Original Article

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Thyroid Function Status in Nephrotic Syndrome in Paediatric Age Group: A Hospital-based Cross-sectional Study

Paediatrics Section

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ABSTRACT

Introduction: Nephrotic syndrome, being one of the common glomerular diseases in the paediatric population, is characterised by massive proteinuria and has a negative impact on thyroid function, necessitating investigation.

Aim: To assess the status of thyroid function in nephrotic syndrome in the paediatric age group.

Materials and Methods: This descriptive cross-sectional study was carried out at Bankura Sammilani Medical College and Hospital (BSMCH) in Bankura, West Bengal, India. The study included 100 children of both sexes, aged one to eight-year-old who had nephrotic syndrome, either newly diagnosed or relapsed, and who were either hospitalised to the Paediatric Department or visited an Outpatient Department (OPD), between April 2020 and September 2021. Thyroid hormone profiles, as well as, other relevant investigations, were estimated in all children. Data was analysed using the Epi-Info (version 3.5.1) software.

Results: Out of 100 children, 64% were males and the rest, 36%, were females. The mean age of presentation was 4.31±1.90 years. A total of 62% of them had a higher serum level of Thyroid Stimulating Hormone (TSH). Low levels of thyroxine (T4) and triiodothyronine (T3) were observed in 56% and 54% of cases, respectively. The serum albumin and serum TSH levels showed a significant negative correlation (r=-0.249, p=0.013). While T3 had a significant positive correlation (r=0.221, p=0.027), serum levels of T4 had a positive correlation (r=0.187), but turned out to be statistically insignificant (p=0.063).

Conclusion: It was found that, 62% of the children having nephrotic syndrome, also had increased levels of TSH. Serum T4 and T3 levels were low in 54% and 56% of the study population, respectively, necessitating further investigation.

Keywords: Hormone, Proteinuria, Thyroxine, Triiodothyronine

INTRODUCTION

Nephrotic syndrome is a common renal disorder in the paediatric population. It is a glomerular disease, characterised by nephrotic-range proteinuria, which is proteinuria greater than 3.5 g/24 hour or a urine protein: creatinine ratio greater than 2, along with the triad of clinical findings associated with it resulting from large urinary protein losses are hypoalbuminaemia (≤2.5 g/dL), oedema, and hyperlipidaemia (cholesterol greater than 200 mg/dL) [1]. Urinary albumin losses are not entirely compensated by increased hepatic synthesis in children with nephrotic syndrome, thus, leading to hypoalbuminaemia. Many other proteins, in addition to albumin, are also excreted in the urine of patients with proteinuria, some of them being hormones and hormone-binding proteins. The substantial urinary losses of thyroid hormones and Thyroxin-Binding Globulin (TBG) have widely been found in patients with proteinuria and validated by several publications [2-5]. In patients with nephrotic syndrome, thyroid hormone loss can result in lower free thyroid hormone levels unless there is also a simultaneous increase in production under the influence of TSH. Also, the loss of albumin and TBG may decrease thyroid hormone binding fractions, resulting in lower total T4 and T3 levels [6]. Thyroid hormones regulates the function of various organ systems, including the urinary system. Thyroid hormones are considered indispensable for the renal growth and development along with regulation of fluid and electrolyte homeostasis [7,8]. According to the researchers, hypothyroidism is associated with decreased glomerular infiltration, hyponatremia, and changes in urine osmolality [9,10]. The primary paediatrician rarely considers hormonal disorders, particularly thyroid disorders caused by excessive protein loss through urine, when treating children with nephrotic syndrome. As a result, subclinical or overt hypothyroidism remains undiagnosed, even though, researchers have known about it for a long-time [11]. It is known that, a chronic hypothyroid condition can cause physical growth and developmental issues. As a result, in terms of the paediatric age group, early detection and treatment of such disorders are critical. Considering this issue, present study was planned to investigate the thyroid function status, in children with nephrotic syndrome.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted in the Department of Paediatrics, BSMCH, Bankura, West Bengal, India, from April 2020 to September 2021. Before the commencement of the present study, ethical clearance from the concerned Institutional Ethical Committee (IEC) had been obtained (No. BSMC/Aca: 381, dated February 4, 2020).

Inclusion criteria: A total of 100 children of either sex, aged one to eight-year-old with nephrotic syndrome, either newly diagnosed or relapsed, and those who were admitted to the Paediatric Department, as well as, those who attended the OPD, during the study period, were included in the present study after taking consent from either parents or guardians. Children with onset of uncomplicated nephrotic syndrome between one and eight years of age are likely to have steroid-responsive minimal change nephrotic syndrome, and steroid therapy may be initiated without a diagnostic renal biopsy. Renal biopsy was not feasible in the study Institution, which is why this particular age group was selected.

Exclusion criteria: Children with derangement of hypothalmo-pituitary axis, thyroid disorders; chronic infections like tuberculosis, diabetes mellitus, cystic fibrosis; malabsorption syndromes, moderate to severe protein energy malnutrition; chronic renal or hepatic diseases; steroid-resistant nephrotic syndrome; and those parents/guardians, who did not give consent were excluded from the present study.

Sample size calculation: A minimum sample size of 100 participants were estimated using modified Cochran's formula; with a 95% confidence interval, a margin of error of 10%, a 68% prevalence of thyroid disorder in children with nephrotic syndrome, as reported by Hajizadeh N et al., and a further 10% increment to decrease type II error [12].

Along with relevant investigations like urine analysis, Complete Blood Count (CBC), Renal Function Test (RFT), serum electrolytes, Liver Function Test (LFT), and lipid profile, the thyroid hormones (T4 and T3) and TSH levels, were estimated to fulfill the inclusion criteria. TSH=0.5-5.5 mIU/L, T4=5.5-13.5 µg/dL, and T3=90-260 ng/dL were considered normal thyroid profile levels. Upon diagnosis of nephrotic syndrome, all children were put on treatment with prednisolone, as per existing standard protocol. All information regarding the demographical profile, detailed clinical examination, and review of medical records of all study populations, were put into the predesigned proforma.

STATISTICAL ANALYSIS

Collected data was entered into a Microsoft Excel Spreadsheet and analysed with Epi-Info (version 3.5.1) software. Continuous variables were expressed as mean±Standard Deviation (SD), whereas categorical variables as percentages and ratios. A Pearson's correlation coefficient (linear regression) test was performed to find out the correlation between serum albumin and thyroid hormone levels. A p-value <0.05 was set as statistically significant.

RESULTS

There were 100 children, with a male to female ratio of 1.78:1. The mean age of presentation was 4.31±1.90 years. Children aged four to six-year-old were affected the most [Table/Fig-1]. All the children came from the countryside.

Gender/Age* (years)	1-3	4-6	7-8	Total (%)
Male	25	29	10	64
Female	14	18	4	36
Total (%)	39	47	14	100

[Table/Fig-1]: Gender and age distribution of the sample.
*Mean age±SD=4.31±1.90 years

Out of 100 participants, 17% of the cases were found to have urinary tract infection and no one had haematuria. Specific gravity and pH in all the participants were within normal limits, whereas granular cast was present in 100% of the cases [Table/Fig-2].

Parameters	Number of patients	Number of abnormal values
Physical examination		
Colour-straw	100	100
Ph- Acidic (6.4-6.6)	100	0
Specific gravity (1.015-1.020)	100	0
Chemical examination		
Protein		100
3+	31	
4+	69	
Blood-nil	100	0
Microscopical examination		
Pus cell/white blood cell		
0-5/*hpf	83	
6-18/*hpf	17	17
†RBC		
0-5/*hpf	100	0
Epithelial cell		
0-5/*hpf	100	0
Granular cast		
Present	100	100

[Table/Fig-2]: Urinalysis in the patients with nephrotic syndrome.
*hpf: High power field; †RBC: Red blood corpuscles
NB: 17 children (male-6 and female-11) had been diagnosed as urinary tract infection and treated successfully before initiation of steroid therapy for nephrotic syndrome

The total serum protein (g/dL) and albumin (g/dL) were 4.54±0.50 and 2.04±0.31, respectively and were lower than normal value. The total cholesterol (mg/dL) level was 282.5±14.20 which was higher than the normal value (<200). The serum urea (mg/dL), creatinine (mg/dL), sodium (mEq/L), and potassium levels (mEq/L) were 18.66±6.27, 0.48±0.12, 136.47±0.89, and 3.67±0.10 respectively, and were considered as normal values [Table/Fig-3] The normal values of various parameters are shown in tables [13].

Laboratory parameters	Normal values [13]	Mean±SD	Minimum	Maximum	Number of subjects with abnormal values
Total protein (gram/dL)	6-8	4.54±0.50	2.3	5.4	100
Albumin (gram/dL)	3.7-5.5	2.04±0.31	1.1	2.5	100
Total cholesterol (mg/dL)	70-200	282.5±14.20	254	316	100
Urea (mg/dL)	5-25	18.66±6.27	14	34	16
Creatinine (mg/dL)	0.12-1.06	0.48±0.12	0.4	0.7	0
Sodium (mEq/L)	136-145	136.4±0.89	135	139	0
Potassium (mEq/L)	3.5-5.5	3.67±0.10	3.5	3.9	0

[Table/Fig-3]: Basic biochemical characteristics.

The mean haemoglobin (gram/dL) level was 10.15±0.85, which was in the anaemic range. About 11% and 18% of the participants were found to be erythropenic and microcytic, respectively. There was no significant leucocytosis or thrombocytopenia [Table/Fig-4].

Parameters	Normal values [13]	Mean±*SD	Maximum	Minimum	Number of abnormal values
Haemoglobin (gram/dL)	11.5-14.5	10.15±0.85	12.5	8	54
*RBC ($\times10^6$/mL)	3.9-5.3	4.10±0.35	4.9	3.4	11
*MCV (fL)	76-90	79.91±6.15	88	66	18
*TLC ($\times10^3$/mm^3)	5-14.5	9.123±0.76	10.5	7.6	0
Platelets ($\times10^3$/mm^3)	140-450	248.57±72.11	391	152	0

[Table/Fig-4]: Complete Blood Count (CBC) results of the patients with nephrotic syndrome.
*RBC: Red blood corpuscles; MCV: Mean corpuscular volume; TLC: Total leucocyte count

The mean serum TSH (mIU/L) level was 9.01±5.25, which was well above the upper cut-off value (0.5-5.5 mIU/L) for the cohort and total serum T4 (µg/dL) and T3 (ng/dL) levels were 5.21±1.57 and 89.08±20.63, respectively, and which are just below the lower limit of normal reference values [Table/Fig-5].

Thyroid profiles*	Normal values	Minimum	Maximum	Mean±SD	Number of subjects with abnormal values
TSH (mIU/L)	38	1.1	19.8	9.01±5.25	62
T4 (µg/dL)	44	1.1	9.5	5.21±1.57	56
T3 (ng/dL)	46	52	135	89.08±20.63	54

[Table/Fig-5]: Thyroid hormone status in nephrotic syndrome.
*Normal reference value in children: TSH (5 months to 20 years): 0.5-5.5 mUI/L, T4 (1-10 years): 5.5-13.5 µg/dl, T3 (1-10 years): 90-260 ng/dL [13]

The Pearson's correlation coefficient (linear regression) test was performed, to find out the relationship between serum albumin with serum thyroid hormones (T4 and T3), and TSH levels [Table/Fig-6]. There was a significant negative correlation (r=-0.249) between serum albumin level and TSH. Whereas, serum albumin with T4 (r=0.187) and T3 (r=0.221) showed a positive correlation. From this observation, it was concluded that, in nephrotic syndrome, urinary loss of albumin along with other macromolecules such as TBG, transthyretin, T3 and T4 is associated with decreased serum thyroid hormones level, which in turn stimulates TSH secretion from anterior pituitary gland via hypothalamic thyroid releasing hormone by positive feedback mechanism.

TSH and thyroid hormones	Pearson correlation coefficient (r)	Degree of freedom (df)	p-value
TSH	-0.249	98	0.013
T4 (total)	0.187	98	0.063
T3 (total)	0.221	98	0.027

[Table/Fig-6]: Thyroid hormones status in nephrotic syndrome. Shows correlation between serum albumin (g/dL) (mean±SD, 2.04±0.31) and serum levels of TSH, T4 and T3.

DISCUSSION

Thyroid dysfunction is fairly common in children with nephrotic syndrome and may also be affected by the specific type of renal pathology. The interactions between thyroid and renal function and the intricacies involved may pose treatment challenges and hence, require proper cooperation between endocrinologists and nephrologists. The present study showed variably affected thyroid dysfunction with respect to TSH, T4 and T3 levels. T4 and T3 serum levels of 5.5-13.5 g/dL and 90–260 ng/dL, respectively, are being used as normal reference values in the study population [14]. The findings of the present study, were comparable to those of Ebadi A et al., and Gattoo I et al., who reported thyroid dysfunction in children with nephrotic syndrome to have low T4 and T3 levels but high TSH levels during the active phase [15,16]. Sharma M et al., found that T3 and T4 readings were normal during active disease, while TSH values were elevated [17]. In the present study, population with nephrotic syndrome, the mean serum levels for TSH were high, and that of T4 and T3 were both low. In a study of 85 nephrotic children aged 2-12 years, Pelletier J et al., also reported that the mean value of TSH during nephrosis was higher than the usual level [18]. In their studies, Gilles R et al., and Junglee NA et al., observed that nephrotic syndrome is associated to abnormalities in serum thyroid hormone levels [6,19]. In addition, Afroz S et al., determined that urinary losses of different binding proteins in nephrotic syndrome leads to transient subclinical hypothyroidism, with serum T3 and T4 levels in the normal range during and after attack, while the levels of TSH increases [2]. Thyroid hormonal alterations may be caused by urinary loss of several macromolecules and binding proteins, including TBG, transthyretin, or prealbumin, and albumin, resulting in a decrease in serum total thyroxin and, in certain cases, total T3 levels which was observed in present study. These shifts in various hormone levels may also be related to the duration of proteinuria.

A definite correlation between serum albumin levels and serum TSH, T4, and T3 levels was further observed. It was found that, the serum level of TSH had a negative correlation (r=-0.249) with serum albumin levels, whereas T4 and T3 have a positive correlation. There are several studies conducted by different authors, which showed a negative correlation between serum albumin and serum TSH in nephrotic syndrome [20,21]. Because tests for the urinary levels of TSH, T4, T3, and free T4 were not done, it was not possible to ascertain the mechanism by which the risk of hypothyroidism increased with the onset of nephrotic syndrome. However, in the presence of massive proteinuria, substantial loss of free and protein-bound hormones in urine may be a major risk factor for hypothyroidism. According to observations of the present study, there was a statistically significant correlation between serum albumin and serum TSH, as well as, serum T3 levels at the onset of nephrotic syndrome, but not with serum T4, implying that other factors such as T4 to T3 conversion ability and thyroid compensatory mechanisms due to nephrotic syndrome may be involved besides urinary loss. Renal tubule injury, which reduces Low Molecular Weight (LMW) protein reabsorption and can disrupt thyroid functions, is well established. Furthermore, when Glomerular Filtration Rate (GFR) diminishes, the incidence of hypothyroidism increases [22,23]. The mean serum total protein (g/dL) and albumin (g/dL) levels observed in the present study were 4.54±0.50 and 2.04±0.31, respectively.

Limitation(s)

The first one was that the thyroid hormone status was investigated, only during the active phase of nephrotic syndrome and not during remission. So, the status of the thyroid function in remission could not be evaluated, to see, whether it remits with resolution of proteinuria or not. Second, due to a lack of facilities in our esteemed Institution, authors could only measured total serum T4 and T3, but not free T4 and free T3, as well. Third, the urinary levels of TBG, T4, and T3 were not measured. Hence, urinary protein losses could not be correlated with urinary thyroid hormone excretion.

CONCLUSION(S)

It was found that, 62% of the study population had high serum levels of TSH. It was also observed that serum T4 and T3 levels were low in 54% and 56% of the study population, respectively. Hence, this abnormal thyroid function must be addressed right from the beginning because if it persists even after remission, it will cause several physiological and developmental changes in the child population. To address such preventable physiological changes, in-depth evaluation of the thyroid functions, both during the active phase and in remission is recommended.

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