Thyroid profile in children with Nephrotic syndrome attending a Tertiary Care Centre in Kerala

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Abstract

Background: Nephrotic syndrome (NS) is a clinical manifestation of glomerular disease characterized by heavy proteinuria. It is relatively common in children, with an incidence of 1–3 per 100,000 among those aged below 16 years. Massive proteinuria in NS leads to the loss of intermediate-sized plasma proteins (4–200 kDa), including thyroxine-binding globulin (TBG), transthyretin, and albumin, resulting in a possible reduction in circulating thyroid hormone levels. Consequently, children with nephrotic-range proteinuria may develop a hypothyroid state due to significant urinary losses of thyroxine (T4), triiodothyronine (T3), and TBG hormones that play crucial roles in growth and development. It remains unclear whether the rise in thyroid-stimulating hormone (TSH) levels during relapse is transient or persistent, and whether thyroid hormone supplementation is warranted. Persistent hypothyroidism can adversely affect growth and neurodevelopment. Therefore, this study was designed to evaluate thyroid function status in children with nephrotic syndrome.

Objectives: To assess and compare thyroid function in children with nephrotic syndrome and healthy controls, and to evaluate thyroid status during the active stage of the disease and in remission.

Methods: This prospective observational study was conducted in the Departments of Paediatrics and Paediatric Nephrology at a tertiary-care hospital in Kochi, Kerala. Serum thyroid hormone levels were measured in children with nephrotic syndrome during the active or relapse phases and compared with age- and sex-matched healthy controls, as well as during their remission phase. Statistical analysis was performed to determine the significance of differences in thyroid profiles between cases and controls, and between active and remission stages.

Results: Among the 30 cases of NS included in the study, 82.6% of children with elevated TSH levels during the active phase returned to normal values in remission, while 17.4% continued to exhibit elevated TSH levels even during remission. Subgroup analysis across various age groups showed that only 76.9% of children with abnormal TSH levels normalized during follow-up.

Conclusion: A transient hypothyroid state was observed among children with nephrotic syndrome in this study. Subgroup analysis indicated a persistence of low fT3 and fT4 levels in the 1–5-year age group, suggesting that younger children may be more vulnerable to thyroid dysfunction during the course of nephrotic syndrome.

Keywords: Nephrotic syndrome, Transient hypothyroidism, Thyroid function.

Introduction

Thyroid Hormone are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis [1,2]. The massive proteinuria observed in Nephrotic Syndrome (NS) leads to increased urinary loss of thyroid binding globulin, transthyretin and albumin, which are the Thyroid Hormone binding proteins. Additionally, in NS, urinary loss of Thyroid Hormone is also increased [3-5]. Hormone loss through the urine does not cause any clinical or biochemical changes in the early stages. Thyroid stimulating hormone (TSH) levels rise in response to these losses if treatment is not received, which can result in subclinical or occasionally overt hypothyroidism [6,7,8] This state can lead to further complications affecting other systems of the body, including impairment of optimal growth and development. Therefore, early identification of changes in the Thyroid Hormone in NS is imperative to prevent long-lasting effects on the growing child. Therefore, assessment of the thyroid profile in patients with NS is important.

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However, very few studies have been conducted to understand the relationship between thyroid status and NS in India. Additionally, assessment and comparison of the thyroid status during active disease and remission stage will also aid in stratification of patients according to the risk. There is a lack of published data on the severity of transient hypothyroidism in nephrotic syndrome cases, particularly in the 1–5-year age group, which if neglected could prove detrimental to the neurodevelopmental outcome and this study strives to probe into this aspect.

Material and Methods

This was a prospective observational study done at the departments of Pediatrics and Pediatric Nephrology, at a tertiary level hospital in Kochi, Kerala over a period of one year. Ethical clearance was secured from the institutional review board (letter number: ECASM-AIMS-2024-432). All patients aged 1 year-15 years of age diagnosed with the first episode of Nephrotic Syndrome as per the diagnostic criteria or are in relapse were enrolled in the study. The controls were patients aged 1-15 years attending the pediatric OPD or admitted in pediatric ward for minor illnesses including respiratory infections, etc. Children who were excluded from the study included those less than age 1 year and those above 16 years of age, those with thyroid disorders, hypothalamo-pituitary axis derangement, chronic infections like tuberculosis, diabetes mellitus, cystic fibrosis, malabsorption syndrome, hyperlipidemia, chronic renal disease or chronic hepatic disease, cases of steroid resistance Nephrotic Syndrome and those patients or parents unwilling to participate in the study. The sample size for our study was calculated based on the findings of a previous study [9], taking into account 80% power and 95% confidence. Based on the findings of the previous study Based on these findings, a total sample size of 60 was calculated, with 30 in each group. Patients meeting the above-mentioned inclusion and exclusion criteria were enrolled into the study. The demographic characteristics were recorded and serum free T3, free T4 and TSH levels were tested among cases during their active and remission stage, and in the controls as well. Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed as frequency and percentage. Continuous variables were presented by mean ±SD or median (25th percentile -75th percentile). The statistical significance of the mean difference of age between two groups was tested using the independent samples t-test. To test the statistical significance of difference in gender between the cases and control groups, the Chi square test was used. The Mann Whitney U test was used to test the statistical significance of the difference in the median of thyroid variables between the cases and control groups. To compare the change of median in the Thyroid Hormone levels between active and remission stage, the Wilcoxon Signed rank test was used.

Results

A total of 60 patients met the inclusion criteria and were enrolled in the study. Of these, 30 patients constituted the case group, while the remaining comprised the control group. Both groups exhibited a similar sex distribution, with males representing 60% and females 40%. Within the case group (n=30), 40% were newly diagnosed with nephrotic syndrome, and the remaining 60% presented with relapse of steroid-sensitive nephrotic syndrome. Age distribution among cases was as follows: 33.3% were between 1 and 5 years, 50% between 6 and 10 years, and 16.7% between 11 and 15 years. In the control group (n=30), 26.7% were aged 1 to 5 years, 43.3% aged 6 to 10 years, and 30% aged 11 to 15 years.

Table 1: Comparison of thyroid hormones between active stage of NS and control group

Thyroid hormones	Group	n	Median (Q1-Q3)	p value
fT3	Active	30	2.2(2.1-2.5)	<0.001
	Control	30	4.7(3.7-5.4)	
fT4	Active	30	0.8(0.6-0.9)	<0.001
	Control	30	1.3(1.0-1.6)	
TSH	Active	30	6.0(5.4-7.5)	<0.001
	Control	30	2.4(1.4-4.5)	

Table 1 shows the median levels of free triiodothyronine (fT3) and free thyroxine (fT4) were significantly lower in the active group compared to the control group (p value <0.001), indicating a decrease in thyroid hormone levels during the active stage of nephrotic syndrome (NS). In contrast, the median thyroid-stimulating hormone (TSH) levels were significantly elevated in the active group relative to controls (p value <0.001), reflecting an increase in TSH concentration in the active stage of NS.

Table 2: Comparison of serum fT3, fT4 and TSH levels in children with NS in their active and remission stages

fT3 levels in the Active stage (n=30)	fT3 levels in the Remission stage		p value
	Normal n (%)	Abnormal (L) n (%)	
Normal (n=7)	7 (100%)	0	<0.001
Abnormal (L) (n=23)	22 (95.6%)	1 (4.34%)	
fT4 levels in the Active stage (n=30)	fT4 levels in the Remission stage		p value
	Normal n (%)	Abnormal (L) n (%)	
Normal(n=7)	6 (85.7%)	1 (14.3%)	0.001
Abnormal (L) (n=23)	18 (78.3%)	5 (21.7%)	
TSH levels in the Active stage	TSH levels in the Remission stage		p value
	Normal n (%)	Abnormal(H) n(%)	
Normal (n=7)	6 (85.7%)	1 (14.3%)	<0.001
Abnormal (H) (n=23)	19 (82.6%)	4 (17.4%)	

Abnormal(L): lower than the normal value; Abnormal(H): Higher than the normal value

As depicted in Table 2, among 23 patients in the active stage of NS with low fT3 levels, 95.6% returned to normal during the remission stage, which was statistically significant ($p < 0.001$), whereas 4.3% remained low. In patients with low fT4 levels during the active stage of NS, 78.3% returned to normal in remission, also statistically significant, while 21.7% remained low. Among 7 patients with normal fT4 levels in the active stage, 14.3% experienced a decrease to low levels during remission. TSH levels were elevated in the active stage of NS in 82.6% of cases, which returned to normal during remission with statistical significance. However, 17.4% of cases maintained elevated TSH levels, as shown in Table 2. Notably, among seven patients with normal TSH in the active stage, 14.3% developed elevated TSH levels during remission. In the 6–10 years age group, among 13 patients with elevated serum TSH during the active stage of NS, 76.9% returned to normal during remission, while 23.1% remained elevated.

Discussion

This study aimed to assess the levels of thyroid hormones during the active and remission stages of patients with nephrotic syndrome and to compare these levels with those in healthy controls. Our findings indicate that the median levels of free triiodothyronine (fT3) and free thyroxine (fT4) were significantly lower in patients with nephrotic syndrome compared to controls. Conversely, thyroid-stimulating hormone (TSH) levels were significantly higher in the nephrotic syndrome group than in the control group.

Table 3: Comparison of mean Thyroid hormone levels in various studies

Study	Thyroid hormone	Cases	Controls	p-value
Present study (n=60)	fT3-pcg/ml(SD)	2.2 (0.6)	4.6(0.9)	<0.001
	fT4-ng/dl(SD)	0.8 (0.3)	1.3(0.3)	<0.001
	TSH-uIU/ml(SD)	7.2 (4.8)	2.9(1.6)	<0.001
Dhanjal et al(2019) (n=60)	fT3-pcg/ml(SD)	1.516 (1.160)	2.087 (0.898)	0.037
	fT4-ng/dl(SD)	1.979 (1.303)	3.457 (2.513)	0.048
	TSH-uIU/ml(SD)	7.243 (1.970)	3.160 (1.970)	0.0001
Kapoor K et al (2014) (n=20)	fT3-pcg/ml(SD)	3 (0.9-4.9)	3.3 (2.4-4.5)	0.695
	fT4-ng/dl(SD)	1.16 (0.8-4.6)	1.2 (0.8-1.8)	0.694
	TSH-uIU/ml(SD)	3.9 (0.5-13)	2.05 (0.6-3.4)	0.06
Marimuthu et al (2017) (n=60)	fT3-pcg/ml(SD)	3.1 (1.3)	2.8 (0.7)	0.30
	fT4-ng/dl(SD)	1.8 (1.7)	1.2 (0.2)	0.05
	TSH-uIU/ml(SD)	4.6 (4.6)	1.9 (1)	<0.01

Our findings are consistent with the study by Dhanjal GS et al. from Haryana, which reported significantly lower mean fT3 and fT4 levels in nephrotic syndrome cases compared to controls [9]. Similar to our results, TSH levels were higher among nephrotic syndrome patients relative to controls. Marimuthu et al. from Puducherry also observed a comparable pattern [10]. In contrast, Kapoor K et al. from New Delhi reported lower fT3 and fT4 levels and higher TSH levels in nephrotic syndrome cases compared to controls; however, these differences were not statistically significant.[11](Table3)

Table 4: Comparison of Mean Thyroid hormone levels in during active stage and remission stage in various studies

Study	Thyroid hormone	Active stage	Remission stage	p-value
Present study (n=60)	fT3-pcg/ml(SD)	2.2(0.6)	4.1(0.8)	<0.001
	fT4-ng/dl(SD)	0.8(0.3)	1.4(0.3)	<0.001
	TSH-uIU/ml(SD)	7.2(4.8)	3.3(1.4)	<0.001
Saffarietal (n-147)	fT3-pcg/ml(SD)	3.91 (1.10)	3.7 (0.85)	0.557
	fT4-ng/dl(SD)	9.6 (2.54)	12.3 (2.8)	0.002
	TSH-uIU/ml(SD)	7.12 (7.9)	2.7 (1.7)	<0.001
Ito et al (n-14)	fT3-pcg/ml(SD)	2.7 (0.4)	3.7 (0.5)	<0.05
	fT4-ng/dl(SD)	0.98 (0.18)	1.35 (0.17)	<0.05
	TSH-uIU/ml(SD)	2.2 (0.5)	0.9 (0.3)	<0.05
Jung SH et al (n-31)	fT4-ng/dl(SD)	1.02 (0.26)	1.38 (0.23)	0.001
	TSH-uIU/ml(SD)	8.05 (3.53)	4.08 (2.05)	0.001

Furthermore, when comparing thyroid hormone levels between the active and remission stages of nephrotic syndrome cases, fT3 and fT4 levels were significantly lower during the active stage, while TSH levels were significantly elevated in the active stage. (Table 4) Saffari et al. from Iran also reported findings similar to ours; however, they did not observe a statistically significant difference in fT3 levels between active and remission stages of nephrotic syndrome. The studies by Ito et al. from Japan and Jung SH et al. from South Korea reported results consistent with our findings, although the South Korean study assessed only fT4 and TSH levels[5,12]. Although not a primary objective of this study, a subgroup analysis by age was conducted out of curiosity to explore whether any particular age group exhibited a higher propensity for persistent hypothyroidism, which could potentially affect neurological outcomes, especially in younger children. However, due to the very small sample sizes within these subgroups, it would be premature to draw any definitive conclusions.

A major limitation of our study is the small sample size, which may restrict the generalizability of the results to the broader population. Additionally, as a single hospital-based study that did not include samples from different relapse stages of the same child, these factors represent inherent limitations of our research.

Conclusion

Transient hypothyroidism was observed in patients with nephrotic syndrome in this study. There is a lack of published data on the severity of transient hypothyroidism in nephrotic syndrome cases, particularly in the 1–5-year age group. This gap is especially important given the potential impact on cognitive and neurodevelopmental outcomes in this vulnerable population.

Recommendations

A multicenter prospective study with a larger sample size is needed to determine whether geographical and racial differences influence thyroid hormone levels. Further research focusing on the 1–5-year age subgroup is warranted to investigate whether transient hypothyroidism persists and if intervention is necessary, considering its potential impact on neurodevelopmental outcomes.

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