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Original Article

Paediatrics Section

Evaluating Thyroid Function in Paediatric Nephrotic Syndrome in a Tertiary Care Hospital of Northern India: A Case-control Study

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ABSTRACT

Introduction: Nephrotic Syndrome (NS) is a glomerular disease characterised by oedema, hypoalbuminaemia and substantial proteinuria, which includes loss of thyroxine binding globulin and thyroid hormones, often resulting in subclinical or overt hypothyroidism. Studies reporting on the relationship between NS and thyroid dysfunction elude consensus.

Aim: To evaluate Triiodothyronine (T3), Thyroxine (T4) and Thyroid Stimulating Hormone (TSH), and lipid levels to identify clinical predictors of thyroid dysfunction in paediatric cases of NS.

Materials and Methods: A hospital based case-control study was undertaken on 100 children, attending Paediatric Nephrology Clinic, from October 2020 to March 2021.Patients were divided into two groups: 50 cases under various stages of nephrotic syndrome, and 50 healthy controls in the age group of 1 to 18 years, of either gender. Investigations on serum creatinine, Haemoglobin (Hb), white blood cell count, platelet count, serum T3, T4, TSH, and blood lipids like: Triglyceride (TG), Total Cholesterol (TC) and Low Density Lipoprotein (LDL), were performed on all the children, and compared for analysis of corresponding data of cases and controls. Statistical analysis was carried out using ANOVA test.

Results: The mean age of the cases and controls was 12.6±4.2 and 11.8±4.0 years, respectively. Mean T3 value in the case group was 117±63 ng/dL, and in control was 176±95 ng/dL (p=0.104). Mean T4 value among the case group (9.9±5.1 µg/dL) was significantly lower than that of controls (14.2±8.4 µg/dL) (p=0.016). The difference of TSH levels in the case group was 3.8±2.9 µIU/mL, and control was 2.5±2.2 µIU/mL (p<0.001). Hypothyroidism was observed in 9 (45%) children with first episode, 7 (53.84%) in remission, and 6 (60%) relapsed patients.

Conclusion: Urinary losses of binding proteins such as Thyroxine Binding Globulin (TBG), transthyretin or prealbumin and albumin, may have caused lower levels of T3 and T4 and higher value of TSH. T3, T4 and TSH are important clinical predictors of thyroid dysfunction in patients with NS, therefore hypothyroidism should be investigated in all children with NS.

Keywords: Chronic kidney disease, Hypothyroidism, Thyroid stimulating hormone, Thyroxine, Triiodothyronine

INTRODUCTION

Nephrotic syndrome is a common glomerular disease among children. It is defined by oedema, substantial proteinuria (>3.5 g/24 hours or >40 mg/ SqM BSA/hour), hypoalbuminemia (<30 g/L), Hypercholesterolaemia (serum cholesterol >250) and hyperlipidaemia. It is also seen associated with thromboembolism and increased risk of infection [1]. Among NS patients, endocrine abnormalities are quite common, while as an essential endocrine organ, the thyroid plays vital part in kidney function [2,3]. Kidneys, on the other hand, have a crucial role in the elimination of thyroid hormone [4]. Subclinical hypothyroidism as well as hypothyroidism have been reported among NS patients, but very less number of studies has been conducted on these subjects [5]. A study had found that membranous nephropathy was the most common pathologic type; with independent risk factors, which predicted thyroid dysfunction, were: substantially increased levels of creatinine, cholesterol, urinary protein and platelets; and at the same time, higher albumin and haemoglobin were found to be protective factors [6]. Another study suggested that a diminishing thyroid reserve may incline patients to hypothyroidism in NS, and that NS may cause or worsen hypothyroidism further [7]. There may be several intermittent reports on the relationship between thyroid dysfunction and NS, but eludes general agreement among researchers.

Therefore, the aim of the study was to evaluate T3, T4 and TSH, to evaluate and compare values of serum albumin and serum cholesterol with T3 and T4; and to evaluate and compare the values of serum albumin and serum cholesterol with TSH and to establish clinical indicators of thyroid dysfunction in patients with NS and to study its association with its pathological characteristics.

MATERIALS AND METHODS

A hospital based case-control study was carried out on a total of 100 children, attending the Paediatric Nephrology Clinic in the Department of Paediatrics, from October 2020 to March 2021. Ethical approval to the study was conveyed by the Institutional Ethics Committee, GMC Jammu, vide no: IEC/GMC/2020/31, dated: 06.02.2020. Fifty paediatric patients, under various stages of nephrotic syndrome, except those under exclusion criteria, and attending the Paediatric Nephrology Clinic, were taken as cases and an equal number of age matched healthy children were included in the study as controls.

Inclusion criteria:

- Children in the age group of 1 to 18 years, of either gender.
- Children with first episode of nephrotic syndrome, as well as relapsing and under remission were included as cases.
- NS was identified as with features of generalized oedema, urine protein excretion >3.5 g/24 hours and serum albumin level less than 30 g/L.
- Age and gender matched children attending the Outpatient Department (OPD) of the Department of Paediatrics, during the stated period, but not presenting any feature of NS, were included as controls.

Exclusion criteria:

- Children less than one year of age or patients above 18 years of age.
- Children with auxiliary causes of nephrotic disorder or significant renal lesions.
- Children having recurring infections like: tuberculosis, diabetes mellitus.
- Children suffering from malabsorption.
- Children with chronic renal or hepatic diseases.
- Children on antiepileptics.
- Children with first episode of nephrotic syndrome, who ceased steroids some six weeks before.

Sample size calculation: Assuming the power of the study at 0.80, confidence level of 95% and odd ratio/ coefficient 'r' taken from the finding of study conducted by Sun HJ et al., the sample size was calculated to be 100, with 50 each as cases and controls [8].

Study Procedure

Before including them in the study, a written and informed consent was duly taken from the parent/guardian of each child. Detailed examination of patients was done and thorough history recorded at the time of collection of samples. About 5 mL venous blood sample will be taken, centrifuged and serum will be sent for estimation.

Investigations on serum creatinine, haemoglobin, white blood cell count, platelet count, serum T3, T4, TSH, and blood lipids like: TG, TC and LDL, were performed on all the 100 children and compared for analysis of corresponding data of cases and controls. The T3, T4 and TSH were determined by chemiluminescence microparticle immunoassay technology, while serum albumin and serum cholesterol were tested using specific kits in the clinical laboratory.

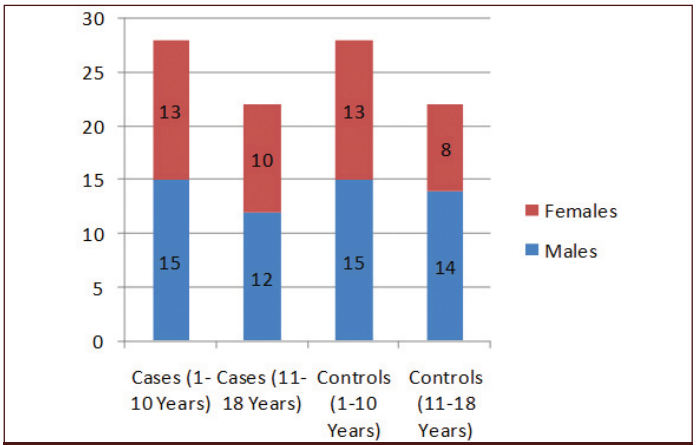
Normal/reference values for TG, TC and LDL were taken as: 0.33-1.62 mmol/L (5^{th}-95^{th} percentile), 2.9-5.39 mmol/L (5^{th}-95^{th} percentile) and 1.63-3.63 mmol/L (5^{th}-95^{th}), respectively. While, normal/reference values for T3, T4 and TSH were taken as: 80 to 269 (ng/dL) for T3, 5.6 to 15.0 (µg/dL) for T4 and 0.7 to 6.4 (µIU/mL) for TSH [9].

STATISTICAL ANALYSIS

The data was statistically analyzed using ANOVA test on MS Excel 2010 software, and for inter-group comparison, T-test was performed. Measure of probability, $p<0.05$ was considered significant.

RESULTS

The data based on gender distribution is presented in [Table/Fig-1,2]. Mean age was comparable in cases (12.6±4.2 years) and controls (11.8±4.0 years). The mean T3 value among cases (117±63 ng/dL) was significantly lower to that of controls (176±95 ng/dL). The mean T4 value among cases (9.9±5.1 µg/dL) was also significantly lower than that of controls (14.2±8.4 µg/dL). TSH levels among the cases were found higher in comparison to controls (3.8±2.9 µIU/mL and 2.5±2.2 µIU/mL, respectively). Levels of TG and LDL were significantly higher among cases [Table/Fig-3].



[Table/Fig-1]: Gender ratio among different age groups

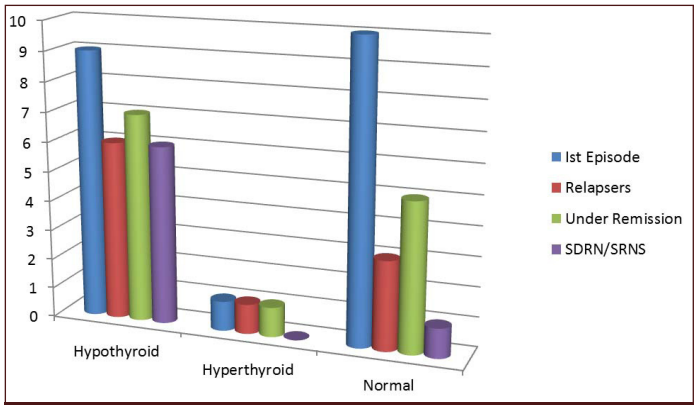
Variables	Cases	Controls	p-value (t-test)
Age (in years)	12.6±4.2	11.8±4.0	0.805
Gender (n)			
Male	27	29	--
Female	23	21	--
Duration of NS (months)	4	--	--
Hb (g/L)	122.74±16.35	135.53±17.60	0.703
TG (mmol/L)	2.61±1.46	1.74±0.98	0.045*
TC (mmol/L)	7.36±3.31	5.22±2.73	0.036*
LDL (mmol/L)	5.02±2.18	3.12±1.09	0.002*
T3 (ng/dL)	117±63	176±95	0.104
T4 (µg/dL)	9.9±5.1	14.2±8.4	0.016*
TSH (µIU/mL)	3.8±2.9	2.5±2.2	<0.001*

[Table/Fig-2]: Comparison of clinical features and laboratory findings (data expressed as numbers or mean±SD.)
*p<0.05 considered significant; SD= Standard deviation

Thyroid hormone status	1st Episode (n=20)	Relapsers (n=10)	SDRN/ SRNS (n=7)	Under remission (n=13)	Total (n=50)
Hypothyroid (T3 <80 ng/dL; T4 <5.6 µg/dL)	9 (45.00%)	6 (60.00%)	6 (85.71%)	7 (53.85%)	28 (56.00%)
Hyperthyroid (T3 >269 ng/dL; T4 >15.0 µg/dL)	1 (5.00%)	1 (10.00%)	0	1 (7.69%)	3 (6.00%)
Normal Levels*	10 (50.00%)	3 (30.00%)	1 (14.23%)	5 (38.46%)	19 (38.00%)

[Table/Fig-3]: Distribution of patients based on frequency and thyroid levels (n=50). Data expressed as numbers and frequency percentage.
SDNS: Steroid Dependent Nephrotic Syndrome; SRNS: Steroid Resistant Nephrotic Syndrome; (*Normal/reference values taken as: 80 to 269 (ng/dL) for T3, 5.6 to 15.0 (µg/dL) for T4 and 0.7 to 6.4 (µIU/mL) for TSH.)

There were 9 (45%) children, with first episode of nephrotic syndrome, having clear deficiency of thyroid hormone manifested as low T3, T4 and raised TSH in comparison to the controls. Hypothyroidism was also observed in majority of patients under remission or relapsing. Hypothyroidism was more in children with SDNS/SRNS (6/7), suggesting that thyroid status is associated with severity of NS [Table/Fig-4].



[Table/Fig-4]: Frequency distribution of thyroid patients.

DISCUSSION

Thyroid hormones are bound to three plasma proteins: TBG, Thyroxine Binding Pre Albumin (TBPA) and albumin. Any abnormalities among these may lead to abnormal values of total hormone levels in the blood, even when protein bound hormones/ free hormones are found normal [4,5,10]. Nephrotic syndrome is known to cause loss of protein in the urine, which may cause changes in the concentrations of thyroid hormones as well. In the present study, hypothyroidism was observed in 9 (45%) of all patients at first episode of NS. Out of the 10 patients who had relapse/multiple relapses of NS, 6 (60%) patients showed abnormally low thyroid hormone levels. There was one patient under the given age group, who experienced multiple relapses but normal thyroid hormone profiles. About 7 (53.85%) patients under remission also showed hypothyroidism, while 5 (38.46%) patients had normal levels. Similarly, Ito S et al., had reported a significant decrease in the concentrations of T3, T4, and TBG in untreated nephrotic children, as compared to the similarly placed patients in remission and age-matched controls [11]. Also, Guo QY et al., found thyroid dysfunction in 73 patients [12]. They reported significantly higher levels of proteinuria, cholesterol and TSH, while lower levels of serum albumin, and free and total T3 and T4 when compared to those of euthyroid patients. Similarly, a study on 208 children with NS by Gattoo I et al., reported higher number of hypothyroid cases below three years, i.e. 47.5% [13]. They found a lower T3 level in 68.3% cases and a lower T4 level in 64.4% of studied population under nephrosis. Afroz S et al., in 2011, had however reported that under similar situations, in nephrotic children, the mean value of serum T3 and T4 in nephrotic children, only the mean values of serum TSH was higher than normal [14]. The authors concluded that NS has a state of mild or subclinical hypothyroidism during proteinuria, even if the patients remain euthyroid clinically.

Choudhury J found that T4 and T3 levels were low and TSH levels were significantly high and in comparison to children >6 years, hypothyroidism was more prevalent in younger children aged less than six years [15]. Similarly, in the index study, the mean T3 value in cases was significantly lower to that of controls. The mean T4 value in cases was also significantly lower than that of controls. Lower levels of T3 and T4 in the cases can be attributed to urinary losses of binding proteins such as TBG, transthyretin or pre albumin and albumin [16]. In comparison to controls, TSH levels were also found higher in the cases. Thyrotropin Releasing Hormone (TRH) is released by hypothalamus in response to low circulating levels of thyroid hormones T3 and T4. The TRH, on the other hand, stimulates the anterior pituitary to produce more TSH.

Patients tend to show a lower T3 and T4 in comparison with normal values, but mean TSH values were quite high in the hypothyroid patients. According to this study, it is important to mention the occurrence of hypothyroidism in every child with nephrotic syndrome. Therefore, in all such patients with prolonged proteinuria, TSH and T4 needs to be measured [17].

At the onset of NS, a significant relation was observed only between serum albumin and serum T3 levels, therefore other factors, like, type of immune suppressive agents, treatment duration, conversion ability from T4 to T3, etc., may be found involved besides urinary loss. Possibility of tubulointerstitial injury due to temporary renal damage is always there. It is a well established fact that renal damage, leading to renal tubule damage, can affect thyroid functions. Incidence of hypothyroidism can increase with the decrease of Glomerular Filtration Rate (GFR) [18,19].

Few studies have been conducted on dosage and need for administration of levothyroxine in patients with hypothyroidism caused by NS. There are no established treatment principles for this condition either, however, it has been reported that an increased dose of levothyroxine, can be useful on the onset of NS [20-22]. Therefore, role of levothyroxine can be further explored as an extension to the present study.

Limitation(s)

The limitation of the study, however, could be the fact that free T3 and free T4 were not measured due to laboratory constraints. Further as, total urinary loss of thyroid hormones of T3, T4, TSH, and free T4, were not measured, the real mechanism behind the risk of hypothyroidism increases at NS onset could not be clearly identified.

CONCLUSION(S)

Thyroid malfunction is common in children with nephrotic syndrome. Thyroid hormone profile abnormal findings were observed in as many as 45% of the paediatric patients with NS in the present study. As T3, T4 and TSH are important clinical predictors of thyroid dysfunction in patients with NS, therefore hypothyroidism should be investigated in all children with nephrotic syndrome, it being a treatable complication. Future studies in this regard are required to be conducted to further verify the findings of this study under different demographic set ups and to create consensus among clinical practitioners.

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