International Journal of Science and Healthcare Research
Vol. 8; Issue: 1; Jan.-March 2023
Website: ijshr.com
Original Research Article *ISSN: 2455-7587*

Thyroid Abnormalities in Children with Sepsis

Dr. Sushila Kumari[1], Dr. Kailash Kumar Meena[2], Dr. Umesh K. Gurjar[3], Dr. Subhash Dhayal[4], Dr. Janak Raj Soni[5]

[1]Resident Doctor, Dept. Of Paediatrics, SMS MC Jaipur
[2]Senior Professor and Unit Head, Dept. Of Paediatrics, SMS MC Jaipur
[3]Assistant Professor, Dept of Pediatrics, SMS MC Jaipur
[4]Resident Doctor, Dept. Of Ophthalmology, PMCH Udaipur
[5]Resident Doctor, Dept. Of Obest. & Gynec, SMS Medical College, Jaipur

Corresponding Author: Dr. Janak Raj Soni

DOI: https://doi.org/10.52403/ijshr.20230133

ABSTRACT

Introduction: Sepsis is the most common cause of mortality in infants and children. A hormonal disorder that often affected in sepsis is thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS). The aim of study was to evaluate thyroid hormones changes and the outcome in children with sepsis.

Materials and Methods: Present study is hospital based observational cohort study.70 children with diagnosed sepsis were required in sample size. Serum free T3, free T4 and TSH was measured on day one and also on follow up (7th day).

Result: on day one Serum FT3 level was low in 40 (57.2%) subjects and Serum FT4 level was low in 12 (17.2%) subjects. TSH was normal in most 66 (94.2%) of subjects. Mortality was more in children with low serum FT3 (22.5%) as compared to those with normal FT3 (3.4%). Mortality was also more in children with low serum FT4 level (41.6%) as compared to those with normal FT4 level (8.7%), (p=0.002). Mortality was more in children with low serum FT3 (29%) on follow up as compared to those with normal FT3 (2.5%) (p=0.001).

Conclusion: Thyroid hormones dysfunctions are common in children with sepsis. Mortality is significantly associated with low levels of serum FT3 & FT4. So Thyroid hormones dysfunctions could be an indicator of disease severity with possible need for hormone supplementation.

Keywords: Thyroid hormones, Serum free T3, free T4, TSH, sepsis, children

INTRODUCTION

Sepsis is the most common cause of mortality in infants and children. The incidence of sepsis and septic shock were increasing in the last 30 to 40 years[1]. Sepsis is SIRS (Systemic Inflammatory Response Syndrome) plus a suspected or proven infection. To define sepsis a child must have a confirmed or suspected infection and signs of that infection. Severe sepsis requires diagnosis of end organ system involvement. Septic shock requires cardiovascular dysfunction that is not resolved by initial fluid resuscitation. These definitions are aimed at identifying sepsis in an early stage to facilitate early intervention, with the goal of stopping further spread of infection and preventing.[2]

Determination of altered physiology is specific to age dependent vital Signs. The timely diagnosis of sepsis in neonates is important as the illness can be rapidly progressive and in some instances fatal[3]. Sepsis in newborn continues to be serious problem leading to significant amount of morbidity and mortality[4]. The inability of neonates to completely suppress the minimum inflammatory response makes them more susceptible to bacterial invasion of the blood stream than older adults and the risks are even higher in preterm infants[5].

Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. A hormonal disorder that often

affected in sepsis is thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome. (NTIS)[6]

Euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome

(NTIS) is a condition of decreased thyroid hormone levels without disruption of thyroid hormone function that occurs in severe systemic non-thyroid disease. Changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death.[7,8]

The critical disease is characterized by complex and multiple changes in the thyroid pathway. Along with worsening of a critical illness, the decrease occurs in not only triiodothyronine (T3) levels but also thyroxine (T4) and thyroid stimulating hormone (TSH). Decreased levels of T4 and TSH showed an indication of worsening of disease and poor prognosis.[9, 10]

World Health Organization (WHO) reported 70% in eight million children under five years' mortalities in developing countries caused by infection diseases which commonly ended in sepsis condition. The incidence of sepsis was 0.56% of 1000 children and 5.6% of 1000

infants with the highest mortality rate as 10.6%. There are few studies about thyroid hormone level changes in sepsis, so we a planned this study to evaluate thyroid hormone changes and the clinical outcomes in children with sepsis.

MATERIALS AND METHODS

Present study is hospital based observational cohort study which was conducted in Department of Pediatrics, SMS Medical College & Hospitals Jaipur from July 2020 to June 2022. Sample sizes were calculated at 95% confidence level expecting 71.2% of low T3 levels among children with sepsis. At 11% absolute allowable error the require sample size were 70 cases of children suffering from sepsis. The study was conducted on children with sepsis fulfilling the inclusion and exclusion criteria.

The inclusion criteria were Patients with confirmed diagnosis of sepsis in age group of 1 month to 18 years. Exclusion criteria were Patients with hypothyroid and hyperthyroid diagnosed before admission and mother having hypothyroid/ hyperthyroid or taking medication for thyroid disorder.

Sepsis was diagnosed clinically and by lab investigation using The International Pediatric Sepsis Consensus Conference definition.3

1. Clinically:

- hypothermia or hyperthermia
- Tachypnea
- Tachycardia/Bradycardia (In less than 1yr children)

2. Lab Investigations:

- CBC with DLC with PBF
- Leucocytosis or leucopenia
- Neutrophilia
- Thrombocytopenia
- Band cells
- CRP
- Chest X-ray
- CSF examination if required
- Blood culture sensitivity
- Urine culture sensitivity

After making diagnosis of sepsis first sample was sent for measuring of free T3, free T4 and TSH on day one. Then second sample for the same was sent on follow up (7th day). All samples were sent for analysis in central lab in our hospital. Lab sample analysis by method- Chemiluminescence immunoassay (CLIA). Detailed history, clinical examinations & investigations were done in each case and were recorded in the Performa. Data analysis- Data was recorded on a Performa. Analyses of data were done with suitable statistical method. For categorical variables chi-square Test was used. For continuous variables independent

samples t-test was used. p-value <0.05 was considered as significant.

RESULTS

The baseline characteristics of the whole Study cohort are given in Table 1. Majority of the children in the study were aged 1 – 60 months (72.8%) followed by 61-120 months (14.3%). About 54.3% of the children were female and 45.7% of the children were males. The male: female ratio in the study was 1: 1.19.

Table1: the baseline characteristics of the whole Study cohort

Distribution of subjects according to age group		
Age group(in months)	**No.**	**%**
1-60	51	72.8
61-120	10	14.3
121-180	8	11.5
>180	1	1.4
Total	70	100
Distribution of subjects according to gender		
Male	32	45.7
Female	38	54.3
Total	70	100

Table 2 depicts thyroid hormone values on day 1 and follow up, on day 1 Serum FT3 level was low in 40 (57.2%) subjects and Serum FT4 level was low in 12 (17.2%) subjects. TSH was normal in most 66 (94.2%) of subjects and equally low and high 2 (2.9%). On follow up, Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%). Serum FT4 level was low in 5 (7.2%) of the subjects and was normal in most 65 (92.8%) of the subjects. TSH was normal in most 68 (97.2%) of subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject.

Table 2: Thyroid hormone levels on day 1 and follow up

Status	**Low (%)**	**Normal (%)**	**High (%)**
Thyroid hormone levels on day 1			
Serum FT3	40(57.2)	30(42.8)	0(0.0)
Serum FT4	12(17.2)	58(82.8)	0(0.0)
TSH	2(2.9)	66(94.2)	2(2.9)
Thyroid hormone levels on follow up			
Serum FT3	31(44.3)	39(55.7)	0(0.0)
Serum FT4	5(7.2)	65(92.8)	0(0.0)
TSH	1(1.4)	68(97.2)	1(1.4)

Table 3 depicts those 10 children with sepsis died giving a mortality rate of 14.3%.

Table 3: Distribution of subjects according to outcome

Outcome	**No.**	**%**
Death	10	14.3
Survived	60	85.7
Total	70	100

Table 4 shows that mortality was more in children with low serum FT3 (22.5%) Day 1 as compared to those with normal FT3 (3.4%) and this difference was found to be statistically significant (p=0.023). Mortality was also more in children with low serum FT4 level (41.6%) as compared to those with normal FT4 level (8.7%), this difference was found to be statistically significant (p=0.002). However serum TSH level was not statistically significant found to be associated with mortality (p>0.05)

Table 4: Association of outcome with Thyroid hormone levels on day 1

Thyroid Hormones	**Levels**	**Outcome**		**Total**	**P Value**
		Death (%)	**Survived (%)**		
Serum FT3	**Low**	9(22.5)	31(77.5)	40(100)	**0.023(S)**
	Normal	1(3.4)	29(96.6)	30(100)	
Serum FT4	**Low**	5(41.6)	7(58.4)	12(100)	**0.002(S)**
	Normal	5(8.7)	53(91.3)	58(100)	
TSH	**Low**	0(0.0)	2(100)	2(100)	**0.702(NS)**
	Normal	10(15.2)	56(84.8)	66(100)	
	High	0(0.0)	2(100)	2(100)	

Table 5 shows that mortality was more in children with low serumFT3 (29%) on follow up as compared to those with normal FT3 (2.5%) and this difference was found to be statistically significant (p=0.001). Serum free T4 and TSH level was not found to be statistically significant associated with mortality (p>0.05)

Table 5: Association of outcome with Thyroid hormone levels on follow up

Thyroid Hormones	Levels	Outcome		Total	P Value
		Death (%)	Survived (%)		
Serum FT3	**Low**	9(29.0)	22(71.0)	31(100)	**0.001(S)**
	Normal	1(2.5)	38(97.5)	39(100)	
Serum FT4	**Low**	1(20.0)	4(80.0)	5(100)	**0.704(NS)**
	Normal	9(13.9)	56(86.1)	65(100)	
TSH	**Low**	0(0.0)	1(100)	1(100)	**0.842(NS)**
	Normal	10(14.7)	58(85.3)	68(100)	
	High	0(0.0)	1(100)	1(100)	

DISCUSSION

Sepsis is the most common cause of mortality in infants and children. Sepsis and septic shock incidences were found to be increasing in the last 30 to 40 years. Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. In sepsis, thyroid hormones disorder observed to occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) [6], further changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death.

In our study we found that on day one serum FT3 level was low in 40 (57.2%) subjects and was normal in 30 (42.8%) subjects. Serum FT4 level was low in 12 (17.2%) subjects and was normal in most 58 (82.8%) subjects. TSH was normal in most66 (94.2%) subjects, low in 2(2.9%) subjects and high in 2(2.9%) subjects. At follow up investigation, Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%) subjects. Serum FT4 level was low in 5 (7.2%) subjects and was normal in most 65(92.8%) subjects. TSH was normal in most 68(97.2%) subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject.

Similar results of low T3 and T4 in sepsis was reported by other authors.

Sikha s et al (2014)[11] found that The FT3 and FT4 hormones levels were significantly decreased ($P < 0.001$) in neonates with sepsis as compared to controls without sepsis. No significant difference was observed in TSH levels between the groups. Agung G et al (2014)[12] found that the free T3, free T4, and TSH levels were decreased in 97%, 50% and 40% of the neonates with sepsis. Bhat K et al (2014)[13] found that Low FT3 level was the most common abnormality found in these patients. High TSH and low FT4 levels were the other common abnormalities.

Pikala Tarakeswara Rao et al (2019)[14] observed that Serum T3, T4, Free T3 and Free T4 levels were significantly lower among cases of neonatal sepsis as compared to gestational age matched control. Yanni G N et al (2019)[15] observed that Level of T3 and T4 were decreased on day 1 in pediatric sepsis. Of 80 subjects, 57 (71.2%) with low level T3 and 41 (51.2%) with low T4 were found. The relationship between T3 and T4 level on day 1 with the length of stay were not found ($P = 0.500$; $P = 0.987$). There was a significant relationship between level of T3 and T4 with outcome ($P = 0.0001$; OR 24.706; $P = 0.014$; OR 3.086).

Den Brinker M et al (2005)[16] was also observed that children had decreased total T3 (TT3)/rT3 ratios without elevated TSH.

In our study 10 children found to have been died with sepsis depicting a mortality rate of 14.3%. Mortality was more in children with Day 1 low serum FT3 (22.5%) as compared to those with normal FT3 (3.4%) and this difference was found to be statistically significant ($p=0.023$). Mortality was also more common in children with low serum FT4 level (41.6%) as compared to those with normal FT4 level (8.7 ($p=0.002$). Serum TSH level was not found to be associated with mortality. On follow up mortality was more found to be among children with low serum FT3 (29%) as compared to those with normal FT3 (2.5%) ($p=0.001$). Mortality was also more common in children with low serum FT4

level (20%) as compared to those with normal FT4 level (13.9%), this difference was however not found to be statistically significant (p>0.05). Serum TSH level on follow up also was not found to be associated with mortality.

Borkowski J et al (2005)[17] also found significant decrease of FT3 and TSH serum levels (respectively 2.36 ± 0.79 pg/ml and 0.76 ± 1.12mU/I), but no survivors had significantly lower TSH serum level (0.37 ± 0.62 mU/I) in comparison to survivors (1.27 ± 1.45 mU/I) in spite of very similar FT3 serum level (respectively 2.45 ± 0.87 pg/ml and 2.22 ± 0.66 pg/ml). They concluded that low TSH serum level could be a significant prognostic factor of death in patient with septic shock especially with low ±T3 serum level.

Wang F et al (2012)[18] observed that the thyroid hormone indicators, FT3 had the greatest power to predict ICU mortality. Sikha s et al (2014)[11] also found that non survivors had lower FT3 and FT4 levels (P < 0.05) compared to sepsis-survivor group.

Pikala Tarakeswara Rao et al (2019)[14] found that the non-survivors among cases had significantly lesser T3, T4 and Free T4 levels as compared to survivors. A scientific report published in nature in 2018 stating the value of decreased thyroid hormone for predicting mortality in septic patient concluded decreased thyroid hormone (TH) has been considered as one of the potential predictors of mortality in sepsis.

Thukral A et al (2006)[19] found that children with septic shock who died (n = 12) had higher TSH levels compared to those who survived (p = 0.04). There was no difference in hormone levels between children with catecholamine responsive and catecholamine resistant septic. Children with septic shock had lower levels of T3, T4, fT3, fT4 and TSH compared to those with sepsis.

CONCLUSION

This study concludes that abnormalities of thyroid hormones are common in children with sepsis. Low level of FT3 was the most common abnormality seen in more than half of the cases of children with sepsis. Mortality was found to be significantly associated with low levels of serum FT3 & FT4 on day one but on follow up mortality was significantly associated with low level of serum FT3 irrespective of the age of the child.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2005;6(3 Suppl):S3–5. Epub 2005/04/29
2. Ruth A, McCracken CE, Fortenberry JD, Hall M, Simon HK, Hebbar KB. Pediatric severe sepsis: current trends and outcomes from the Pediatric Health Information Systems database. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2014;15(9):828–38. Epub 2014/09/17.
3. Weiss SL, Fitzgerald JC, Maffei FA, Kane JM, Rodriguez-Nunez A, Hsing DD, et al. Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. Critical care. 2015;19:325. Epub 2015/09/17. This article is the first to publish the discordance of clinically diagnosed sepsis and consensus criteria diagnosed sepsis
4. Balamuth F, Weiss SL, Neuman MI, Scott H, Brady PW, Paul R, et al. Pediatric severe sepsis in U.S. children's hospitals. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2014;15(9):798–805. Epub 2014/08/28.

5. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. American journal of respiratory and critical care medicine. 2015;191(10):1147–57. Epub 2015/03/04. Landmark publication on the incidence of sepsis, as defined by consensus criteria, worldwide. Large prospective study with etiologic, treatment, and outcome information.
6. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Critical care medicine. 2014;42(11):2409–17.
7. Mathias B, Lipori G, Moldawer LL, Efron PA. Integrating "big data" into surgical practice. Surgery. 2015 Epub 2015/11/26.
8. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. American journal of respiratory and critical care medicine. 2015;191(3):309–15. Epub 2014/12/10.
9. Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, et al. The pediatric sepsis biomarker risk model. Critical care. 2012;16(5):R174. Epub 2012/10/03
10. Paul R, Melendez E, Stack A, Capraro A, Monuteaux M, Neuman MI. Improving adherence to PALS septic shock guidelines. Pediatrics. 2014;133(5):e1358–66. Epub 2014/04/09.
11. Shikha Sharma, Pradeep Kumar Dabla. Thyroid Hormone Dysfunction and CRP Levels in Neonates With Sepsis.JEM, 2013;3(3):32-36
12. Agung G. Tanurahardja, Antonius H. Thyroid hormone profile and PELOD score in children with sepsis. Paediatr Indones,2014; 54(4): 245-249.
13. Bhat K, Sharma S, Sharma K , Singh RK. Assessment of thyroid function in critically ill patients. Biomedical Research 2016; 27 (2): 449-452.
14. Pikala Tarakeswara Rao. Thyroid Hormone Abnormalities in Septic Neonates. Indian Journal of Neonatal Medicine and Research. 2019 Jan, Vol-7(1): PO05-PO08
15. Yanni G N, Destariani C P, Lubis L. Thyroid Hormone Profile in Children with Sepsis: Does Euthyroid Sick Syndrome Exist?. Journal of Medical Sciences,2019 : 7(7):1110-1113.
16. Den Brinker M, Joosten KF, Visser TJ, Hop WC, de Rijke YB. Euthyroid sick syndrome in meningococcal sepsis: the impact of peripheral thyroid hormone metabolism and binding proteins. J ClinEndocrinol Metab. 2005 Oct;90(10):5613-20
17. Borkowski J, Siemiatkowski A, Wołczyński S, Czaban SL, Jedynak M. Assessment of the release of thyroid hormones in septic shock--prognostic significance. Pol MerkurLekarski. 2005 Jan;18(103):45-8.
18. Wang F, Pan W, Wang H, Wang S, Pan S, Ge J. Relationship between thyroid function and ICU mortality: a prospective observation study. Crit Care 2012; 16: R11
19. Thukral A,Lodha R,Irshad M,Arora NK.Performance of Pediatric Risk of Mortality(PRISM),Pediatric Index of Mortality(PIM),and PIM2in a pediatric intensive care unit in a developing country. Pediatric Critical Care Med.2006;7:356_61

How to cite this article: Sushila Kumari, Kailash Kumar Meena, Umesh K. Gurjar et.al. Thyroid abnormalities in children with sepsis. *International Journal of Science & Healthcare Research.* 2023; 8(1): 234-239. DOI: *https://doi.org/10.52403/ijshr.20230133*

******