

Original Research Article

Thyroid hormones as a marker to diagnose the severity of fungal sepsis in neonates

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Received: 07 October 2019

Revised: 26 October 2019

Accepted: 31 October 2019

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ABSTRACT

Background: Sepsis due to fungi in the neonatal period occurs in infants admitted to the ICU for long periods of time, especially affecting infants with a birth weight <1500 g. In this case series thyroid insufficiencies have been used as a marker to diagnose the severity of fungal sepsis and outcome of those babies. Objectives of this study was to describe thyroid hormone variations in new-borns with fungal sepsis and to find the correlation between thyroid hormone deficiency and severity of fungal sepsis

Methods: It is a prospective observational study of 100 infants done in Sree Balaji Medical College, chrompet. Thyroid profile was done to all patients. Patients with Low T3 syndrome and Low T3, T4 syndrome were divided into group A and B and statistical analysis was done to find the correlation between thyroid insufficiency and severity of the fungal sepsis.

Results: Significant correlation was noted between low T3, low T4 levels and fungal sepsis.

Conclusions: Thyroid insufficiency, with the variables described, could be a marker of disease severity with the possible need for hormone supplementation to decrease the mortality.

Keywords: Fungal sepsis, Marker of sepsis, Thyroid insufficiency

INTRODUCTION

Late-onset neonatal sepsis is directly related to postnatal factors and the multiple invasive procedures to which these infants are submitted at the neonatal intensive care unit (NICU). These procedures include tracheal intubation, percutaneous catheters, venipuncture, and parenteral nutrition.¹ Hospital microorganisms are the main causative agents of sepsis, including bacteria and fungi, and can be transmitted horizontally through the staff and from the professionals' hands.² Sepsis may affect various tissues and modify the action of certain enzymes, including those responsible for the formation of thyroid hormones in peripheral tissues, causing the so-called non-thyroidal illness syndrome (NTIS), which is characterized by the presence of abnormalities in thyroid

hormone serum levels, but without the classic thyroid disease that can affect adults, children and even infants.³ NTIS has been used as an interesting parameter of severity since it has been verified that more severe patients have more prolonged alterations and later recovery and that the prognosis in adults is poor, and may even lead to death.⁴ However, there are still no reports of there being a worse prognosis in infants, let alone those presenting fungal sepsis. It is believed that most episodes of candidemia are of endogenous origin, through the translocation of the pathogen via gastrointestinal tract mucosa, where colonization by this fungus occurs in up to 70% of the normal population.⁵ Any variable that causes an imbalance in the microbiota or harm to the gastrointestinal mucosa can be a facilitating agent for the

translocation of *Candida* spp. from the intestinal lumen to the mesenteric capillaries.^{6,7}

Thyroid hormones in the newborn^{8,9}

Soon after umbilical cord clamping, term infants present high T3 values, reaching 3 to 6 times the fetal serum levels, concomitant with an abrupt increase in thyroid-stimulating hormone (TSH) and catecholamines in response to the temperature differences between the intra- and extra-uterine environments, and the stress of labor. T4 also rises 30 minutes after delivery, with serum levels that can reach 80 to 100 mU/L. All of these hormones decrease within 24 hours, remaining at higher levels than those of the cord blood for 2 to 3 days. In the same manner, as the thyroid hormones, there is a rapid increase in cortisol in term infants at birth, which can reach 20 µg/dL. This hormone stimulates the increase in serum T3, which is essential for activation of type 1 deiodinase (D1) enzyme between 4 and 6 hours after birth, and very low levels of reverse T3. Currently, four stages of NTIS are recognized in adults and children, known as low T3 syndrome, low T3-T4 syndrome, high T4 syndrome, and mixed syndromes.

Low T3 syndrome^{9,10}

This is characterized by low serum levels of T3, normal or slightly increased TSH, and normal free T4 and T4. The level of reverse T3 may be normal or increased. This change is due to inhibition of the activity of the D1 enzyme, which is responsible for both peripheral degradation of T4 to T3 as well as lower clearance of reverse T3. The decline in T3 levels appears to occur a few hours after the onset of sepsis. Recovery occurs in parallel with the improvement of the underlying disease. Low T3 syndrome is the most frequent NTIS abnormality in adults and children. Evidence indicates that low T3 syndrome may be an adaptive response to stress, without association with worse prognoses or increased mortality. For Papanicolaou, low T3 syndrome corresponds to the first stage of non-thyroidal illness syndrome.

Low T3-T4 syndrome^{11,12}

This is characterized by the presence of low T4 and T3, with low TSH being frequent, alongside normal or high reverse T3. This situation has been observed in seriously ill and dying adults and children. Initially, this type of NTIS was explained by the presence of a probable inhibitor of T4 binding to thyroglobulin in the serum. It is currently believed that a mechanism occurs in this type of NTIS related to the effects of cytokines in the hypothalamic-pituitary axis, associated with reduced peripheral T4 action. The response of TSH to thyrotropin-releasing hormone (TRH) seems to be reduced in patients in critical clinical condition. There is evidence that in certain periods of the severe disease there may be genuine central and transient hypothyroidism, in which there is not a nighttime peak in TSH, as well as

evidence of changes in the glycosylation process regulated by TRH. Studies have also suggested reduced T4 action in tissue levels, varying from tissue to tissue, through the demonstration of low serum levels of the angiotensin-converting enzyme, which in turn is stimulated by thyroid hormones. In the recovery phase, there may be a temporary increase in TSH. High T4 syndrome. This is characterized by high serum levels of T4, normal or slightly increased T3 and high reverse T3. Free T3 and free T4 are usually normal or low. The prevalence of this syndrome is usually low. In the initial phase, the decrease in the peripheral metabolism of T4 through inactivation of the D1 enzyme may cause increased rates of this hormone; however, the situation is reversed in a few hours, causing a decline in T4 levels.

Mixed syndromes¹³⁻¹⁵

In mixed syndromes, a combination of the abnormalities described above can be found. When completing our master's thesis, authors noted thyroid abnormalities in infants with bacterial sepsis, and in the present study, we also found six infants with fungal infection. As authors found no published cases in the literature, authors decided to write this article in order to present the changes in thyroid hormones in fungal sepsis. The infants with fungal sepsis made up 17.9% of the total sample (six infants). These infants had laboratory manifestations of sepsis, as well as positive blood cultures for fungi in five of them and one positive urine culture, as well as clinical and radiological signs of fungal sepsis. Infants with severe asphyxia, surgical and cardiac malformations, major surgeries, infants born to mothers with thyroid disease, with congenital infections, and intrauterine growth delay were excluded because these conditions could alter their hormone levels.

The blood samples to test the hormone levels were collected from peripheral veins at the same time as routine tests for sepsis (blood count, C-reactive protein and blood culture). One extra milliliter of blood was taken from the selected patients in order to measure total T4, free T4, T3, reverse T3 and TSH levels. NTIS was considered present when abnormalities were found in the serum levels of thyroid hormones, such as the presence of low T3, low T3-T4, high T4, and mixed levels. Five of the infants with fungal sepsis presented positive blood cultures, with four for *Candida albicans* and one for *Candida tropicalis*. One infant presented urine culture positive for *Candida albicans*. Low T3 syndrome was observed in four infants (66.7%) and low T3-T4 in two infants (33.3%). Two infants with low T3 syndrome (50%) had septic shock and two with low T3-T4 syndrome also progressed with septic shock (100%).

Objectives of this study was to describe thyroid hormone variations in newborns with fungal sepsis and to find the correlation between thyroid hormone deficiency and severity of fungal sepsis.

METHODS

This was a prospective observational study carried in 100 infants between 2 years from 2017-July- 2018-February at Sree Balaji medical college and hospital, Chennai. In this single-center, retrospective, observational study, 100 infants admitted in pediatric wards and ICUs, irrespective of diagnosis were included. Patients with previous thyroid disorders and those with a family history of thyroid disorders were excluded. Fasting venous blood samples received from these patients were subjected for hormone analyses. Admission into wards or ICUs was based on the presentation of the patient and underlying clinical conditions unrelated to the study objectives, fT3, fT4 and TSH levels were assessed using chemiluminescence slide technique. The normal reference range for thyroid hormones in our laboratory is as follows: fT3 (4.26-8.10 pmol/l), fT4 (10.0-28.2 pmol/L) and TSH (0.465-4.68 mIU/l). Any deviation from the normal range is considered to be abnormal (low or elevated). The hormonal assays were not repeated second time or prior to discharge in survivors. Statistical analysis was done between two group of infants to find the correlation between thyroid hormones and severity of sepsis.

RESULTS

The clinical and laboratory variables of infants with fungal sepsis at admission in which Group A are infants with low T-3 syndrome and Group B are infants with low T-3,T-4 syndrome. It shows that the mean weight of the babies in group A is 2947.5 and that of group B is 2930. The mean Temperature of babies in group A is 38.3 C and that of group B is 36.9 C. The mean heart rate of babies in group A is 176/min and that of group B is 192/m.in. The mean respiratory rate of babies in group A is 67/min and that of group B 62/min. The mean Leucocyte count of babies in group A is 25,4445 cells and that of group B is 14,655 cells. The mean CRP of babies in group A is 51.8 and that of group B is 189.5. The mean INR of babies in group A is 0.14 and that of group B is 0.2. The mean immature cells in babies of group A is 0.18% and that of group B is 0.27%. When the two groups are compared using Chi square test, it shows that variables like Leucocyte count, CRP, immature cells and INR were found to be statistically significant. Variables like weight, temperature, heart rate and respiratory rate were not found to be statistically significant (Table 1).

Table 1: Clinical and laboratory variables of the infants with fungal sepsis at admission.

Data	Group	Median	Standard deviation	Mean	Standard error	Range	p value
Weight (g)	A	2825	670.6	2947.5	335.3	1905-3500	0.10
	B	2930	1301.1	2930	920.0	2010-3850	
Temperature	A	37.72	1.35	38.30	0.67	35.7-38.5	1.0
	B	36.95	2.19	36.95	1.55	35.4-38.5	
Heart rate	A	169.75	21.48	176.5	10.74	140-186	0.16
	B	192.5	14.85	192.5	10.50	182-203	
Respiratory Rate	A	67.50	13.30	67	6.65	52-84	0.70
	B	62.00	25.46	62	18.00	44-80	
Leukocyte	A	21215	11477.02	25445	5738.51	4270-29700	0.0001*
	B	14655	3613.32	14655	2555.00	12100-17210	
Immature < 10%	A	0.28	0.21	0.18	0.10	0.15-0.61	0.0005*
	B	0.27	0.17	0.27	0.12	0.15-0.4	
INR	A	0.19	0.11	0.14	0.05	0.12-0.37	0.0001*
	B	0.20	0.10	0.20	0.07	0.13-0.28	
C-reactive Protein	A	75.75	81.95	51.8	40.97	5.4-194	0.0044*
	B	189.55	30.61	189.55	21.65	167.9-211.2	

Table 2: Laboratory variables of infants with fungal sepsis during convalescence period.

Data	Group	Median	Standard deviation	Mean	Standard error	Range	p
C-reactive	A	69.12	58.12	71.35	29.35	7.4-126.4	0.0001*
Protein	B	92.87	58.48	111.45	20.67	3.2-159.9	

Laboratory variable of infants with fungal sepsis during convalescence period which shows that the mean CRP

value of the babies in Group A is 71.3 and that of babies in Group B is 111.4. When these 2 groups are compared

using Chi Square test it shows statistically significant results (Table 2). Arithmetic mean of Thyroid profile during evolution of sepsis in Low T3 syndrome in which the value of T3 during admission (a) convalescence (b) and cure(c) was 59.9, 101.3 and 206.2 respectively and that of T4 was 7.8, 12.9 and 12.5 respectively (Table 3).

When T3 levels in b and c were compared, it shows that they are statistically significant, a and c also show statistically significant values. Whereas a and b were found not to be significant. T4 values when compared during all the three periods i.e. a, b, c was found not to be significant.

Table 3: Arithmetic mean of thyroid profile during evolution of sepsis in Low T3 syndrome.

Variable	Progression			
Hormone	The median±standard deviation			
Thyroid hormones	Admission (a)	Convalescence (b)	Cure (c)	p
T3	59.97±36.27	101.3±77.98	206.25±39.98	a x b=0.80 b x c=0.002* a x c=0.001*
T4	7.80±2.16	12.99±6.29	12.52±2.65	a x b=1.0 b x c=1.0 a x c=1.0

Table 4: Arithmetic mean of thyroid profile during sepsis in low T3,T4 syndrome.

Variable	Progression			
Hormone	The median±standard deviation			
Thyroid hormones	Admission (a)	Convalescence (b)	Cure (c)	p
T3	46.5±3.5	73.58±44.9	76.50±108.19	a x b=0.80 b x c=0.0020* a x c=0.0010*
T4	3.8±1.57	7.78±3.9	5.5±7.78	a x b=1.0 b x c=1.0 a x c=1.0
Free T4	1.28±0.30	1.16±0.55	0.88±1.2	a x b=0.58 b x c=0.39 a x c=0.77 a x c > 0.05
Reverse T3	59.0±83.44	70.15±16.05	33.9±47.9	a x b=0.30 b x c=0.075 a x c=0.009 *
TSH	0.74±1.0	2.82±2.21	1.7±2.4	a x b=1.0 b x c=1.0 a x c=1.00

The arithmetic means of thyroid profile during sepsis in Low T-3,T-4 syndrome in which the T3 values when compared shows that a and b were not statistically significant whereas b and c, a and c were found to be statistically significant. TSH values when compared shows that only a and c were statistically significant. T4 and Free T4 values when compared were not significant (Table 4).

DISCUSSION

Sepsis due to fungi in the neonatal period occurs in infants admitted to the ICU for long periods of time,

especially affecting infants with a birth weight <1500 g. Authors emphasize that this study only included term infants, but even so, authors noted six infants presenting the condition.¹⁶ In Brazil, a multicenter study conducted in the 1990s by Colombo et al, in the cities of São Paulo and Rio de Janeiro observed 145 patients, including adults and children, with positive blood culture for Candida: albicans (37%), parapsi- loss (25%), tropicalis (24%), rugosa (5%), and glabrata (4%).¹⁷

De Zegher F et al, at a neonatal intensive care unit with ten beds at a Tertiary University Hospital, in the city of Uberlândia, regardless of the gestational age, found 19

cases of candidemia, with *Candida albicans* also being the most common, similar to all of the studies cited to date [nine cases of *Candida albicans* (47.9%), five of *Candida Kru-sei* (26.3%), two of *Candida parapsilosis* (10.5%), two of *Candida glabrata* (10.5%), and one of *Candida tropicalis* (5.3%).¹⁸ Das BK et al, found seven cases of *Candida albicans* (29.2%) and 17 cases of *Candida non-albicans*, 16 cases of which were *Candida parapsilosis* (66.7%) and one case of *Candida glabrata* (4.2%). The mortality rate of these children was around 21%. In this case series, authors also observed the presence of *Candida non-albicans*, a finding that is becoming increasingly common.¹⁹

In this study author had one case of *Candida parapsilosis*, and none of the six infants died, despite four of them having presented septic shock. The Spanish study reports 21% mortality. Even though the sample comprised newborn, similar rate was found with a predominance of *Candida albicans* (66.8%) and *Candida tropicalis* (16.6%), as shown in other studies described above.²⁰ In the past, the majority of fungal infections in the population were labeled as *Candida* spp., although the vast majority was *Candida albicans*.²¹

From the 1990s onwards, there was a significant increase in the number of infections caused by *Candida non-albicans*, such as *Candida parapsilosis* and other types of *Candida* in the global population. Low T3-T4 syndrome described in critically ill adults and children is linked to poor prognosis and greater severity of the disease.²²

All of the infants with fungal sepsis survived, so it is not possible to relate this type of syndrome with poor prognosis. However, it was possible to relate the greater severity of the disease, as two of the six infants with low T3 (50%) and two infants with low T3-T4 (100%) had shock, demonstrating that it would be possible to use these hormones as markers of severity, even with a small case series.²³ Another possibility would be the treatment of these changes in children with septic shock, where despite our patients not having progressed to death, the cases remained extremely severe and had prolonged hospitalization. More studies and larger case series are necessary to prove this.²⁴

Nevertheless, there are studies on older septic patients in which thyroid hormones were administered, leading to clinical improvement.²⁵

CONCLUSION

Fungal sepsis is becoming more common among newborn admitted to the NICU and thyroid insufficiency, with the variables described, could be a marker of disease severity with the possible need for hormone supplementation. The goal of TFTs in the ICU should mainly be the identification of previously unrecognized thyroid dysfunction that would require therapeutic intervention. When hypothyroidism is suspected

clinically in an ICU patient (e.g. hypothermia, bradycardia, respiratory acidosis, pleural effusions, failure to wean), and the evaluation suggests central hypothyroidism.

ACKNOWLEDGEMENTS

Authors would like to thank the whole team at the NICU and Pediatrics Department's Clinical and Experimental Research Centre of Sree Balaji Medical college and Research for helping with data collection and laboratory analyses.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Vatti R, Selvendran C. Thyroid hormones as a marker to diagnose the severity of fungal sepsis in neonates. *Int J Contemp Pediatr* 2020;7:14-9.