, especially thyroid and infants with clinical goitre were excluded from the study. The nature and purpose of the study was carefully explained to parents of all the subjects and their consent was taken before including them in the study.

Thyroid Function Tests

Thyroxine (T4), tri-iodothyronine (T3) and thyroid stimulating hormone (TSH) were measured on two occasions: (a) at the time of admission before instituting treatment for the disease; and (b) at the time of discharge or during the terminal stage prior to or at death.

Five ml venous blood was collected without anticoagulant and serum was stored in airtight containers at -20°C till the

analysis was performed. Similarly, samples were collected for the controls. Serum thyroxine and tri-iodothyronine were measured by radioimmunoassay technique and serum levels of thyroid stimulating hormone were measured by immunoradiometric assay. The radioimmunoassay kit for thyroxine (Code RIAK -5/5A) and tri-iodothyronine (Code RIAK -4/4A) and TSH immunoradiometric assay kit (IRMA -9) were supplied by Board of Radiation and Isotope Technology, Bhabha Atomic Research Centre, Bombay. All the samples were tested in duplicate. Protocol provided along with the kits was strictly adhered to during analysis.

Statistical analysis was done using Student's 't' test. Null hypothesis was rejected with level of significance <0.05.

Results

Thirty children in the age group of 1 mo to 12 mo with a mean of 4.33 ± 3.28 mo (± 1 SD) were studied. The outcome of patients was recorded in the form of death (n=14) or discharge (n=16). The average period of stay in the hospital in discharge and death cases was 7.6 and 2.07 days, respectively.

The mean plasma concentration of T3 during sickness at admission was 0.62 ± 0.63 ng/ml which was markedly low as compared to the control values (1.90 ± 0.62 ng/ml) ($p < 0.001$). However, the level of serum T3 came back to normal level 1.67 ± 0.75 ng/ml at the time of discharge ($p > 0.01$). Mean serum T3 levels at the time of discharge when compared to levels at admission (n=16), also showed a significant difference ($p < 0.001$).

Thyroid function indices of cases at admission, death and discharge are depicted in *Table I*. Serum T3 levels of patients who died, when compared with their initial

TABLE I—Thyroid Function of Cases at the Time of Admission, Death and Discharge

Sampled population	T3 ng/ml	T4 µg/dl	TSH IU/ml
At admission (n=14)	0.54 ± 0.52 [#]	7.62 ± 2.74 [#]	1.07 ± 0.79
At death (n=14)	0.13 ± 0.28	3.94 ± 2.39	1.45 ± 2.01
At discharge (n=16)	1.67 ± 0.75 [*]	9.81 ± 2.80 [*]	1.32 ± 0.90
Control (n=30)	1.90 ± 0.62	9.24 ± 2.49	0.84 ± 0.46

* p <0.001; # p <0.01

admission values, were significantly reduced. Also, serum T3 levels of patients at recovery, when compared with infants who died, showed a significant difference (p <0.001).

Serum T4 levels at admission were not much altered, but the levels increased significantly at the time of discharge though the levels were still in the normal range. Serum T4 levels decreased significantly if the outcome was death. Six out of 14 infants who died had serum T4 values <3 µg/dl. The fall in serum T4 was more than fall in T3 in those who died when compared with the admission levels (p <0.001). Serum TSH levels did not show any significant change at admission and at death in patients when compared to the controls. However, the levels at discharge were higher than the control values.

No significant difference in T3, T4 and TSH levels was observed with regard to sex, age (<6 mo and >6 mo), nutritional status, serum proteins (low and normal) and to C-reactive protein.

Discussion

Under normal circumstances, 100% of T4 and 10-20% of T3 in the serum are directly secreted by the thyroid gland. The remaining 80% of T3 is derived from periph-

eral monodeiodination of T4 by the enzyme 5'deiodinase. In adults and in children many medical and surgical illnesses lead to euthyroid sick syndrome(1,5,7). Several studies have correlated both the serum T4 and T3 levels with increased mortality in adults but little is known in children especially in infants(7,10).

We observed significantly low serum T3 levels in infants at the time of admission as compared to the controls (p<0.001) which returned to normal at the time of discharge. Twenty eight of 30 medically ill infants had low levels of T3 within 24 hours of admission. Serum T4 and TSH levels did not show any significant change at the time of admission. Zucker *et al.* (8) and Uzel and Neyzi(10) had found similar changes in their studies.

In children in whom the course of the disease was fatal, serum T3 or T4 levels at or just prior to death were significantly low as compared to their admission levels. Also when compared to infants who were discharged, the serum T3 values of patients who died were very low (p <0.001). This shows that there was a marked fall in serum T3 values in infants whose illness was severe enough to end in mortality. McLarty *et al.* in a study of 30 patients of myocardial

infarction showed a sequential and progressive fall in serum T3 and T4 levels from the time of admission reaching abnormally low in all six patients who died in their series(11). However, prognosis cannot be ascertained at the time of admission. Retrospectively, when thyroid indices at admission of infants who died were compared to infants who were discharged, no significant difference could be found in serum T3, T4 and TSH levels in the present study. In various studies nadir value of T4 and T3 or sequential decrease in the values has been correlated to mortality. Kaptein *et al.* in a study of 195 critically ill medical patients correlated clinical outcome with the lowest of serial T4 values as well as other thyroid indices. Mortality was inversely related to nadir serum T4 concentration(12). Our study also had 6 infants with T4 <3 µg/dl and all six of them died. Uzel and Nezi in their study of 13 infants also showed serum T4 value to be very low in 8 cases who died(10).

The importance of changes in thyroid hormone level with non-thyroidal illness is uncertain. At present, there is no evidence that T4 administration is required in euthyroid sick syndrome. Brent and Hershman studied effects of thyroxin therapy on patients with severe NTI and low serum thyroxin concentration. Thyroxin administration rapidly normalized serum T4 concentration but T3 concentration did not increase. Thyroxin therapy in the said study did not augment thyroid hormone action nor did it improve survival. Decreased conversion of T4 to T3 in the periphery has been postulated to be the predominant cause of low T3 levels inspite of T4 therapy(13).

Our study demonstrated prospectively that euthyroid sick syndrome occurred in the majority of sick infants studied and progressive decline in T3 and T4 values is

related to the prognosis of NTI. If thyroid indices are measured early in the course of critical illness, which is predictive of subsequent outcome, the clinical value of such laboratory assessment will be enhanced because presumably there will be time available for intensive therapeutic intervention.

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