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PREVALENCE OF HYPOTHYROIDISM IN PAEDIATRIC PATIENTS WITH NEPHROTIC SYNDROME ADMITTED IN A TERTIARY MEDICAL COLLEGE AND HOSPITAL OF ASSAM, INDIA

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Keywords:

Nephrotic syndrome, Hypothyroidism, Proteinuria, Prevalence, Pediatric patients

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ABSTRACT: Background: Nephrotic syndrome is a kidney disorder characterized by heavy proteinuria, hypoalbuminemia, and often hyperlipidemia. Thyroid hormones play a crucial role in growth, development, and overall metabolic function. In the circulatory system, these hormones are primarily bound to specific proteins for proper distribution and regulation throughout the body. The substantial loss of these binding proteins innephrotic syndrome may lead to a reduction in circulatory levels of thyroid hormones, potentially resulting in a hypothyroid state. We conducted this study to find out the prevalence of hypothyroidism in pediatrics patients in Barpeta region of Assam, India. **Methods:** An observational, cross-sectional study of 67 patients was conducted, admitted in the Department of Pediatrics, diagnosed with nephrotic syndrome fulfilling the inclusion criteria were enrolled. Consecutive sampling method was used. Statistical analysis was performed using SPSS software (version 21.0). Categorical data was expressed as frequency and percentage, while continuous data was expressed as mean and standard deviation. **Results:** Hypothyroidism was present in 32.8% of cases and no statistically significant difference in hypothyroidism prevalence was found across age groups orgender. **Conclusion:** Present study provides valuable insights into the prevalence and characteristics of hypothyroidism in pediatric patients with nephrotic syndrome. The findings reveal a significant prevalence of hypothyroidism (32.8%) among these patients, highlighting the importance of regular thyroid function monitoring in this population.

INTRODUCTION: Nephrotic syndrome is a complex kidney disorder characterized by heavy proteinuria, hypoalbuminemia, and often hyperlipidemia [1]. This disorder, which can impact both adults and children, has multiple underlying causes, including membranous nephropathy, focal segmental glomerulosclerosis, and minimal change disease.

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In children, nephritic syndrome typically manifests between the ages of 2 and 9 years, with minimal change disease accounting for about 80% of cases in those under six years old [2]. Nephrotic syndrome is caused by damage to the kidney's filtering units, the glomeruli, which results in excessive protein loss through urine.

Protein loss, especially of intermediate-sized plasma proteins (between 4 and 200 kDa), can have a profound impact on a number of body processes. Of particular interest is the potential impact on thyroid hormone metabolism, as the key thyroid hormone binding proteins – thyroid binding globulin (TBG), transthyretin, and albumin - fall

within this size range [3]. Thyroid hormones play a crucial role in growth, development, and overall metabolic function. In the circulatory system, these hormones are primarily bound to specific proteins for proper distribution and regulation throughout the body [4]. The substantial loss of these binding proteins in nephrotic syndrome may lead to a reduction in circulatory levels of thyroid hormones, potentially resulting in a hypothyroid state. This is particularly concerning in children with nephrotic range proteinuria, as it may have significant implications for their physical and cognitive development [5].

Recent research has highlighted an intricate relationship between nephrotic syndrome and thyroid function, particularly in pediatric patients [6, 7]. Several studies have reported varying prevalence rates of hypothyroidism among children with nephrotic syndrome, ranging from subclinical to overt hypothyroidism [8, 9]. During active illness phases, this thyroid dysfunction appears to be more pronounced, with periods of remission indicating some recovery. The mechanism underlying this thyroid dysfunction in nephrotic syndrome is thought to involve the urinary loss of thyroid hormones and their binding proteins [10].

This loss results in lower blood levels of T3 and T4, which may cause thyroid-stimulating hormone (TSH) to rise in response. Despite the absence of clinical symptoms, the ensuing hormonal profile can resemble that of hypothyroidism. The evaluation and treatment of thyroid function in these individuals are made more difficult by the dynamic character of nephrotic syndrome, which includes phases of remission and relapse. Certain researchers propose that thyroid dysfunction could be transient, showing improvement during periods of disease remission. Others, however, stress the necessity of routine screening and possible therapy, particularly in situations involving chronic or recurrent nephrotic syndrome. Given the critical role of thyroid hormones in childhood growth and development [4], understanding the prevalence and characteristics of hypothyroidism in children with nephrotic syndrome is of paramount importance. This study aims to evaluate the frequency of hypothyroidism in pediatric patients with nephrotic syndrome, exploring its relationship with disease duration, severity of proteinuria, and other clinical parameters. By elucidating these associations, we aim to contribute to the growing body of evidence guiding thyroid function monitoring and management in pediatric nephritic syndrome [11]. This research may help inform clinical practice, potentially leading to improved protocols for thyroid assessment in these patients. Ultimately, for children with nephrotic syndrome, early identification and effective treatment of thyroid dysfunction maybe essential to maximizing their growth, development and general health outcomes [5].

MATERIALS AND METHODS: This observational cross-sectional study was conducted over a period of one year (July, 2023 to June, 2024) in the Department of Biochemistry in collaboration with Department of Pediatrics, Fakhruddin Ali Ahmed Medical College & Hospital, Barpeta, Assam.

Prior approval was obtained before conducting this study from the Institutional Ethics Committee of FAAMCH, Barpeta, Assam. The IEC approval number is No. FAAMC&H/IEC_PG/498/2020/4974 dated: 01/06/2023. Written informed consent was taken from the guardian of each patient after explaining the study procedure to them in their own understandable language. They had the full liberty to withdraw from study at any stage. The sample size was calculated by Leslie Kish formula. This was adjusted to the available population according to the clinics record and a sample size of 67 patients was obtained. Consecutive sampling method was used. All patients admitted in the Department of Pediatrics, diagnosed with nephrotic syndrome, fulfilling the inclusion criteria were enrolled for the study.

Inclusion Criteria:

1. Children less than 12 years of age with the diagnosis of primary nephrotic syndrome admitted in Pediatric ward.
2. Both newly diagnosed and previously known cases of nephrotic syndrome.
3. Steroid-sensitive patients.
4. Parents/guardians providing written informed consent.

Exclusion Criteria:

1. Previously known cases of hypothyroidism.
2. Steroid-resistant patients.
3. Patients currently receiving thyroxine replacement therapy.
4. Patients diagnosed with other endocrinopathies or malignancies.

Study Procedure: Patients fulfilling the inclusion criteria was scrutinized and enrolled for the study. Detailed study process was explained to the parent/guardian. Written informed consent (bilingual) was obtained as per appropriate designed proforma.

Thorough clinical history was taken, and clinical examination findings were documented. Intravenous blood sample of 2 ml was collected under all aseptic and antiseptic conditions in a clot-activator vial. The investigations were performed on the same day of collection of samples.

Biochemical Investigations: All the Biochemical tests were done in the Central Clinical laboratory (CCL) of Department of Biochemistry, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta using Automated Biochemical Analyzer (VITROS 5600 Integrated System & Analyzer).

The following parameters are assessed for each case:

- Serum TSH by Chemiluminescence Immunoassay method
- Serum free $T_3$by Chemiluminescence Immunoassay method
- Serum free $T_4$by Chemiluminescence Immunoassay method
- Serum Albuminby Bromocresol Green (BCG) method

Statistical Analysis: Data was compiled using MS Excel and statistical analysis was done using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 21.0 Chicago, SPSS Inc.) software. Continuous data was expressed as mean and standard deviation, whereas categorical data was expressed as frequency and percentage. Continuous variables were assessed using Pearson Correlation Coefficient, Regression analysis and student's t-test. P-value less than 0.05 was considered statistically significant.

RESULTS:

Age and Gender Distribution: Table 1 and **Fig. 1** shows that, the minimum age reported was of 1 year of age, while maximum age was 12 years. Patients were equally distributed among different age groups. Out of 67 patients enrolled, 38.8% were between 5-10 years of age followed by 37.3% less than 5 years of age and 23.9% more than 10 years of age.

TABLE 1: DISTRIBUTION OF CASES AS PER DIFFERENT AGE GROUPS

Age Groups (Years)	No. of Cases	Percentage (%)
< 5	25	37.3
5-10	26	38.8
>10	16	23.9
Total	67	100.0

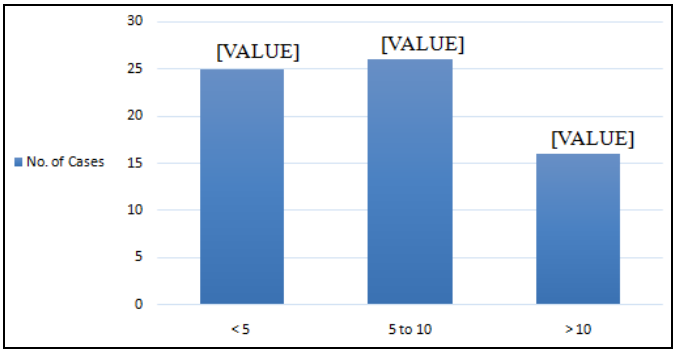

FIG. 1: GRAPHICAL PRESENTATION OF DISTRIBUTION OF CASES AS PER DIFFERENT AGE GROUPS

Table 2 shows that out of 67 total cases, 37 (55.2%) were female, and 30 (44.8%) were male.

TABLE 2: DISTRIBUTION OF CASES ACCORDING TO GENDER

Gender	No. of Cases	Percentage (%)
Female	37	55.2
Male	30	44.8
Total	67	100.0

Table 3 and **Fig. 2** shows that 41.8% of patient shad trace or no proteinuria on dipstick. Among those with significant proteinuria on dipstick, 25.4% had "2+" protein, 17.9% had "1+" protein, and 14.9% had "3+" protein.

TABLE 3: DISTRIBUTION OF CASES ACCORDING TO DEGREE OF PROTEINURIA ON DIPSTICK ON ADMISSION

Degree of Proteinuria on dipstick on admission	No. of Cases	Percentage (%)
Trace or Nil	28	41.8
1+	12	17.9
2+	17	25.4
3+	10	14.9
Total	67	100.0

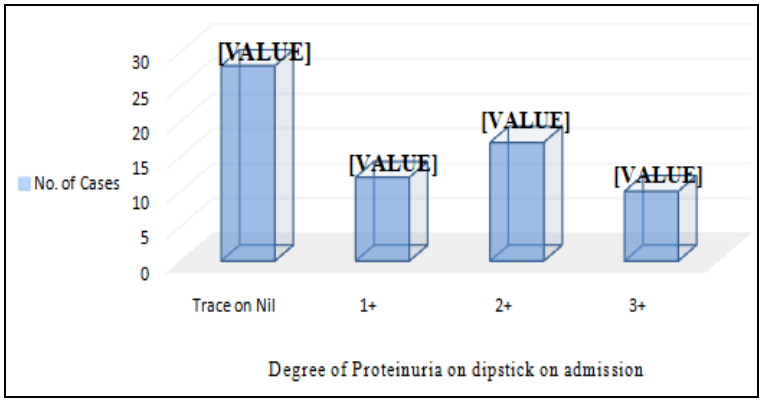

FIG. 2: GRAPHICAL PRESENTATION OF DISTRIBUTION OF CASES ACCORDING TO DEGREE OF PROTEINURIA ON DIPSTICK ON ADMISSION

Table 4 shows that majority of cases (49.3%) had serum albumin levels between 2.5-3.5 gm/dL, indicating moderate hypoalbuminemia. 35.8% of cases had normal levels (3.5-5.5 gm/dL), while 14.9% had severe hypoalbuminemia with levels below 2.5 gm/dL.

TABLE 4: DISTRIBUTION OF CASES ACCORDING TO SERUM ALBUMIN LEVELS

Serum Albumin (gm/dL)	No. of Cases	Percentage (%)
< 2.5	10	14.9
2.5-3.5	33	49.3
3.5-5.5	24	35.8
Total	67	100.0

Table 5 shows that, hypothyroidism, a potential complication of Nephrotic Syndrome, was present in 32.8% of cases, while 67.2% did not have hypothyroidism.

TABLE 5: DISTRIBUTION OF CASES ACCORDING TO PRESENCE OF HYPOTHYROIDISM

Hypothyroidism	No. of Cases	Percentage (%)
Present	22	32.8
Absent	45	67.2
Total	67	100.0

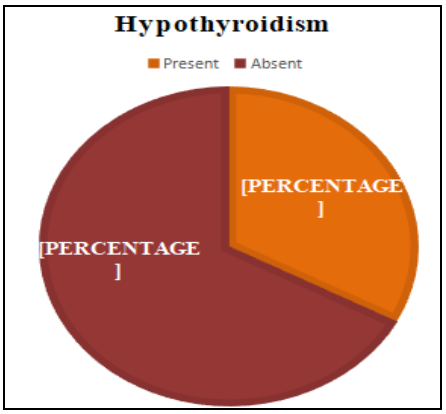

FIG. 3: GRAPHICAL PRESENTATION OF DISTRIBUTION OF CASES ACCORDING TO PRESENCE OF HYPOTHYROIDISM

Table 6 shows that the distribution of hypothyroidism was relatively similar across age groups: 28.0% in those under 5 years, 38.5% in the 5-10 years group, and 31.3% in those over 10 years. The chi-square test showed no statistically significant difference (p=0.720) in hypothyroidism prevalence among these age groups.

TABLE 6: DISTRIBUTION OF CASES ACCORDING TO PRESENCE OF HYPOTHYROIDISM ACROSS DIFFERENT AGE GROUPS

Age Groups (Years)	Hypothyroidism				Chi-square Statistic	p-value
	Present		Absent			
	N	%	N	%		
< 5	7	28.0	18	72.0		
5-10	10	38.5	16	61.5	0.656	0.720
>10	5	31.3	11	68.5		

[N= No. of Cases, % = Percentage]

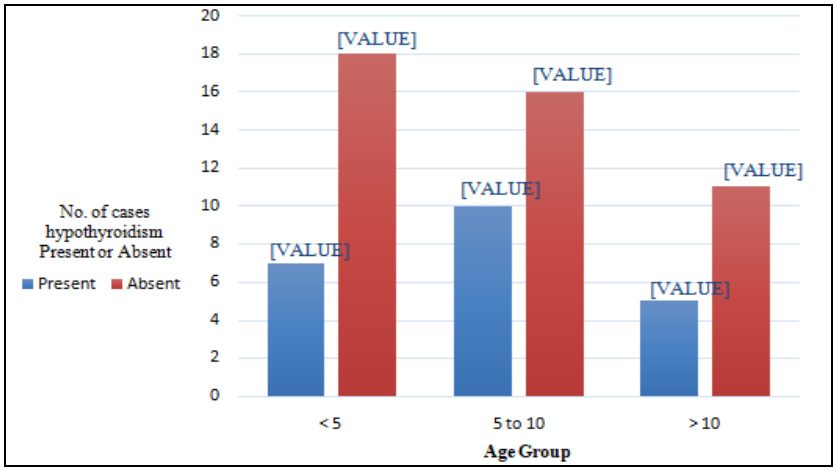

FIG. 4: GRAPHICAL PRESENTATION OF DISTRIBUTION OF CASES ACCORDING TO PRESENCE OF HYPOTHYROIDISM ACROSS DIFFERENT AGE GROUPS

Table 7 shows that out of 67 total cases, 20.9% of the patients had been suffering from Nephrotic Syndrome for less than 6 months, 25.4% for 6-12 months, 25.4% for 12-18 months, and 28.4% for 18-24 months.

TABLE 7: DISTRIBUTION OF CASES ACCORDING TO DURATION OF NEPHROTIC SYNDROME

Duration of Nephrotic Syndrome (Months)	No. of Cases	Percentage (%)
< 6	14	20.9
6-12	17	25.4
12-18	17	25.4
18-24	19	28.4
Total	67	100.0

DISCUSSION: The intricate relationship between nephrotic syndrome and thyroid function, particularly in pediatric patients, has been a subject of increasing interest in recent years [3]. This study aimed to explore the prevalence and characteristics of thyroid dysfunction in children with nephrotic syndrome, a condition marked by substantial proteinuria and its consequent effects on protein-bound hormones. The findings of this investigation contribute to the growing body of evidence suggesting a significant interplay between nephrotic syndrome and thyroid function, with potential implications for patient management and long-term outcomes. The demographic profile of present study population provides important insights into the age and gender distribution of pediatric patients with nephrotic syndrome. Present study included patients ranging from 1 to 12 years of age, with a relatively even distribution across different age groups. The largest proportion of patients (38.8%) fell within the 5-10 years age range, closely followed by those under 5 years (37.3%), with a smaller percentage (23.9%) over 10 years of age.

These findings are generally consistent with previous studies on nephrotic syndrome in pediatric populations. For instance, Nithya M. *et al.*, 2022 [11] reported that the most common age range for presentation of nephrotic syndrome was 3-6 years, accounting for 68% of their cases. The age distribution in our study suggests that nephrotic syndrome affects children across a wide age range, with a tendency towards younger children, which is a well-established characteristic of the disease. Vivarelli M. *et al.*, 2017 [2] noted that minimal change disease, the most common cause of nephrotic syndrome in children, typically affects those under 6 years old. The relatively even distribution across age groups in our study, with a slight predominance in the 5-10 years range, may reflect the varied etiologies of nephrotic syndrome, including both minimal change disease and other forms that can affect older children.

Regarding gender distribution, present study found a slight predominance of female patients (55.2%) over male patients (44.8%). This observation contrasts with some previous reports in the literature. For example, Thapa K. *et al.*, 2024 [6] reported a majority (69.39%) of male children affected by nephrotic syndrome in their study.

The difference in gender distribution observed in present study compared to others could be attributed to several factors. It may reflect regional variations in the epidemiology of nephrotic syndrome, differences in healthcare-seeking behavior, or could simply be a result of the specific sample in the present study. It is important to note that while many studies report a male predominance in childhood nephrotic syndrome, the gender distribution can vary across different populations and studies.

The findings regarding proteinuria and serum albumin levels in present study population provide valuable insights into the clinical status of children with nephrotic syndrome. The majority of patients (41.8%) showing trace, or no proteinuria suggests that a significant proportion of present study patients had well-controlled disease at the time of assessment. This aligns with the findings of Tumwesige M. *et al.*, 2023 [7], who reported that 61.4% of participants in their study were in remission. However, the presence of significant proteinuria in the remaining patients, particularly those with 2+ (25.4%) and 3+ (14.9%) protein on dipstick, indicates ongoing disease activity in a substantial subset of present population.

The serum albumin levels provide further insight into the disease severity. While 35.8% of cases had normal levels, the majority (49.3%) exhibited moderate hypoalbuminemia (2.5-3.5 gm/dL), and 14.9% had severe hypoalbuminemia (<2.5 gm/dL). Gilles R. *et al.*, 2008 [16] observed in their study of 159 patients with proteinuria that the median serum albumin level was 29 g/l (which falls within our moderate hypoalbuminemia range). This distribution is particularly relevant when considering the findings of Saffari F. *et al.*, 2020 [9], who observed that thyroid dysfunction was more common in patients with active disease compared to those in remission. The presence of hypoalbuminemia in present study participants suggested that a significant proportion of patients may be at risk for thyroid abnormalities.

Hypothyroidism is a common endocrine disorder with varying prevalence across different regions and populations. According to a retrospective analysis that combined data from the National Health and Nutritional Examination Survey (NHANES) reports from 2009 to 2019, 4.6% of Americans were predicted to have hypothyroidism [12].

The prevalence of hypothyroidism among patients of nephrotic syndrome in present study was significant, affecting 32.8% of cases. This result is consistent with several previous studies that have reported thyroid dysfunction in children with nephrotic syndrome. For instance, Thapa K. *et al*., 2024 [6] found an even higher prevalence of 71.01%, while Tumwesige M. *et al.*, 2023 [7] reported a lower rate of 23%. Present study results fall within this range, confirming that thyroid dysfunction is indeed a common complication in pediatric nephrotic syndrome.

Interestingly, the distribution of hypothyroidism was relatively uniform across different age groups, with no statistically significant differences ($p=0.720$). This suggests that the risk of developing hypothyroidism in nephrotic syndrome is not strongly age-dependent, contrasting with the

general trend of increasing thyroid dysfunction with age in the general population. Similarly, present study found no significant gender difference in hypothyroidism prevalence (p=0.333), although females showed a slightly higher rate (35.1%) compared to males (30.0%).

These results highlight the significance of regular thyroid function monitoring in all pediatric nephrotic syndrome patients, regardless of age or gender. The substantial prevalence of hypothyroidism in present study supports the recommendations made by several studies, including Saffari F. *et al.,* 2020 [9], for routine thyroid screening in these patients.

Present study also revealed a significant association between the duration of nephrotic syndrome and the prevalence of hypothyroidism. Patients with longer disease duration showed a markedly higher incidence of thyroid dysfunction. Specifically, hypothyroidism was present in only 7.1% of patients with disease duration less than 6 months, increasing to 17.6% in the 6-12 months group, and dramatically rising to over 52% in patients with disease duration exceeding 12 months. This trend was statistically significant (p=0.012).

These findings align with the observations of Ebadi A. *et al.,* 2016 [10], who noted that prolonged proteinuria in nephrotic syndrome can lead to sustained loss of thyroid hormones and binding proteins. The progressive increase in hypothyroidism prevalence with disease duration suggests a cumulative effect of protein loss on thyroid function.

The sharp increase in hypothyroidism prevalence after 12 months of disease duration is particularly noteworthy. It implies that patients with chronic or frequently relapsing nephrotic syndrome are at substantially higher risk of developing thyroid dysfunction. This observation underscores the importance of regular and long-term monitoring of thyroid function in patients with persistent or recurrent nephrotic syndrome.

Recent literature continues to underscore the clinical significance of thyroid dysfunction in pediatric nephrotic syndrome. A 2024 observational study by Kumari *et al.* emphasized that up to 36.3% of children with nephrotic syndrome exhibited abnormal thyroid profiles, affirming the high burden of subclinical hypothyroidism in this group [13]. In a comprehensive 2024 review, Mizdrak *et al.* further illustrated how proteinuria-induced losses of thyroid-binding globulin and transthyretin alter endocrine homeostasis in nephrotic patients [14]. Mikulevič *et al.* 2023 documented a case of overt hypothyroidism with severe growth retardation in a child with poorly controlled nephrotic syndrome, reinforcing the need for early thyroid evaluation in prolonged disease courses [15]. Another notable study by Matyjek *et al.* 2024established a link between severe nephrotic syndrome and impairments in thyroid, nutritional, and coagulation parameters, suggesting that thyroid screening should be integrated into routine care [16]. Similarly, Omar *et al.* 2024 demonstrated that glucocorticoid therapy may confound thyroid function assessments, necessitating judicious interpretation of results in steroid-treated pediatric nephrotic patients [17]. Finally, Chapagain *et al.* 2024 reinforced the clinical utility of baseline and periodic thyroid testing by highlighting a higher-than-expected prevalence of hypothyroidism among newly diagnosed nephrotic children in tertiary care settings [18].

CONCLUSION: Present study provides valuable insights into the prevalence and characteristics of hypothyroidism in pediatric patients with nephrotic syndrome. The findings reveal a significant prevalence of hypothyroidism (32.8%) among these patients, highlighting the importance of regular thyroid function monitoring in this population.

These findings of this study underscore the need for routine thyroid function screening in all pediatric patients with nephrotic syndrome, particularly those with prolonged disease duration, significant proteinuria, or hypoalbuminemia. Early detection and management of thyroid dysfunction in these patients could potentially improve overall outcomes and quality of life. To understand the mechanisms behind this connection and to create focused therapies, more study is necessary for this vulnerable population.

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