

Original Research Article

Serum Cortisol and Thyroid Hormones in Critically Ill Infants

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ABSTRACT

The degree to which adrenal and thyroid functions are affected by serious illnesses and their correlation with mortality was evaluated. Forty infants (27 M, 13 F) with a mean age of 433 ± 3.28 months (± 1 SD), with severe acute systemic illness (AIOS) and 40 healthy controls, age and sex matched, were studied for total serum cortisol, T3, T4 and TSH levels at admission and recovery or before death. All these 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 cortisol levels were significantly raised in study group (216.4 ± 66.5) as compared to controls. Cortisol levels were comparable to controls at the time of discharge. Levels were again significantly raised (235.8 ± 112) in those who died. Serum T3 levels in study group were significantly lower (0.57 ± 0.49 ng/ml) than the controls (1.90 ± 0.61 ng/ml) ($p < 0.001$), with normal T4 and TSH levels at admission. Both serum T3 and T4 levels increased with recovery. Out of 40 infants studied, 11 died whereas 29 were discharged. It was noticed that T3 and T4 values were significantly reduced at or near death when compared with the admission levels ($p < 0.001$). If these 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 for intensive therapeutic intervention.

Key words: Thyroid function, Systemic illness, cortisol.

INTRODUCTION

Despite advances in medical management, the mortality rate of critically ill children continues to be considerable. In health and disease homeostasis is generally maintained by series of neuroendocrine and metabolic responses. It is known that microbial infections, tissue damage, autoimmune process and endotoxic shock are associated with variety of endocrine and metabolic changes such as activation of pituitary adrenal systems, alteration of serum thyroid hormone levels, inhibition of

reproductive systems and altered carbohydrate metabolism. ⁽¹⁾ The release of mediator substances, the adrenal & thyroid response of endocrine system is often tailored to the magnitude of stress in critically ill. Recognition of endocrine dysfunction is made more difficult in the critically ill patients because of the unavailability of a reliable history, delay in reporting of diagnostic laboratory results, and comorbidities that obscure a definite diagnosis. Thus, measurement of these hormones in critically ill patients may help in predicting severity of their illness, and

chances of survival. Keeping these facts in mind present work was planned to explore the adrenal and thyroid responses in critically ill children with an additional aim to know the extent of their association with the severity and outcome (prognosis) of illness.

MATERIALS & METHODS

Study group comprised of 40 critically ill children in the age group 1

month to 12 month. Bronchopneumonia was the commonest illness, others being septicemia, meningitis, encephalitis, bronchiolitis and severe spasmodic bronchitis etc. Child was defined critically ill according to "Acute illness observation scale" taken from McCarthy et al, 1982. (2) The criterion taken into account is shown in table (1).

Table 1: Acute illness observation scoring

S.No.	Observation item	Normal	Moderate impairment	Severe impairment
1.	Quality of cry	Strong with normal tone or content and not crying	Whimpering or scobbing	Weak or moaning or high pitched
2.	Reaction to parent stimulation: effect on crying, when held patted, jiggled or carried	Cried briefly then stops or content and not crying	Cries off & on	Continuous cry or hardly responds
3.	State variation	If awake then stays awake or if asleep and stimulated then wakes up quickly.	Eyes close briefly then awakes or awakes with prolonged stimulation	Will not arouse or falls to sleep
5.	Hydration: Moisture in skin eyes & mouth	Skin normal and eyes mouth moist	Skin, eyes normal and mouth slightly dry	Skin doughy and tented and eyes sunken and dry eyes and mouth.
6.	Response to social overtures: being held kissed, hugged, touched, talked to	Smiles or alerts (2month or less)	Briefs smile or alerts briefly	No smile, face anxious, impression less or no alerting

Each item was scored as normal (=1), moderate (=3) and severe impairment (=5). Score of 6 indicates best physical states and 30, worst physical state. Children with score >10 were included in study after taking informed parental consent. Complete systemic examination was done in detail in all the study subjects to evaluate the exact cause of illness. Children with congenital anomalies or with suspected congenital metabolic disorder and infants < 1 months of age were not included in the study. All these patients were followed up till discharge. Outcome was noted as discharge/death. Equal number of age and sex matched healthy children (mostly siblings of patients) were taken as control.

Measurement of cortisol and thyroid hormones: Cortisol and thyroid hormones (T3, T4 & TSH) were measured at 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 of illness. 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 cortisol, thyroxine and triiodothyronine were measured by radioimmunoassay technique and serum levels of thyroid stimulating hormone were measured by immunoradiometric assay. The radioimmunoassay kit for cortisol (RIAK 240CT), thyroxine (Code RIAK - 5/5A) and triiodothyronine (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: Statistical analysis was done using Student's 't' test (with SPSS software) to compare the levels of cortisol, TSH and T3, T4 among controls and study population. Null hypothesis was rejected with level of significance <0.05.

RESULTS

Forty children in the age group of 1 month to 12 month with a mean of 4.33 ± 3.28 mo (± 1 SD) were studied. Male to female ratio in our study was 2.07. 60% of children had their AIOS >22. Of 40 study subjects, 29(72.5%) were discharged following improvement and 11(27.5%) died. The average duration of hospital stay among discharge and death cases was 7.6 and 2.07 days, respectively. The mean serum cortisol levels at admission was $196.4 \pm 66.5 \mu\text{g/dl}$ in study group which was significantly higher than control group

$16.7 \pm 10.6 \mu\text{g/dl}$ ($p=0.014$). Serum cortisol levels at the time of discharge were comparable to that of control group. However cortisol levels ($235.8 \pm 112 \mu\text{g/dl}$) were even more significantly raised ($p<0.001$) in subjects who died. The mean plasma concentration of T3 in study group at admission (0.57 ± 0.49 ng/ml), was markedly lower as compared to the control group (1.90 ± 0.61 ng/ml) ($p <0.009$). However, the level of serum T3 (1.63 ± 0.72 ng/ml) at the time of discharge were not significantly different from the controls ($p >0.01$). Mean serum T3 levels at the time of discharge when compared to levels at admission ($n=29$), showed a significant difference ($p <0.001$). Both cortisol and thyroid function indices of cases at admission, in expired and at discharge are depicted in *Table 2*.

Table 2: Hormone values in study and control groups

Sampled population	Cortisol $\mu\text{g/dl}$	T3 ng/ml	T4 $\mu\text{g/dl}$	TSH IU/m
At admission(n=40)	196.4 ± 66.5	$0.57 \pm 0.49^*$	7.67 ± 2.69	1.10 ± 0.79
Expired(n=11)	$235.8 \pm 112^*$	$0.15 \pm 0.29^*$	$3.98 \pm 2.28^*$	1.39 ± 1.97
At discharge(n=29)	16.5 ± 5.65	1.63 ± 0.72	9.71 ± 2.77	1.37 ± 0.88
Control(n=40)	16.7 ± 10.6	1.90 ± 0.61	9.22 ± 2.44	0.99 ± 0.42

^o $p<0.001$; ^{*} $p<0.01$

Serum T3 levels of patients at recovery (1.63 ± 0.72 ng/ml), when compared with subjects who died (0.15 ± 0.29 ng/ml), showed a significant difference ($p <0.001$) but difference was not significant when cortisol levels at recovery were compared with controls. Serum T4 levels at admission ($7.67 \pm 2.69 \mu\text{g/dl}$) were not much altered, but the levels increased significantly at the time of discharge ($9.71 \pm 2.77 \mu\text{g/dl}$) though the levels were still in the normal range. Serum T4 levels ($3.98 \pm 2.28 \mu\text{g/dl}$) were decreased significantly in subjects who died. Four out of 11 infants who died had serum T4 values $<3 \mu\text{g/dl}$. The fall in serum T4 was more than fall in T3 in those who died when compared with the control group ($p <0.001$). 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.

DISCUSSION

We included only infants in our study because an extreme of age is a high risk because of relative immaturity of the immunological system. Higher male to female ratio in our study is consistent with the observation by Anu Thuckral et al ⁽³⁾ who also noticed the male to female ratio of 1.78. Reason for this difference could be that the male children are better cared for and brought to the referred hospital and also males are genetically inferior in our community. High frequency of children with greater severity of illness (AIOS>22 in 60% of children) seen in our study is

mainly because of referral nature of our hospital which may lead to selection of more critically ill children.

Serum cortisol levels in the study group were significantly raised as compared to controls but levels became similar to controls at the time of discharge. The higher values of cortisol in critically ill children can be explained not only on the basis of physical stress but also due to liberation of cytokines into plasma by immune cells during the inflammatory process which modulate the release of hormone by stimulating hypothalamus pituitary adrenal axis, both synergistically and independently. ⁽⁴⁾ In this study nonsurvivors had significantly higher cortisol values than those who were discharged. Results were consistent with other study.

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 peripheral monodeiodination of T4 by the enzyme 5'deiodinase. In adults and in children many medical and surgical illnesses lead to euthyroid sick syndrome. ⁽⁵⁻⁷⁾ We observed significantly low serum T3 levels in infants at the time of admission as compared to the controls (p=0.009) which returned to normal at the time of discharge. Thirty seven of 40 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. Uzel et al and Zucker *et al* had found similar changes in their studies. ^(8,9) In children in whom the course of the disease was fatal (expiry), serum T3 or T4 levels 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. ⁽¹⁰⁾ 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. ⁽¹¹⁾ Our study also had 4 infants with T4 <3 µg/dl and all four 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. ⁽⁸⁾ 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. ⁽¹²⁾ 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 these 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. One limitation of our study is that we have considered only hospital mortality not the follow up mortality. This may not be significant in children as once they are cured they survive unlike in adults having age and degenerative problems.

CONCLUSION

1. Serum cortisol levels are significantly raised, and T3 levels are significantly lower in critically ill children. TSH levels did not show any correlation with the severity or outcome of illness.
2. Both serum cortisol and Thyroid hormones (T3, T4) can be used in predicting severity and outcome of illness.

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