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Non-thyroidal Illness in Children with Congestive Heart Failure

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What is already known on this topic?

The sick euthyroid state is seen in critically ill patients and adversely affects outcomes. Thyroid hormones affect cardiac function and contractility.

What this study adds?

The sick euthyroid state was seen in 46% of children with congestive heart failure. Raised brain-natriuretic peptidelevels, a marker of heart failure, significantly affected low free T3 levels. A free T3/reverse T3 ratio of < 1.86 pg/ng predicted mortality.

Abstract

Objective: To estimate the proportion and risk factors of non-thyroidal illness (NTI) in children with congenital heart disease (CHD) with congestive heart failure (CHF).

Methods: This study enrolled children (6 weeks to 60 months age) with CHD and CHF. The clinical profile and disease severity, derived from the Pediatric Early Warning Score (PEWS) was recorded. Baseline blood samples were taken within 24 hours of hospitalization and evaluated for free tri-iodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), N-terminal pro-brain natriuretic peptide (NT pro-BNP) and reverse T3.

Results: A total of 80 (64 acyanotic CHD) children of median (interquartile range) age 5 (2.5, 8.0) months were enrolled. NTI was seen in 37 (46%) of whom 27 had low fT3 levels. The proportion of NTI was highest in children with severe disease (20/30), than moderate (4/9) or mild disease (13/41) (p = 0.018). Ten (27%) patients with NTI died compared to 2 (4.7%) without NTI with unadjusted odds ratio (OR) [95% confidence interval (CI)] 7.593 (1.54, 37.38); p = 0.006. After adjusting for NTI, shock and NT-pro-BNP levels, PEWS was the only significant predictor of mortality (OR: 1.41, 95% CI: 1.03, 1.92; p = 0.032). Linear regression for fT3 identified a significant relationship with log NT-BNP [beta -3.541, (95% CI: -1.387, -0.388)] and with TSH [beta 2.652 (95% CI: 0.054, 0.383)]. The cutoff (area under the curve, 95% CI) that predicted mortality were fT4 < 14.5 pmol/L (0.737, 0.60, 0.88), fT3/rT3 index < 1.86 pg/ng (0.284, 0.129, 0.438) and NT pro-BNP > 3725 pg/mL (0.702; 0.53, 0.88).

Conclusion: NTI was present in a significant proportion of children with CHD and CHF. fT3 level was significantly associated with NT-BNP levels and thus severity of CHF.

Keywords: Non-thyroidal illness, free T3, reverse T3, NT pro-BNP, Pediatric Early Warning Score

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Introduction

Cardiovascular structure and function in the pediatric age group is affected by changes in body size and metabolic demands, as well as hormonal effects. The effect of thyroid hormones (TH) on the adult cardiovascular system (CVS) has been studied widely. The CVS is a well-known target for TH as is exhibited by its profound effects on cardiac contractility, heart rate, systemic vascular resistance, ventricular mass and body's blood volume (1,2). Cardiomyocytes express thyroid receptors (TRα and TRβ) (3). The genetic transcription of contractile proteins of myosin heavy chains is dependent on TH in fetal and postnatal life suggesting their association (4).

Non-thyroidal illness (NTI), also known as sick euthyroid syndrome, is frequently reported in critically sick patients. It is postulated to be a state of adaptive response where the body adapts to assume a low metabolic state to conserve energy, like calorie restriction in acute illness. During prolonged illness, this state represents the abnormal effect of illness on the hypothalamic-pituitary axis where there is low generation of TH. Low free tri-iodothyronine (fT3) results from reduced enzyme activity of 5' monodeiodinase (type 1 and 2) which is responsible for peripheral conversion of thyroxine (T4) to T3 (1,5). There is an increase in activity of deiodinase type 3 that increases the generation of reverse T3 (3,3',5'-triiodothyronine or rT3), the inactive form, and also suppression of release of thyrotropin releasing hormone (TRH) from the pituitary in prolonged disease states (6,7).

Generally, NTI is associated with poor disease outcomes and mortality. An association between lower fT3 level, raised rT3 level and lower cardiac ejection fraction has been seen in patients with acute myocardial infarction, heart failure and after coronary artery bypass surgery (1). A few studies have reported the occurrence of NTI in critically sick children, which was associated with a worse prognosis (5,8,9,10). Congenital heart diseases (CHD) are one of the most common cardiovascular diseases in children that usually present with congestive heart failure (CHF). Children with CHF are usually sick at presentation with an increased risk of repeated hospitalizations and require follow-up. The associated hepatic congestion in CHF may cause an inhibition of hepatic deiodinase type 1 with resultant lower T3 levels (9). A suboptimal thyroid status in children with CHD and CHF can inturn compromise the cardiac function further. In animal models, poorly controlled CHF with decompensated left ventricular hypertrophy and low cardiac output can further decrease the TH compared to animals with preserved cardiac output (11).

The primary objective of this study was to evaluate the proportion of children with CHD and CHF with NTI. We also aimed to study the association of TH with cardiac contractility (ejection fraction) and clinical outcomes, including duration of hospitalization and mortality.

Methods

This observational study was conducted at the Department of Pediatrics and Cardiology in a large tertiary care public hospital from July 2021 until June 2022 after approval of the Institutional Ethics Committee Maulana Azad Medical College, New Delhi (letter F No.1/IEC/MAMC/82/10/2020/no. 125 dated: 14 Jan 2021). Written parental consent was taken before enrollment. The study protocol was in agreement with the Declaration of Helsinki for conduct of research and registered under clinical trials registry with registration number: CTRI/2021/03/032417.

Children in the age group of six weeks to 60 months and diagnosed with CHD (cyanotic or acyanotic heart disease) with CHF were eligible for inclusion. Children with a past history of thyroid disease (congenital hypothyroidism) or history of intake of thyroxine in the preceding three months, congenital anomalies such as Down syndrome, Turner syndrome or Williams-Beuren syndrome, and children with a history of birth asphyxia, cardiomyopathy or myocarditis were excluded. All eligible children were enrolled within 24 hours of hospitalization.

Sample Size

Sample size calculation was done using Open Epi software with a proportion of NTI as 24.5% in patients with underlying heart failure (1). A sample size of 72 was calculated with 5% alpha error and power of 80%. A total of 80 children were recruited for the study.

The demographic details, birth and developmental history and feeding history were elicited and recorded. The age of diagnosis of CHD, disease progression, details of prior hospitalization (if any) and treatment history for decongestants or other drugs were noted. Children with CHF who were controlled on medications and those who presented in decompensated CHF were both enrolled. The vital sign data, including temperature, heart rate, respiratory rate and blood pressure were measured, followed by physical examination including anthropometry. The WHO 2006 standards were used to interpret anthropometry in terms of standard deviation (SD) scores (SDS) (12). Non-invasive blood pressure was measured as per standard protocol and interpreted as per the American Academy of Pediatrics (AAP) (13). Cardiac lesions were further classified as acyanotic CHD (ACHD) or cyanotic CHD (CCHD), based on clinical examination and confirmed on echocardiography.

A prognostic clinical scoring was done at hospitalization using the Pediatric Early Warning Score (PEWS) (14). The score recorded a value from 0 to 3 (0 for best and 3 for worst) for each of three variables: behaviour;cardiovascular; and respiratory. As per PEWS, patients were categorized as mild, moderate or severe sickness for a score of 0-3, 4-6 or 7-9, respectively. The outcome of all children was recorded until discharge or death. The duration of hospitalization and oxygen need were also recorded in total days. A venous blood sample was collected and processed for biochemical investigations. One serum aliquot was separated and stored at -80 °C for thyroid functions. Liver function test, serum creatinine and C-reactive protein (CRP) were measured at the time of enrolment. The liver function tests and serum creatinine was measured on an autoanalyzer (Vitros 5600, Quidel Ortho, USA). CRP was measured using ELISA with normal range < 5 mg/L. A three-fold rise in CRP was taken to be suggestive of infection and affected patients were evaluated further for sepsis.

The thyroid stimulating hormone (TSH), fT3, and fT4 were processed on a weekly basis and reverseT3 (rT3) level was processed as a single batch by electrochemiluminescence (ECLIA). NTI (or sick euthyroid illness) was defined as low T3 and/or low T4 with normal TSH values and elevated rT3 levels. Hypothyroidism was defined as elevated TSH (> 10 mIU/L) with low fT4. Subclinical hypothyroidism was defined as elevated TSH between 5-10 mIU/L with normal fT4 values.The normal ranges were: TSH 0.46-4.68 mIU/L; fT3 4.26-8.10 pmol/L; fT4 10-22.8 pmol/L; and rT3 0.06-0.76 ng/mL (< 250 pg/mL).The fT3/rT3 index (in pg/ng) was mathematically derived, by converting fT3 pmol/L to pg/mL (multiply by 0.651) and the ratio was calculated versus rT3 (in ng/mL). The intra and inter-assay coefficient of variation (CV) for fT4 was 1.7-5.7% and 3-10.7%, for fT3 1.1-3% and 1.9-8.2% and for TSH 1.5-4.2% and 2.4-6.3%, respectively.

One mL of blood sample for serum N-terminal pro-brain natriuretic peptide (NT pro-BNP) was measured within 24 hours of collection by ECLIA with a maximum storage limit at 2-8 °C of 3 days. The normal range for serum NT pro-BNP (children > one-month age) was 20-40 pg/mL (15). NTI was classified as NTI-1 or Low T3 syndrome, in which there is decrease total or free T3 with normal T4 and TSH level and NTI-2 or low T4 syndrome, with significant fall in both T3 and T4 with normal or low TSH level (16).

A plain chest radiograph was done at enrolment to document the cardiac size and any other lung abnormality. A standard electrocardiogram was done at the bedside of the patients after standard calibration and abnormalities recorded. Echocardiography was done using a EPIQ CVX ultrasound machine (Philips, Netherlands) at a frequency of 7-12 Hz in M mode to measure ejection fraction (EF) once the child was stable for transport. EF was defined as percentage of blood volume ejected per cardiac cycle. EF was calculated using Simpson's biplane method and the formula used was EF = (EDV-ESV)/EDV or EF = SV/EDV where EF = ejection fraction, EDV = end diastolic volume, ESV = end systolic volume, and SV = stroke volume.

Statistical Analysis

Data were entered in Microsoft Excel and were analyzed using Statistical Package for the Social Sciences, version 25.0 (IBM Inc., Armonk, NY, USA). The normality of continuous variables was checked using the Kolmogorov-Smironov test. Categorical variables were described as frequencies and proportions, median (interquartile range-IQR) and mean (SD) were calculated for baseline characteristics, such as age, growth parameters, and biochemical parameters. Continuous variables were compared using t-test or Mann-Whitney U test, as appropriate. Parameters between three categories of PEWS were compared using ANOVA or Kruskal-Wallis test (for non-parametric data). Proportions for those with and without NTI were compared by chi-square test or Fisher's exact test. Odds ratio (OR) [95% confidence interval (CI)] was calculated to predict mortality with categorical risk factors (sex, type of CHD, previous hospitalization, failure to thrive, NTI, shock and PEWS category). Binary logistic regression analysis was used, using the enter and forward selection method, to estimate the risk of mortality based on covariates. NT pro-BNP levels were transformed logarithmically for regression analysis.The correlation between continuous variables wasperformed using Spearman's rank correlation coefficient (r) for non-parametric variables. Stepwise multiple linear regression was used, with fT3 as the dependent variable and other variables being independent (TSH, NT pro-BNP, PEWS score); fT4 and rT3 were not considered independent for fT3 levels and not included. Receiver operating curve was constructed to measure cutoff points for serum NT pro-BNP, fT4 and fT3/rT3 index to predict mortality. A p value less than 0.05 was taken as significant.

Results

A total of 122 patients were screened during the study period, out of whom 42 patients were excluded (26 had Down syndrome, 8 Down phenotype, 1 Turner syndrome, 3 dysmorphism with renal abnormalities, and 4 with primary hypothyroidism who were on thyroxine treatment). A total of 80 children were enrolled, including 49 (61.25%) males, and 64 (80%) had acyanotic heart disease. The median (IQR) age was 5 (2.5, 8) months and age at diagnosis was

2.25 (1.5, 4) months. Feeding difficulty and poor weight gain were seen in 57 (71.3%) and 52 (65%), respectively, with a median (IQR) weight-for-age Z score of 3.3 (-4.56, -2.21) and weight-for-length Z score of -3.02 (-4.03, -1.38). Sixteen children with CCHD and three children with ACHD and severe pulmonary hypertension had cyanosis. As per PEWS, 41 (50%) children had mild, 9 (11.3%) had moderate and 30 (38.7%) had severe disease at hospitalization, with shock in 12 (15%) children. Elevated CRP (more than three times upper limit of normal) was seen in 12 children, one of whom also had septic shock.

The comparison of biochemical parameters as per disease severity is shown in Table 1. A total of 37 (46.25%) patients had NTI; 27 (33.8%) had NTI-1 and 10 (12.4%) had NTI-2. The dispersion of fT3, fT4, rT3 and TSH levels as per disease severity in those with and without sick euthyroid syndrome is shown in Figure 1A, 1B, 1C and 1D respectively.

Table 2 shows the comparison of clinical and laboratory parameters in children with or without NTI. Only 3/12 children with elevated CRP had NTI. Similarly, 9/12 children with shock had NTI with an OR of 4.286 (95% CI: 1.06, 17.23) of developing NTI (p = 0.031). Logistic regression was performed for predicting mortality with a model based on variables including disease severity (PEWS), presence or absence of shock, rT3 levels, log NT pro-BNP levels, and presence of NTI. The model (using enter method) explained 44.3% variation in mortality and correctly classified 86.5% of patients with only PEWS as a statistically significant variable (adjusted OR: 1.41, 95% CI: 1.03, 1.92; p = 0.032). PEWS remained the only significant variable with adjusted OR: 1.63 (95% CI: 1.25, 2.13; p < 0.001) in the second model (forward conditioning) explaining 37.2% of variation.

The fT3 levels showed significant correlation with TSH (r = 0.461, p < 0.001), fT4 (r = 0.373, p < 0.001), rT3 (r = -0.488, p < 0.001), NT pro-BNP (r = -0.430, p < 0.001), and insignificant weak correlation with PEWS (r = -0.162, p = 0.154). A significant positive correlation was observed between rT3 level and serum NT pro-BNP (r = 0.311, p = 0.007), and a negative correlation with ejection fraction (r = -0.233, p = 0.044). Likewise, serum NT pro-

Table 1. Clinical and Biochemical parameters by Pediatric Early Warning Score (PEWS)

Parameters	PEWS mild (n = 41)	PEWS moderate (n = 9)	PEWS severe (n = 30)	p
Age (mo)	5 (2.5, 11)	6 (2.5, 23)	4.5 (2.8, 7.0)	0.541
Duration of stay (d)	8 (7, 10.75)	9 (7.5, 12.5)	14 (10.75, 20.75)	**< 0.001**
Duration oxy (d)	4 (2, 7)	4 (1.5, 8)	11 (8, 19.25)	**< 0.001**
WAZ score	-3.36 (-4.56, -2.35)	-2.65 (-4.03, -1.63)	-3.65 (-4.68, -2.74)	0.356
H/LAZ score	-1.85 (-2.95, -0.71)	-2.18 (-2.88, -0.36)	-1.92 (-3.02, -0.98)	0.939
WHZ/WLZ score	-2.96 (-3.82, -1.48)	-2.23 (-3.91, -0.47)	-3.3 (-4.33, -1.40)	0.677
Male*	26 (63.4%)	4 (44.4%)	19 (63.3%)	0.566
ACHD*	34 (82.9%)	9 (100%)	21 (70%)	0.12
Expired*	2 (4.8%)	0	10 (33.3%)	**0.002**
Past hospitalisation*	33 (80.4%)	8 (88.9%)	25 (83.3%)	0.896
Shock*	1 (2.4%)	0	11 (30.55%)	**< 0.001**
Sick euthyroid illness*	13 (32%)	4 (44.4%)	20 (66.6%)	**0.018**
fT3 (pmol/L)	4.76 (3.75, 6.16)	4.9 (2.55, 6.77)	4.07 (3.13, 5.43)	0.275
fT4 (pmol/L)	15.3 (12.65, 23.02)	18.5 (17.85, 21.75)	14.35 (12.17, 15.8)	0.059
TSH (IU/mL)	2.38 (0.91, 3.85)	1.62 (0.96, 2.26)	1.61 (0.43, 3.43)	0.453
rT3 (ng/mL)	0.7 (0.61, 0.91)	0.88 (0.72, 1.24)	0.85 (0.65, 1.15)	0.086
fT3/rT3 index (pg/ng)	5.36 (2.74, 6.88)	4.13 (1.91, 5.99)	2.54 (1.51, 3.44)	**0.019**
NT-pro BNP (pg/mL)	2966 (1099, 14008)	8396 (672, 26517)	9690 (2721, 23515)	0.277
Creatinine (mg/dL)	0.2 (0.2, 0.3)	0.3 (0.25, 0.44)	0.3 (0.2, 0.38)	0.226
CRP (mg/dL)	2 (0.61, 4.51)	2.13 (0.5, 5)	3 (0.68, 9)	0.915
AST (IU/mL)	40.5 (34.5, 56.75)	37 (30, 53)	67 (38, 99.2)	**0.040**
ALT (IU/mL)	33.5 (18, 50.5)	37 (23.5, 43)	50 (30.25, 78.5)	**0.037**
Ejection fraction (%)	60 (55.25, 60)	60 (55.5, 60)	55 (50, 60)	**0.042**

Values shown in *numbers (%) for categorical variables or median (IQR) for continuous variables; comparison by *chi-square test or Kruskal-Wallis test.
AST: aspartate transaminase, ALT: alanine transaminase, BNP: brain natriuretic peptide, CRP: C-reactive protein, fT3: free tri-iodothyronine, fT4: free thyroxine, HAZ/LAZ: height or length for age Z score, Duration oxy: duration of oxygenation, rT3: reverse T3, TSH: thyroid stimulating hormone, WHZ/WLZ: weight-for-height/length Z score, fT3/rT3 index: units as pg/mL for fT3 and ng/mL for rT3

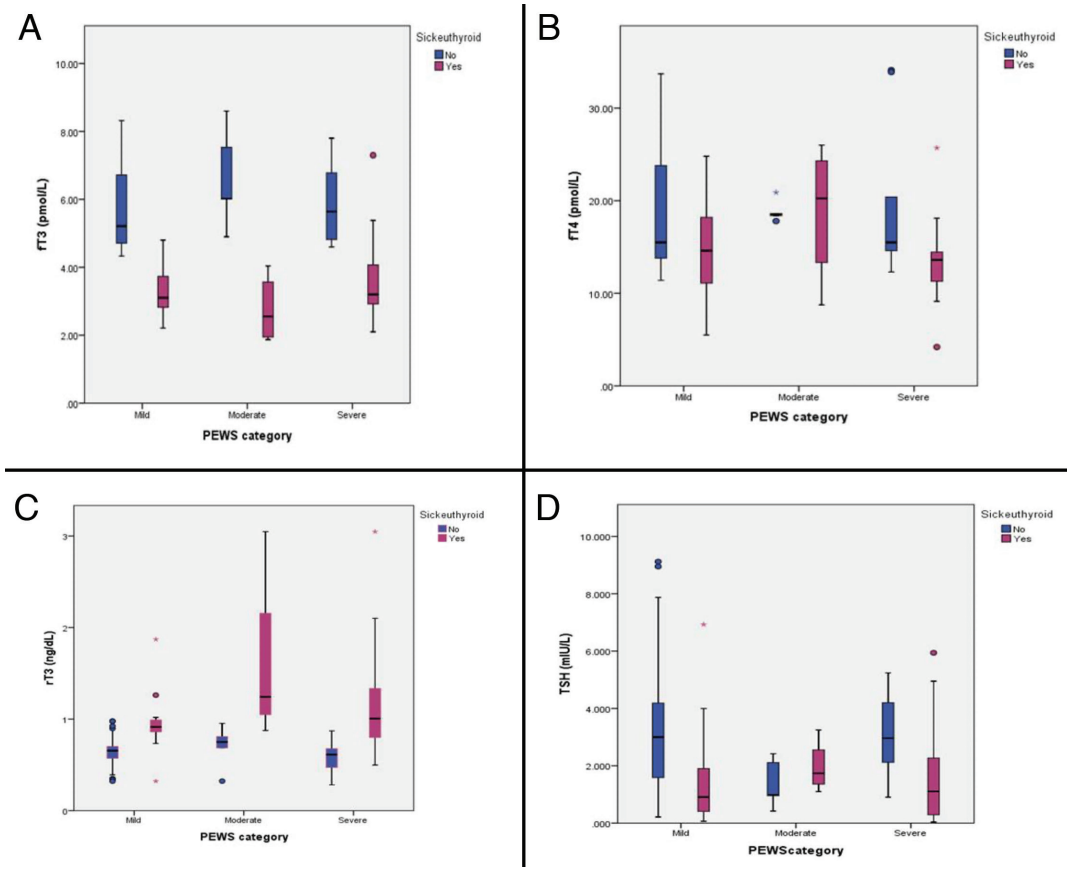

Figure 1. Box and Whisker plot showing (A) fT3 levels, (B) fT4 levels, (C) rT3 and (D) TSH levels in non-thyroidal illness versus severity of PEWS score

PEWS: Pediatric Early Warning Score, TSH: thyroid stimulating hormone

Table 2. Comparison of clinical and laboratory parameters as per sick euthyroid status

Parameters	Non-SES (n = 43)	SES (n = 37)	p
Age (mo)	6 (3, 11)	4.5 (2, 6)	0.096
Duration of Stay (d)	9 (7, 12.25)	11 (7.5, 15.5)	0.099
Duration of oxygenation (d)	5 (2, 10)	8 (4.5, 12.5)	**0.012**
PEWS	2 (1.75, 3.5)	5 (2, 9)	**0.003**
WAZ	-3.25 (-4.59, -2.68)	-3.35 (-4.47, -2.01)	0.563
HAZ/LAZ	-1.68 (-2.75, -0.57)	-1.97 (-2.99, -0.91)	0.311
WHZ/WLZ	-3.26 (-4.05, -2.04)	-2.57 (-3.92, -0.83)	0.108
fT3 (pmol/L)	5.7 (4.8, 6.8)	3.2 (2.7, 3.9)	**< 0.001**
fT4 (pmol/L)	17.1 (14.4, 23.6)	14.2 (10.95, 17)	**0.001**
TSH (mIU/L)	2.66 (1.4, 4.0)	1.1 (0.32, 2.2)	**< 0.001**
rT3 (ng/mL)	0.66 (0.47, 0.71)	0.97 (0.85, 1.26)	**< 0.001**
fT3/rT3 index (pg/ng)	6.19 (5.11, 7.72)	2.08 (1.42, 2.72)	
NT-pro BNP (pg/mL)	2786 (725, 8893)	14900 (3345, 26392)	**0.001**
Creatinine (mg/dL)	0.2 (0.2, 0.3)	0.3 (0.2, 0.39)	0.165
Ejection fraction (%)	50 (55, 60)	58 (50, 60)	0.053

Values shown in median (IQR) for continuous variables, comparison by Mann-Whitney U test.
AST: aspartate transaminase, ALT: alanine transaminase, BNP: brain natriuretic peptide, CRP: C-reactive protein, fT3: free tri-iodothyronine, fT4: free thyroxine, HAZ/LAZ: height or length for age Z score, PEWS: Pediatric Early Warning Score, rT3: reverse T3, SES: Sick euthyroid syndrome, TSH: thyroid stimulating hormone, WHZ/WLZ: weight-for-height/length Z score, fT3/rT3 index: units as pg/mL for fT3 and ng/mL for rT3

BNP had a significant negative correlation with TSH (r = -0.392, p < 0.001), ejection fraction (r = -0.307, p = 0.006) and a weaker insignificant correlation with fT4 (r = -0.082, p = 0.475). Multiple linear regression model for fT3 with independent variables PEWS, TSH, and log NT pro-BNP showed statistical significance with TSH and log NT pro-BNP levels as shown in Table 3. The statistical values to predict mortality as per the TH and serum NT pro-BNP are shown in Table 4.

Discussion

The present study showed a high proportion of NTI in children with CHD and CHF that manifested as low fT3 levels in the majority. The presence of severe disease predicted NTI and increased risk of mortality.

NTI has been reported in intensive care settings in pediatric studies (8,9,16) and adult studies (17,18). The pooled prevalence of NTI in adults with CVD was 21.7% (95% CI: 18.4-25.3); and was highest in patients with CHF (24.5%; 95% CI: 18.5-31.7), followed by acute myocardial infarction (18.9%; 95% CI: 10.4-31.9) and acute coronary syndrome (17.1%; 95% CI: 8.5-31.3) (1). NTI has also been reported in children who were critically ill or had undergone surgical repair of CHD (19). The present study also reported NTI in a significant proportion of enrolled children with CHF that corroborated with disease severity.

The overall median values of TH (fT4 and fT3) and TSH were normal in this study, in contrast to median rT3 levels that were higher than the normal range, suggesting that rT3 is the earliest affected thyroid parameter in acute sickness. The TSH levels appeared within normal range, but the loss of pulsatile fraction, decreased pulse amplitude, and absence of response to TRH has been reported earlier (20). These parameters were not assessed in the present study but it is likely,although unproven, that these were also affected.

Among natriuretic peptide neurohormones that are secreted as a result of myocardial stretch, NT pro-BNP is a biochemically stable molecule with a longer half-life than BNP, though biologically inactive (21). The levels increase in CHF and higher levels are associated with poor outcome (15,22). A few studies have reported in patients with surgical repair for CHD and higher serum BNP level that there were poorer outcomes (22,23,24). However, there is limited data on NT pro-BNP levels in children with CHF and the association with thyroid function that was measured in this study. The median NT pro-BNP levels were clearly more elevated than normal and higher in those with severe condition, as shown by the PEWS score association. Serum NT pro-BNP levels showed a significant correlation with fT3, TSH and rT3 in this study, as has been reported previously (25,26).

Low fT3 levels have been associated with poor outcomes in children and adults with illness in earlier studies (26,27,28). The presence of low T3 and raised BNP levels strongly predicted one-year all-cause mortality in acute decompensated CHF in adults, and weakly for in-hospital mortality (29). Serial trends in TH levels in 40 sick children with shock showed a decrease in the proportion of low fT3 levels as the sickness improved (82.5% at baseline to 72.5% five days after shock reversal) (30). The fT3 levels were significantly affected by raised BNP levels in this study, although PEWS disease severity remained the only significant predictor of mortality.

Table 3. Linear regression analysis for low free T3 levels

Model	R square change	Model	Beta	95% CI	p
1	0.207	Log NT-BNP	-0.455	-1.59, -0.61	< 0.001
2	0.275	Log NT-BNP TSH	-3.541 2.652	-1.387, -0.388 0.054, 0.383	0.001 0.010

PEWS excluded during stepwise regression analysis in the mode.
BNP: brain natriuretic peptide, fT3: free tri-iodothyronine, PEWS: Pediatric Early Warning Score, TSH: thyroid stimulating hormone, CI: confidence interval

Table 4. Laboratory cutoffs of thyroid hormones to predict mortality

Parameter	Value	Sensitivity	Specificity	AUC	95% CI	p
fT4 (pmol/L)	< 14.5	75%	64.2%	0.737	0.60, 0.88	**0.009**
fT3 (pmol/L)	< 4.15	66.7%	63.2%	0.600	0.41, 0.79	0.269
rT3 (ng/mL)	> 0.77	83.3%	52.4%	0.741	0.60, 0.88	**0.009**
NT-BNP (pg/mL)	> 3725	75%	49.3%	0.702	0.53, 0.88	**0.026**
fT3/rT3 (pg/ng)	< 1.861	87.3%	50%	0.284	0.129, 0.438	**0.018**

BNP: brain natriuretic peptide, fT3: free tri-iodothyronine, fT4: free thyroxine, rT3: reverse T3, fT3/rT3 index: units as pg/mL for fT3 and ng/mL for rT3, CI: confidence interval, AUC: area under the curve

Critical illness, such as infection and inflammation, are associated with NTI. A small proportion of children in this study had associated sepsis, and fewer among them had NTI, suggesting the etiology of NTI in the majority was cardiac in origin and less likely to be due to infection. A study in critically sick children with haemato-oncological and multisystemic disease reported that a fT4 cutoff of 16.6 pmol/L and fT3/rT3 ratio of 11.61 pg/ng predicted mortality (31). Our study had a lower threshold of fT4 (14.5 pmol/L) and fT3/rT3 ratio (1.86 pg/ng) to predict mortality, suggesting a lower threshold to monitor sick children with an underlying heart disease.

A few studies have analysed the cardiac response to thyroid supplementation in NTI and have reported contentious results. A meta-analysis did not conclude any beneficial role of either levo-thyroxine or triiodothyronine in NTI (32). An experimental study with the addition of levothyroxine preoperatively in children undergoing cardiac surgery showed a decrease in the inotrope requirement and post-operative cardiac injury (33). Similar results were also concluded in a meta-analysis of nineteen studies on children undergoing cardiac surgery for CHD with NTI that evaluated the role of preoperative levothyroxine. However, there were no significant improvements in clinical parameters, such as duration of hospitalisation, duration of oxygen supplementation, mechanical ventilation support, cardiac index or mortality (34). There is a lack of similar evidence of thyroxine supplementation in non-operative critical illnesses with NTI and this should be evaluated in the future.

Study Limitations

This is one of the few studies that have evaluated the TH axis in children with CHD during hospitalization with consideration to various clinical outcomes, taking into account the level of sickness as represented by the PEWS score. The limited observational period without a prospective follow-up until resolution of NTI was a limitation in this study. The intense severity scoring scales, like PRISM/sequential organ failure assessment were not performed due to logistic reasons.

Conclusion

NTI was seen in a significant proportion of children with CHD presenting with CHF. The severity of illness and CHF predicted poorer thyroid function status that was associated with mortality. This study highlights the need to monitor thyroid functions in children with CHD and CHF during acute sickness.

Ethics

Ethics Committee Approval: This observational study was conducted at the Department of Pediatrics and Cardiology in a large tertiary care public hospital from July 2021 until June 2022 after approval of the Institutional Ethics Committee Maulana Azad Medical College, New Delhi (letter F No.1/IEC/MAMC/82/10/2020/no. 125 dated: 14 Jan 2021).

Informed Consent: Written parental consent was taken before enrollment.

Authorship Contributions

Concept: Biswajit Sahoo, Aashima Dabas, Binita Goswami, Design: Aashima Dabas, Anurag Agarwal, Sumod Kurian, Data Collection or Processing: Biswajit Sahoo, Aashima Dabas, Binita Goswami, Anurag Agarwal, Sumod Kurian, Analysis or Interpretation: Biswajit Sahoo, Aashima Dabas, Sumod Kurian, Literature Search: Aashima Dabas, Binita Goswami, Anurag Agarwal, Writing: Biswajit Sahoo, Aashima Dabas, Binita Goswami, Anurag Agarwal, Sumod Kurian.

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References

1. Wang B, Liu S, Li L, Yao Q, Song R, Shao X, Li Q, Shi X, Zhang JA. Non-thyroidal illness syndrome in patients with cardiovascular diseases: A systematic review and meta-analysis. Int J Cardiol 2017;226:1-10. Epub 2016 Oct 18
2. Yadav Y, Saikia UK, Sarma D, Hazarika M. Cardiovascular Risk Factors in Children and Adolescents with Subclinical Hypothyroidism. Indian J Endocrinol Metab 2017;21:823-829.
3. Gloss B, Trost S, Bluhm W, Swanson E, Clark R, Winkfein R, Janzen K, Giles W, Chassande O, Samarut J, Dillmann W. Cardiac ion channel expression and contractile function in mice with deletion of thyroid hormone receptor alpha or beta. Endocrinology 2001;142:544-550.
4. Barjaktarovic M, Korevaar TIM, Gaillard R, de Rijke YB, Visser TJ, Jaddoe VWV, Peeters RP. Childhood thyroid function, body composition and cardiovascular function. Eur J Endocrinol 2017;177:319-327. Epub 2017 Jul 19
5. Jacobs A, Derese I, Vander Perre S, van Puffelen E, Verstraete S, Pauwels L, Verbruggen S, Wouters P, Langouche L, Garcia Guerra G, Joosten K, Vanhorebeek I, Van den Berghe G. Non-Thyroidal Illness Syndrome in Critically Ill Children: Prognostic Value and Impact of Nutritional Management. Thyroid 2019;29:480-492. Epub 2019 Mar 11
6. Razvi S. Novel uses of thyroid hormones in cardiovascular conditions. Endocrine 2019;66:115-123. Epub 2019 Oct 15
7. Halsall DJ, Oddy S. Clinical and laboratory aspects of 3,3',5'-triiodothyronine (reverse T3). Ann Clin Biochem 2021;58:29-37. Epub 2020 Nov 4
8. Sayarifard F, Yaghmaie B, Sayarifard A, Sayarifard A, Mohammadpour M, Sharifzadeh M, Abbasi F, Taghi Haghi-Ashtiani M, Kouhnavard M. Thyroid function tests in critically ill children; any correlation with disease severity or outcome? Iran J Pediatr 2018;28:e69397.

9. Schmidt-Ott UM, Ascheim DD. Thyroid hormone and heart failure. Curr Heart Fail Rep 2006;3:114-119.
10. Suvarna JC, Fande CN. Serum thyroid hormone in critically ill children. Indian J Pediatr 2009;76:1217-1221.
11. Simonides W, Tijsma A, Boelen A, Jongejan R, de Rijke Y, Peeters R, Dentice M, Salvatore D, Muller A. Divergent Thyroid Hormone Levels in Plasma and Left Ventricle of the Heart in Compensated and Decompensated Cardiac Hypertrophy Induced by Chronic Adrenergic Stimulation in Mice. Metabolites 2023;13:308.
12. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450:76-85.
13. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM; SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 2018;140:e20171904.
14. Kowalski RL, Lee L, Spaeder MC, Moorman JR, Keim-Malpass J. Accuracy and Monitoring of Pediatric Early Warning Score (PEWS) Scores Prior to Emergent Pediatric Intensive Care Unit (ICU) Transfer: Retrospective Analysis. JMIR Pediatr Parent 2021;4:e25991.
15. Auerbach SR, Richmond ME, Lamour JM, Blume ED, Addonizio LJ, Shaddy RE, Mahony L, Pahl E, Hsu DT. BNP levels predict outcome in pediatric heart failure patients: post hoc analysis of the Pediatric Carvedilol Trial. Circ Heart Fail 2010;3:606-611. Epub 2010 Jun 23
16. Lerner RK, Gruber N, Pollak U. Congenital Heart Disease and Thyroid Dysfunction: Combination, Association, and Implication. World J Pediatr Congenit Heart Surg 2019;10:604-615.
17. Guo J, Hong Y, Wang Z, Li Y. Analysis of the Incidence of Euthyroid Sick Syndrome in Comprehensive Intensive Care Units and Related Risk Factors. Front Endocrinol (Lausanne) 2021;12:656641.
18. Pontes CDN, Rocha JLGD, Medeiros JMR, Santos BFBD, Silva PHMD, Medeiros JMR, Costa GG, Silva IMS, Gomes DL, Santos FM, Libonati RMF. Low T3 syndrome as a prognostic factor in patients in the intensive care unit: an observational cohort study. Rev Bras Ter Intensiva 2022;34:262-271.
19. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal Illness Syndrome Across the Ages. J Endocr Soc 2019;3:2313-2325.
20. Wajner SM, Maia AL. New Insights toward the Acute Non-Thyroidal Illness Syndrome. Front Endocrinol (Lausanne) 2012;3:8.
21. Gaggin HK, Januzzi JL Jr. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta 2013;1832:2442-2450. Epub 2013 Jan 9
22. Cowley CG, Bradley JD, Shaddy RE. B-type natriuretic peptide levels in congenital heart disease. Pediatr Cardiol 2004;25:336-340.
23. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol 2009;30:3-8. Epub 2008 Jul 4
24. Brozaitiene J, Mickuviene N, Podlipskyte A, Burkauskas J, Bunevicius R. Relationship and prognostic importance of thyroid hormone and N-terminal pro-B-Type natriuretic peptide for patients after acute coronary syndromes: a longitudinal observational study. BMC Cardiovasc Disord 2016;16:45.
25. Takahashi H, Kashiwagi Y, Nagoshi T, Tanaka Y, Oi Y, Kimura H, Minai K, Yoshimura M. Low triiodothyronine levels correlate with high B-type natriuretic peptide levels in patients with heart failure. Sci Rep 2021;11:21865.
26. Yanni GN, Destariani CP, Lubis AN, Deliana M. Thyroid Hormone Profile in Children with Sepsis: Does Euthyroid Sick Syndrome Exist? Open Access Maced J Med Sci 2019;7:1110-1113.
27. Miao G, Pang S, Zhou Y, Duan M, Bai L, Zhao X. Low T3 syndrome is associated with 30-day mortality in adult patients with fulminant myocarditis. Front Endocrinol (Lausanne) 2023;14:1164444.
28. Strich D, Israel A, Edri S, Gillis D. Age and Gender Adjusted FT3 Levels as Novel Predictors of Survival. J Clin Endocrinol Metab 2023;108:3295-3301.
29. Zhao X, Zhang R, Jiang H, Liu K, Ma C, Bai M, An T, Yao Y, Wang X, Wang M, Li Y, Zhang Y, Zhang J. Combined use of low T3 syndrome and NT-proBNP as predictors for death in patients with acute decompensated heart failure. BMC Endocr Disord 2021;21:140.
30. El-Nawawy A, Elwafa RAHA, Khalil Abouahmed A, Rasheed RA, Omar OM. Evaluation of non-thyroidal illness syndrome in shock patients admitted to pediatric intensive care unit in a developing country. Eur J Pediatr 2024;183:769-778. Epub 2023 Nov 23
31. Carreras L, Riaño I, Vivanco A, Avello N, Iglesias T, Rey C. Non-thyroidal illness syndrome and its relationship with mortality risk in critically ill children. Front Pediatr 2023;11:1142332.
32. Sciacchitano S, Capalbo C, Napoli C, Anibaldi P, Salvati V, De Vitis C, Mancini R, Coluzzi F, Rocco M. Nonthyroidal Illness Syndrome: To Treat or Not to Treat? Have We Answered the Question? A Review of Metanalyses. Front Endocrinol (Lausanne) 2022;13:850328.
33. Zhang JQ, Yang QY, Xue FS, Zhang W, Yang GZ, Liao X, Meng FM. Preoperative oral thyroid hormones to prevent euthyroid sick syndrome and attenuate myocardial ischemia-reperfusion injury after cardiac surgery with cardiopulmonary bypass in children: A randomized, double-blind, placebo-controlled trial. Medicine (Baltimore) 2018;97:e12100.
34. Flores S, Loomba RS, Checchia PA, Graham EM, Bronicki RA. Thyroid Hormone (Triiodothyronine) Therapy in Children After Congenital Heart Surgery: A Meta-Analysis. Semin Thorac Cardiovasc Surg 2020;32:87-95. Epub 2019 May 22