

Thyroid Functions in Newborns with Septicemia

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- ✓ To investigate the alternations in thyroid functions the concentrations of total triiodothyronine (TT₃), total tyroxine (TT₄), free triiodothyronine (FT₃), free tyroxine (FT₄), tyroxine binding globulin (TBC), albumin and tyroxine binding prealbumine (TBPA) were measured in 32 newborns with septicemia on days 1, 5 and 10 of hospitalisation and compared with age-matched controls. FT₃ and FT₄ levels of patients were significantly lower on the first day but returned to normal on the fifth and tenth days. On contrary to this TT₃ and TT₄ levels were lower on all three occasions but no significant changes were observed in TSH concentrations. TBPA and albumin levels were significantly lower in patients on the first and fifth days. A positive correlation between low TT₃ and TT₄ levels on the tenth day and mortality rate was also shown.

Key words: *Thyroid functions, septicemia, newborn*

✓ Sepsisli Yenidoğanlarda Tiroid Fonksiyonları

Yenidoğan sepsisinde tiroid fonksiyonlarındaki değişiklikleri araştırmak amacı ile sepsisli 32 yenidoğanda hastaneye yatışlarının 1., 5., ve 10. günlerinde serum total T₄, total T₃, serbest T₃, serbest T₄, tiroksin bağlayan globulin ve tiroksin bağlayan prealbumin konsantrasyonları ölçüldü ve sonuçlar benzer yaşlardaki kontrol grubu ile karşılaştırıldı. Birinci günde hastaların serum serbest T₃ ve serbest T₄ seviyeleri anlamlı derecede düşük idi fakat 5. ve 10. günlerde değerler normale döndü. Buna karşın total T₃ ve T₄ değerleri üç ölçümde de düşük seviyelerde saptandı ve TSH düzeyi her zaman normal sınırlarda kaldı. Tiroksin bağlayan prealbumin ve albumin değerleri 1. ve 5. günlerde düşük idi. Onuncu günde düşük total T₄ ve total T₃ değerleri ile mortalite arasında pozitif bir ilişki olduğu görüldü.

Anahtar kelimeler: *Tiroid fonksiyonları, sepsis, yenidoğan*

INTRODUCTION

The endocrine system helps to maintain homeostasis in severe diseases, such as trauma or septicemia. Profound alterations in peripheral thyroid hormone metabolism may occur in patients with severe nonthyroidal illnesses of either acute or chronic nature. Despite low serum T₃ or T₄ levels these patients are euthyroid as evidenced by normal basal TSH concentrations and a

normal TSH response to TRH administration. This syndrome is called the euthyroid sick syndrome (ESS)^(1,2). The abnormal thyroid functions gradually return to normal as the patient improves from the primary illness. Extensive studies have been performed to evaluate the hormonal changes in adults and children with severe systemic illness, but limited research has been done in neonates⁽³⁻⁵⁾. In a study it has been shown that low

serum T_4 levels are associated with increased mortality in adult intensive care unit patients⁽⁶⁾. The present study aims to investigate whether a similar relationship exists for neonates with septicemia, a very severe disease in the first month of the life.

MATERIALS AND METHODS

The study comprised 32 neonates with septicemia aged 0-28 days (mean 14.3 days) and 25 postnatal age-matched (mean 15.6 days) healthy controls. The diagnosis of septicemia was based on clinical and laboratory findings. The first blood samples from sick neonates were obtained just after admission to the hospital during routine evaluation for infection and repeated on days 5 and 10. On the same days blood samples were taken from controls who were selected among babies with hyperbilirubinemia either due to ABO incompatibility or physiologic jaundice but healthy in other aspects. The management of the patients was started as soon as possible and it consisted of appropriate antibiotics and supportive care, but medications, which would effect thyroid functions, were avoided. The levels of TT_3 , TT_4 , FT_3 , FT_4 , TBG, albumin and TBPA were measured by radioimmunoassay or chemiluminimetric assay as suggested by the manufacturer (Diagnostic Products Corporation, Los Angeles, USA). Data were analysed by Mann-Whitney U test for comparisons between patients and controls, by Wilcoxon paired t test for comparison of data of the subjects on various occasions, and by correlation analysis for closeness of the relation between laboratory findings and mortality rate.

RESULTS

The study group included 17 males and 15 females with a mean weight of 2914 ± 450

gr (2500-4000 gr) and control group 16 males and 9 females with a mean weight of 3114 ± 345 gr (2500-3750). Age and weight distribution of the study and control subjects was not statistically significant ($p > 0.05$). The mothers of both groups had no problem concerning thyroid functions. The predominant microorganisms isolated were *Staphylococcus aureus*, *Escherichia coli* and *Salmonella* species in blood, cerebrospinal fluid and urine cultures of the patients.

When we compared the thyroid hormone levels of the patients on the first day: TT_3 , FT_3 , TT_4 , FT_4 levels were significantly lower in comparison to controls ($p < 0.05$) (Table). On the fifth and tenth days of the management FT_3 and FT_4 levels were similar, but TT_3 and TT_4 levels were still lower than those controls. TSH concentrations were similar in both groups on all three occasions. TBPA and albumin levels were significantly ($p < 0.05$) lower in patients on the first and fifth days. TBPA concentrations returned to normal on the tenth day in spite of persistent low levels of albumin. TBG levels of patient were lower on all three occasions but not statistically significant ($p > 0.05$). Low levels of TT_3 and TT_4 on the tenth day were weakly correlated with mortality rate (r values were 0.54 and 0.43 respectively and $p < 0.05$ for both). TSH levels did not change during the follow-up period ($p > 0.05$).

DISCUSSION

Abnormalities of thyroid function in systemic nonthyroidal illnesses have been classified as 1) low T_3 syndrome, 2) low T_3 -low T_4 syndrome, 3) high T_4 syndrome, and 4) other abnormalities⁽⁷⁾. Low serum TT_3 is the most common abnormality in systemic nonthyroidal illnesses. It is observed in about 70% of hospitalized patients⁽⁸⁾. In a study of 86 intensive care unit patients, T_4 levels less

Table. Thyroid Hormone Levels of Patients On Days 1, 5 and 10.

	Subjects (n: 32)		Controls (n: 25)		p
	Mean	SD	Mean	SD	
TT3-1 (ng/ml)	110.00	48.41	195.48	52.27	.000
TT3-5 (ng/ml)	138.40	49.24	192.25	52.10	.000
TT3-10 (ng/ml) ^a	136.00	54.36	189.50	52.12	.000
TT4-1 (µg/dl)	9.93	4.57	18.10	3.75	.000
TT4-5 (µg/dl)	11.41	4.77	17.20	3.25	.000
TT4-10 (µg/dl)	11.01	4.85	17.65	3.42	.000
FT3-1 (pg/dl)	2.03	1.08	2.93	1.33	.007
FT3-5 (pg/dl)	2.63	1.54	2.98	1.35	.453
FT3-10 (pg/dl)	2.77	1.73	2.65	1.25	.698
FT4-1 (ng/dl)	1.12	0.49	1.62	0.51	.001
FT4-5 (ng/dl)	1.41	0.59	1.48	0.45	.177
FT4-10 (ng/dl)	1.29	0.56	1.56	0.47	.146
TSH-1 (mIU/ml)	5.53	4.13	4.06	2.90	.163
TSH-5 (mIU/ml)	5.48	4.29	4.26	2.95	.171
TSH-10 (mIU/ml)	5.03	4.71	4.45	2.98	.396
TBG-1 (mg/dl)	2.85	0.50	3.25	1.80	.058
TBG-5 (mg/dl)	2.50	0.45	2.80	1.92	.580
TBG-10 (mg/dl)	2.75	0.65	3.25	1.53	.580
TBPA-1 (mg/dl)	8.93	3.25	10.45	1.88	.044
TBPA-5 (mg/dl)	8.29	3.59	10.90	1.90	.015
TBPA-10 (mg/dl)	10.59	4.15	11.25	1.92	.876
ALB-1 (g/dl)	3.80	0.72	4.25	0.44	.020
ALB-5 (g/dl)	3.35	0.54	4.18	0.43	.000
ALB-10 (g/dl)	3.21	0.85	4.16	0.42	.000

TT3: Total triiodothyronin, TT4: total thyroxine, FT3: free triiodothyronin, FT4: free thyroxine, TSH: thyroid stimulating hormone, TBG: thyroxine binding globuline, TBPA: thyroxine binding prealbumine, ALB: albumine

than 3 µg/dl were associated with an 84% mortality rate compared with a 15% rate in those patients with T₄ levels greater than 5 µg/dl and patients with low T₄ who had very low serum T₃ levels had the worst prognosis⁽⁶⁾. In the majority of these mentioned patients TSH levels similar to our cases remained normal. Zucker and co-workers⁽⁹⁾ studied 9 medical and 18 surgical children admitted to an intensive care unit with various non-endocrine diagnoses. Six of 9

medical patients had low T₄-T₃ levels within 24 hours of admission, 14 of 18 surgical patients had low T₄-T₃ levels by the end of cardiac bypass, and levels declined further over the next 24 hours. TSH levels were normal except one who later had been diagnosed as primary hypothyroidism. In about 10-30% of adult patients without thyroid disease in intensive care units increased total and free T₄ levels have been reported, though the patients were clinically

euthyroid. Trials of supplemental thyroid hormone did not improve mortality, and such treatment may even be harmful⁽¹⁰⁾.

Pathogenesis of these changes has not been completely understood. Alterations in serum binding of thyroid hormones is clearly an important factor contributing to changes in thyroid hormone levels in systemic nonthyroidal illnesses⁽⁸⁾. A circulating tissue product or metabolite is believed to be responsible for inhibiting T_4 binding to TBG in these patients⁽¹¹⁾. Further, there is evidence for decreased conversion of T_4 to T_3 in extrathyroidal tissues in the systemic nonthyroidal illnesses^(12,13). The mechanism of inhibition of the conversion of T_4 to T_3 is not entirely clear. This may be related to decreased activity and/or concentration of 5'-monodeiodinase⁽¹⁴⁾. Diminution in the uptake of T_4 by tissues can also explain the decreased generation of T_3 in tissues⁽¹⁵⁾. The decreased free T_4 concentrations result from decreased production, presumably secondary to suppression of the hypothalamic-pituitary axis⁽¹⁶⁾. But in most of these patients TSH levels and response to TRH stimulation tests were normal⁽¹⁷⁾. Some cytokines (e.g. $TNF\alpha$) which are increased during septicemia has also been implicated. TNF administration to rats has been shown to decrease serum TSH levels, and decrease the thyroid response to TSH⁽¹⁸⁾. It is not known if low circulating T_3 or T_4 levels represent tissue hypothyroidism in children⁽¹⁹⁾. However, in an autopsy study of adult patients who have died from trauma and other acute illness, low T_4 levels were present in some tissues⁽²⁰⁾. Studies in premature infants with respiratory distress syndrome (RDS) have shown lower levels of T_4 and T_3 and occasionally, lower levels of TSH and TBG relative to control prematures without RDS⁽²¹⁻²³⁾. Although it has been suggested that thyroid hormone

administration decreased mortality in neonates with RDS, this has not been confirmed⁽²⁴⁾.

In our study which to the best of our knowledge is the largest series published on thyroid hormone changes in the neonatal septicemia, thyroid hormone levels, especially TT_3 and TT_4 decreased during the early stage of the clinical picture and increased with the progression of the illness. In addition, a positive correlation was shown between the prognosis of the septicemia and thyroid hormone levels. With these results we conclude that thyroid hormone levels decrease transiently in neonatal septicemia and they may be used as prognostic indicators in the clinical evaluation of these patients.

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