

Thyroid Profile in Idiopathic Childhood Steroid-Sensitive Nephrotic Syndrome

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ABSTRACT

Background: Nephrotic syndrome (NS), the most common glomerular disease of childhood, characterized by massive proteinuria which may have a negative impact on the circulating thyroid hormone status necessitating thyroid hormone supplementation in these children. **Aim:** The aim was to determine the thyroid status in steroid-sensitive NS during the time of relapse and remission. **Materials and Methods:** In this single-center prospective observational study, we documented thyroid hormone profile (thyroid-stimulating hormone [TSH], thyroxine, and triiodothyronine) in fifty children at presentation (first attack or relapse) and again 4 weeks after remission. Baseline characteristics were noted in the prestructured proforma. **Results:** Out of the total fifty children analyzed, 29 were male and 21 females. Although both T3 and T4 levels were within the normal range in all participants during attack/relapse and in remission, there was a statistically significant difference in absolute levels of both T3 and T4 at relapse and remission ($P = 0.001$). There was a significant rise of TSH levels during attack/relapse which normalized to normal values after 4 weeks of remission (13.08 ± 7.9 vs. 2.43 ± 1.00 mIU/L, $P = 0.0001$). None required thyroid hormone replacement therapy. **Conclusion:** The rise of TSH level during relapse is mostly transient and usually does not require thyroid hormone supplementation.

KEYWORDS: Children, steroid-sensitive nephrotic syndrome, thyroid hormone status

INTRODUCTION

Nephrotic syndrome (NS) is a glomerular disease manifesting clinically as edema, massive proteinuria, hypoalbuminemia, and hyperlipidemia. It affects 1–3 per lakh children below 16 years of age. Approximately, 90% of these NS is idiopathic, out of which 80% are steroid sensitive.^[1]

Thyroid hormones in circulation are bound to proteins namely thyroid-binding globulin (TBG), prealbumin, and albumin. Massive proteinuria in NS results in loss of intermediate size plasma proteins (4–200 kDa), which includes TBG, transthyretin, and albumin with a resultant possibility of reduction in the circulatory level of thyroid hormones. Hence, in children with nephrotic range proteinuria, there is a possibility of hypothyroid state due to significant loss of thyroxine (T4), triiodothyronine (T3), and TBG which

may have an important bearing on children of growing age.^[2] Developing hypothyroidism may necessitate thyroid hormone supplementation in these children. There is also a significant rise of thyroid-stimulating hormone (TSH) level during attack or relapse of NS. It needs to be seen if this rise of TSH level during relapse is minor and transient or significant and persistent requiring thyroid hormone supplementation.

This study was undertaken with an objective to determine the thyroid status in steroid-sensitive NS (SSNS) during the time of heavy proteinuria and at remission and to find if the thyroid status correlates with serum albumin and if any of these derangements

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of thyroid status is severe enough to need thyroid hormonal replacement.

MATERIALS AND METHODS

All children attending the outpatient department or admitted indoors in a tertiary care teaching institute in Kolkata with a diagnosis of NS, either first attack or in relapse, between 1 and 12 years were considered to be included in the study. NS relapse or remission was diagnosed according to the criteria laid down by the Indian Pediatric Nephrology Society.^[3] Steroid-dependent and frequently relapsing patients were included provided they went into complete remission and maintained that remission for at least 4 weeks for them to be eligible to undergo repeat thyroid function tests. Children with chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m²), those having previously known thyroid disease, and those whom the exact pattern of relapses and remissions could not be delineated due to irregular follow-up and unavailability of documents were excluded from the study.

Requisite clearance from the Institutional Ethics Committee of NRS Medical College, Kolkata (NMC/7558 dated December 27, 2014) was taken. Written informed consent was obtained from the guardians of those included in the study. The demographic, clinical, investigational, and treatment details were entered in a predesigned structured proforma. Thyroid studies were done at the time of presentation and again 4 weeks after remission. For accurate comparison with established normal values of thyroid function, fasting morning serum samples were used. Serum T3 and T4 were done by competitive enzyme immunoassay (AccuBind, Monobind Inc., USA) and results expressed as µg/dl and ng/dl, respectively. TSH level in serum was determined by microplate immunoenzymometric assay and results expressed as µIU/L.

Statistical analysis

Baseline characteristics were compared in a descriptive way. Quantitative variables were compared with the use of Student's *t*-test, paired *t*-test, or Wilcoxon rank sum test as appropriate. Categorical variables were analyzed with Chi-square test. A scatter plot was performed to reveal correlation serum albumin and TSH values and serum cholesterol and TSH values at the time of attack/relapse and remission. The data are expressed as mean \pm 2SD, median (upper and lower extremes), and percentage, as appropriate, and $P < 0.05$ was considered statistically significant. The SPSS for Windows version 16 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

RESULTS

Out of a total of 63 cases considered, 56 were initially included in the study after excluding the rest based on the criteria as stated above. Data of fifty children could finally be analyzed as the rest six were lost to follow-up at 4 weeks. Of these fifty, 29 were male and 21 were female children. Gender, age, and NS pattern distribution is shown in Figure 1.

Although serum T3 and T4 levels were within the normal limits in all participants both at attack/relapse and in remission, there was a statistically significant difference in absolute levels at relapse and remission ($P = 0.001$) [Table 1]. There was an out of range significant rise of TSH levels during attack/relapse which normalized to normal values after 4 weeks of remission (13.08 ± 7.9 vs. 2.43 ± 1.00 mIU/L, $P = 0.0001$). As TSH values normalized in all patients when in remission, these patients were not treated with TSH supplement.

While trying to correlate the TSH values with serum albumin, it was seen that with reducing albumin levels, the serum TSH level tends to rise which might be a reflection of a reduction of thyroid hormone status stimulating more TSH secretion, probably a state of subclinical hypothyroidism. The scatter plot [Figure 2]

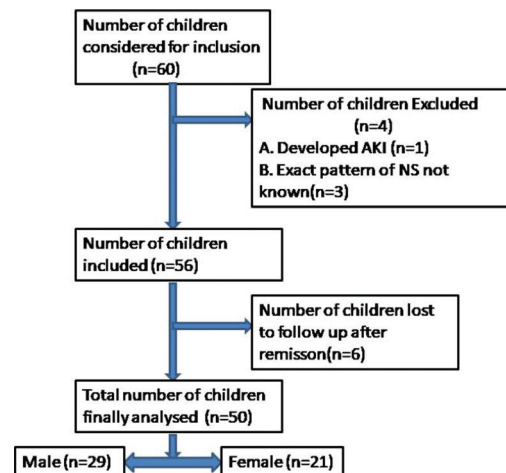


Figure 1: Flow of study participants

Table 1: Comparison of thyroid status at the time of attack/relapse and 4 weeks after remission

Thyroid hormones	Mean \pm SD		<i>P</i>
	During attack/relapse	During remission	
T3 (ng/dl)	84.02 \pm 60.31	166.06 \pm 29.04	0.0001
T4 (µg/L)	4.06 \pm 3.23	8.89 \pm 1.32	0.0001
TSH (µIU/L)	13.08 \pm 7.9	2.43 \pm 1.00	0.0001

TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, SD: Standard deviation

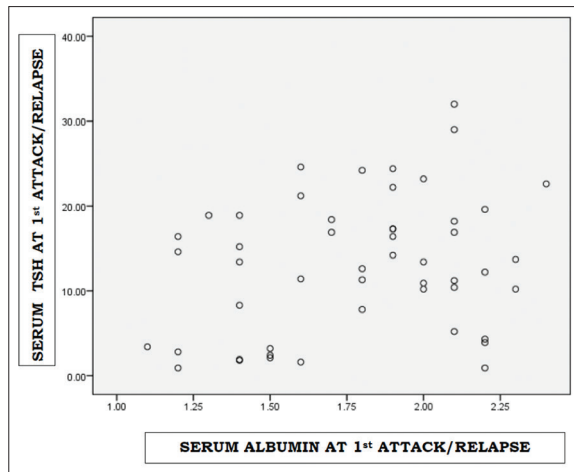


Figure 2: Scatter plot showing a correlation between serum albumin and thyroid-stimulating hormone during the first attack/relapse indicating when there is low serum albumin, thyroid-stimulating hormone level is high

shows a negative correlation between serum albumin and TSH levels with a tendency for normalization of serum TSH with normalization of serum albumin on remission [Figure 3]. On analyzing the data based on gender- and age-based categorization (1–6 years and 6–12 years), there seemed to be no statistically significant difference both during attack and at remission [Tables 2 and 3].

DISCUSSION

NS results in a massive loss of plasma proteins in the urine leading to their deficiencies. Many of the physiologically important molecules bound to plasma proteins are lost in the urine. It is hypothesized that some of the abnormalities that could arise as a result of heavy proteinuria include hypothyroidism, Vitamin D deficiency, and iron deficiency due to urinary loss of TBG, Vitamin D binding globulin, and transferrin, respectively. But now, the possible cause, degree, and severity of hypothyroidism in NS appear to be much more complex than just this hypothesis. Initially, it was thought that these individuals are metabolically euthyroid, as evidenced by their normal plasma free T4 (FT4) levels and free T3 (FT3) levels. The decrease in total T4 (TT4) was often attributed to the urinary loss of TBG and the resulting increase in unbound hormone suppressing further thyroid hormone secretion from the gland. But in that case, the levels of TSH are not expected to rise. But contrary to this expectation, TSH levels are found to be high in most of the studies, and the degree of rise often correlates with the degree of proteinuria and hypoalbuminemia. This leads to the possibility that significant amounts of TBG along with T4 bound to it are also lost in proteinuric

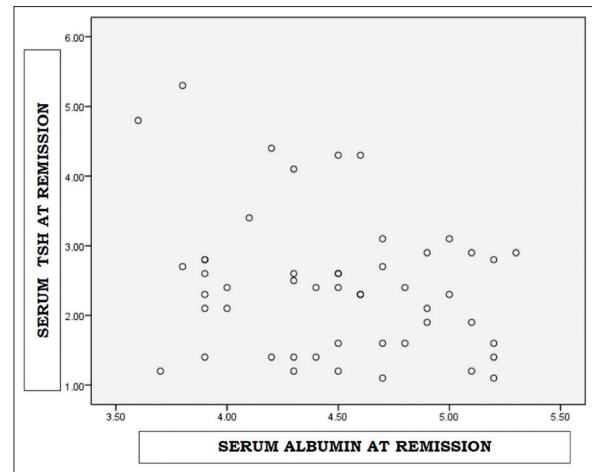


Figure 3: Scatter plot showing a correlation between serum albumin and thyroid-stimulating hormone at remission indicating with normalization of serum albumin, thyroid-stimulating hormone level also tends to normalize

states resulting in stimulation of TSH production. In situations of long-standing heavy proteinuria, it results in clinically significant hypothyroidism.^[2,4] However, in the absence of urinary TBG, TSH, T4, and T3 levels, it is difficult to surmise the exact pathophysiology behind this phenomenon of rising TSH during attack with subsequent normalization on remission from our study.

The results of our study more or less correlate with other previously published studies regarding thyroid function status in NS.^[4-13] Table 4 lists a series of previous studies on the thyroid status in NS. Studies done in both children and adults have shown a transient but significant change in thyroid status during the time of nephrosis which comes back to normal levels with remission of massive proteinuria. Similar to the findings of the present study, most of the previous studies have also reported that despite a fall in T3/T4 levels and rise of TSH levels during attack, none required treatment with levothyroxine except researchers in one study used levothyroxine during attack.^[8]

The intimate relation between thyroid hormone status and massive proteinuria of NS is also evident from the fact that some series and case reports have revealed the increased need of dose of levothyroxine in known cases of hypothyroidism when they suffer from NS.^[13-17]

A recent study from China^[18] has shown that high levels of urinary protein, creatinine, cholesterol, and platelets were independent risk factors predicting thyroid dysfunction, whereas higher albumin and hemoglobin were protective factors. We could show a correlation of TSH levels with serum albumin, but as protein: creatinine ratio, cholesterol, hemoglobin, and platelet levels were not done in all cases, especially the relapse ones, our study could not make any conclusions on these

Table 2: Gender-wise comparison of thyroid hormone levels during attack and while in remission

Thyroid hormones (mean±SD)	In males during attack	In females during attack	P	In males during remission	In females during remission	P
T3 (ng/L)	76.96±60.76	93.76±59.74	0.3352	163.44±30.17	169.66±27.71	0.4544
T4 (µg/L)	3.89±3.31	4.28±3.18	0.6760	8.72±1.27	9.1±1.38	0.3263
TSH (µIU/L)	13.45±8.61	12.56±7.19	0.6929	2.07±0.614	2.91±1.22	0.0073

TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, SD: Standard deviation

Table 3: Age-wise comparison of thyroid hormone levels during attack and while in remission

Thyroid hormones (mean±SD)	1-6 years age during attack (n=30)	1-6 years age during remission	P	6-12 years age during attack (n=20)	6-12 years age during remission	P
T3 (ng/L)	105.23±68.87	167.26±27.15	0.0001	52.2±19.04	164.25±32.31	0.0001
T4 (µg/L)	5.30±3.63	8.83±1.18	0.0001	2.19±0.767	8.9±1.52	0.0001
TSH (µIU/L)	11.203±9.04	2.29±1.09	0.0001	15.89±5.05	2.64±1.09	0.0001

TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, SD: Standard deviation

Table 4: Comparison of the important findings of the present study with previously published studies

Author/year/place of study	Number of patients/age/sex of distribution	Results
Karethimmaiah <i>et al.</i> /2016/India	39 adult patients	Significantly elevated TSH and reduced T3 and T4 in NS patients with partial improvement in parameters on remission
Ebadi <i>et al.</i> /2016/Iran	20 children	High TSH and low T3 and T4 in NS children. T4 significantly low
Gattoo/2015/Srinagar, India	208 children with 1 st episode NS	Elevated TSH in 50% Low T3 in 68.3% Low T4 in 64.4%
Sahni <i>et al.</i> /2014/Rohtak, India	35 children between 1 and 8 years of age	T3 and T4 normal during nephrosis. TSH higher but none requiring treatment
Hajidadeh <i>et al.</i> /2015/Tehran, Iran	104 children	58.6% had low T3, T4 requiring treatment during nephrosis 61 cases were treated with levothyroxine during nephrosis
Choudhury/2016/Odisha, India	60 children from 1 to 8 years 30 NS and 30 controls	Children <6 years had statistically significant hypothyroidism
Sawant <i>et al.</i> /2011/Mumbai, India	60 NS patients 20 controls	Nephrotic patients lose significant amounts of thyroid hormones along with protein in the urine, which affect thyroid status, but this is reversible on remission
Gilles <i>et al.</i> /2008/the Netherlands	159/40-62 years	TSH levels higher in proteinuria. One patient had overt hypothyroidism requiring treatment
Ito/1994/Japan	7 children	T3 and T4 levels significantly lower and TSH levels higher during nephrosis
Afroz <i>et al.</i> /2011/Dhaka, Bangladesh	85 children, 2-12 years	TSH levels increased during nephrosis. None had overt hypothyroidism

TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, NS: Nephrotic syndrome

issues. Moreover, we could not surmise the relation of thyroid status with the histopathological category of NS, as our patients have not undergone biopsy.

As thyroid hormones play an important role in the physical and mental growth of children, at least some, if not all, children suffering from NS stand the risk of periods of hampered growth, especially if the duration of NS is prolonged or the attacks of NS occur recurrently. Although most of the published studies have inferred a situation of subclinical hypothyroidism, larger studies are needed to firmly conclude how many of these are really “subclinical” or if repeated episodes of “subclinical” hypothyroidism could have a bearing on the final growth and development status of these children, especially

when the attacks of NS are more frequent and prolonged. Its time definite guidelines are formulated for screening and treatment of thyroid function status in children having massive proteinuria of NS.

Limitations

Although this study throws some significant light on the changes in thyroid status in idiopathic childhood NS, it has its share of limitations. First, the sample size was small. Second, serum TSH could not be compared with the duration of proteinuria and hypoalbuminemia as it was difficult to delineate exactly how many days the child was proteinuric before presenting to us. That comparison could have thrown some light if the thyroid

status varies with the duration of proteinuria. Third, we could not do urinary T3, T4, TSH, and TBG levels which would have given us an idea how urinary albumin and thyroid hormones correlate. Moreover, as it is not there in our unit protocol, we could not do serum cholesterol and urinary protein: creatinine ratio in all cases, especially the relapse ones, we could not compare these values with thyroid status. And finally, our study did not have any separate control limb. Each child served as his/her own control when in remission and had become nonproteinuric.

CONCLUSION

This study involving fifty children with idiopathic SSNS shows that the levels of T3, T4, and TSH levels vary significantly at attack/relapse compared to at remission. While the T3 and T4 levels remained within the normal limits, there was an out of range rise of TSH levels at the time of attack/relapse. More long-term, multicentric follow-up studies of longer duration are needed to study the overall impact of proteinuria on thyroid status and come to a conclusion where it can be firmly recommended whether NS children require thyroid hormone supplementation or not to avoid multiple episodes of possible impediments to growth in their rapidly growing years.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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