ORIGINAL ARTICLE

# A Study of Hypothyroidism in Children With Steroid-Resistant Nephrotic Syndrome

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## ABSTRACT

Non autoimmune hypothyroidism is a variably reversible and potentially treatable complication of Steroid Resistant Nephrotic Syndrome (SRNS) in children. The massive prolonged losses of thyroid hormone leads to hypothyroid state in patients with SRNS. The current study was carried out to find out the proportion of SRNS patients with hypothyroidism and risk factors associated with development of hypothyroidism. This cross sectional study was conducted in 85 children aged 1 to 18 years who were steroid resistant and 85 controls which were age and sex matched healthy children attending paediatric OPD. The prevalence of hypothyroidism among SRNS cases was 29.4%, significantly higher than controls. Mean level of TSH (5.4mIU/L) in cases were higher than control (1.8 mIU/L). Among hypothyroid, cases subclinical hypothyroidism was more common presentation than overt hypothyroidism. Also, among subclinical cases, stage 2 and 3 were more common than stage 1. Though the minimal change disease was commonest entity (80%), the prevalence of hypothyroidism was not different among other histopathological profiles. An increased risk of hypothyroidism was observed with early age of onset (OR =1.2;95% CI:1.00-1.37; P=0.045), duration of nephrotic syndrome (OR =1.195%CI:1.03-1.12;P=0.001), low serum albumin (OR=1.9% CI:0.89-3.81;P=0.001) and non-remission status of disease(OR=1.7;95%CI:1.12-3.35;p=0.007). We found a significant positive correlation of concentration of TSH with Serum cholesterol (r= 0.253, P=0.0001), and negative correlation with serum albumin (r= -0.253, P=0.00010.8711). We concluded that prevalence of both overt and subclinical hypothyroidism was higher in idiopathic SRNS. An early age of onset, long duration of nephrotic syndrome, low serum albuminand non-remission status of SRNS were the risk factors associated with increased prevalence of hypothyroidism.

**Keywords :** Steroid resistant nephrotic syndrome (SRNS), TSH (Thyroid Stimulating Hormone).

## INTRODUCTION :

Nephrotic Syndrome is the most common glomerular disease in childhood.[1] Although more than 85% of children with nephrotic syndrome respond to corticosteroids, approximately 10-15% remain unresponsive or later become steroid-resistant.[2,3] The prolonged urinary loss of biomolecules secondary to proximal tubular damage, reducing absorption of proteins, albumins, thyroxine binding globulin, transthyretin and pre-albumin in Steroid-Resistant Nephrotic Syndrome (SRNS) state may result to a reduction in serum total thyroxine (T4) and T3 which may manifest as subclinical or overt hypothyroidism depending on thyroid reserve.[4] Thyroid hormone increases GFR through both pre-renal and renal

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effectsand also plays an important role in the mitochondrial energy metabolism enzymes in the cells of proximal convoluted tubule[5]. Hypothyroidism can further derange lipid profile, renal blood flow, bone mineral density, fluid and electrolyte homeostasis in SRNS patients which are known to be already compromised in these patients[6].

In view of common occurrence of nephrotic syndrome in children in Indian population, an effective community-based study on hypothyroidism in SRNS patients are lacking. So the present study was undertaken with the aims to find out the proportion of SRNS patients with hypothyroidism and the risk factors and clinical features associated between SRNS and hyprothyroidism by estimating thyroid hormone level.

## METHODOLOGY

It was a hospital based cross-sectional study, carried out in Department of pediatric medicine, SMS Medical College, Jaipur, from June 2018 to May 2019. Children of Age group 1 year to 18 years with SRNS presenting to pediatric nephrology clinic and those admitted in nephrology ward were included in the study. Those excluded were: secondary nephrotic syndrome(Lupus nephritis, Henoch schonle in purpura nephritis), critical patients requiring ICU, congenital nephrotic syndrome, hypothyroidism before onset of nephrotic syndrome and patient on drugs for any coexisting illness other than nephrotic syndrome causing hypothyroidism.85 age and sex matched healthy children were taken as controls. They were required to have clinically undetectable thyroid swelling, absence of proteinuria, no clinical features suggestive of hypothyroidism or hyperthyroidism, not on thyroid hormone, carbimazole or any drug causing hypothyroidism and not diagnosed with autoimmune disorders like type 1 diabetes,Systemic Lupus Erythematos us, rheumatoid arthritis, celiac disease and pernicious anemia.

SRNS was defined as failure to achieve remission despite 2mg/kg/day of daily prednisolone for 4 weeks. Complete remission in SRNS was defined as urine protein: urine creatinine<0.2, serum albumin >2.5 and no edema; partial remission was defined as urine protein: urine creatinine ratio between 0.2 and 2, serum albumin >2.5 or edema. No remission was defined as Up: Uc .>2, serum albumin <2.5g/dl or edema. Overt hypothyroidism was defined as (TSH > 4.5 mIU/L and low free T4).Subclinical hypothyroidism was graded as 1, 2, and 3 based on TSH level (4.5-6 mIU /L), (6-12 mIU/L) and (>12 mlU /L) respectively with normal T4 level (0.7-2 ng /ml)[7,8].

Each patients enrolled in the study was subjected to complete medical history including age of onset of nephrotic syndrome, duration of disease, edema followed by complete clinical examination including general examination, anthropometric measurements (height, weight and body mass index), blood pressure recordings and history of immune suppressants prescribed. Type of steroid resistance, remission state and histopathological profile were also studied. Baseline investigations like blood urea, creatinine, albumin, cholesterol and urinary examination for proteinuria were done. Fasting serum levels of free T3, free T4, TSH, Anti TPO unit of SRNS patients and controls were estimated by competitive immunoassay using direct chemiluminescence method were recorded. Reference range of <60.00U/ml was taken as negative for anti TPO antibody. Renal biopsy were performed in all cases. The subsets of population were categorized into overt and subclinical hypothyroidism grade 1,2, and 3 respectively according to values of high TSH and low FT4. Oral Levothyroxine treatment was prescribed for Patients with grade-3 subclinical and overt hypothyroidism. All evaluation and management was accomplished as per Indian Society of pediatric nephrology guidelines.

## STATISTICALANALYSIS:

The analysis included profiling of patients on different demographic, clinical and laboratory parameters, and outcomes parameters separately for cases and controls. Comparable information was presented for both. Quantitative continuous data was presented in terms of means and standard deviation. Categorical/binary data were presented in terms of proportions & percentages. Chi- square test was used for association between nominal or categorical variables whereas independent t-test and two proportion z- test were used for comparison of individual quantitative parameters. Pearson correlation coefficient was applied to find out correlation between continuous variables. P-value < 0.05 was considered statistically significant. Odds ratio was calculated for risk factors.

## RESULTS

In the present study, 85 children with SRNS between 1 year and 18 years of age and 85 age and sex matched children as healthy controls were included. The mean age of subjects among cases and controls were 7.2±4.9 years and 7.0±3.4 years respectively. Abdominal swelling (42.3%) was the most common presentation followed by paraorbital swelling (37.6%), oliguria (35.2%), infections (31.7%), shock (1.1%) and hypertensive encephalopathy (1.1%). The mean values of body surface area, blood urea, serum creatinine and serum Cholesterol were significantly higher; and that of serum albumin were significantly lower in cases compared to controls(p=<.005)

The prevalence of hypothyroidism among cases was 29.4% which was significantly higher than controls ( 3 . 5 %). Out of 25 cases with hypothyroidism, 8 (9.4%) had overt and 17 (20%) had subclinical hypothyroidism. The grade 1,2, and 3 subclinical forms were found in in 4 (4.7%), 2 (2.35%) and 11(13.1%) patients respectively. Thus, subclinical hypothyroidism was more common presentation than overt hypothyroidism among cases. Also, among subclinical hypothyroidism, grade 2 and 3 were more common than grade 1 subclinical hypothyroidism. All t he controls with hypothyroidism had subclinical form; 2 controls with grade 3(2.4%) while 1 with grade 2(1.2%). (Table 1)

**Table 1: Grades of hypothyroidism among cases and controls**

| Parameters | Cases (n=85) | Control (n=85) | Total (n=170) |
|---|---|---|---|
| Hypothyroidism | 25 (29.4%) | 3 (3.5%) | 0.0006* |
| Anti TPO antibody positive | 0 | 0 | |
| Over hypothyroidism Subclinical Hypothyroidism | 8 (9.4%) | 0 (0.0%) | 0.036 |
| Grade-3 | 11 (13%) | 2(2.4%) | 0.031 |
| Grade-2 | 2(2.4%) | 1(1.2%) | |
| Grade-1 | 4(4.7%) | 0(0.0%) | |

The mean value of free T4 (1.2±0.4) was significantly lower (p=0.0001) whereas of TSH (5.6±3.1) was significantly) higher (p=0.0001) in cases than free T4 (1.8±0.7) and TSH value (1.8±1.0) in controls.

An increased risk of hypothyroidism was observed with early age of onset (OR =1.2;95% CI:1.00-1.37;P=0.045), duration of nephrotic syndrome (OR=1.195% CI:1.03-1.12;P=0.001), serum albumin (OR=1.9% CI:0.89-3.81;P=0.001) and non-remission status of disease (OR=1.7;95% CI:1.12-3.35;p=0.007) (Table 2; Figue 1). We found a significant positive correlation of concentration of TSH with Ser. cholesterol (r= 0.253, P=0.0001), and negative correlation with ser. Albumin (r= -0.253, P=0.00010.8711). (Table 3)

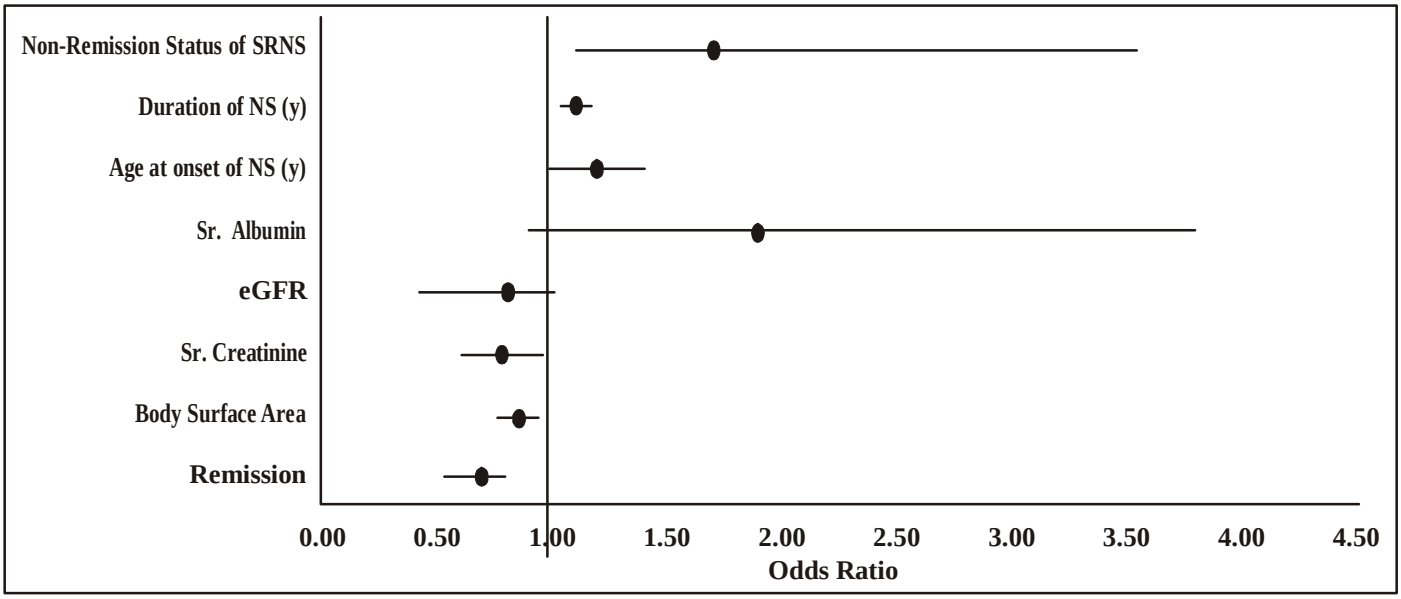


**Figure1: Risk factors for development of hypothyroidism in SRNS**

**Table 2 : Risk Factors for development of hypothyroidism in SRNS**

| | Odds Ratio | 95% C.I. | | p-value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Complete Remission | 0.66 | 0.54 | 0.78 | 0.894 |
| Body Surface Area | 0.87 | 0.76 | 0.92 | 0.532 |
| Serum Creatinine | 0.81 | 0.59 | 0.9 | 0.871 |
| Serum Albumin | 1.9 | 0.89 | 3.81 | 0.0001* |
| EGFR (mL/min/1.73m2) | 0.84 | 0.44 | 1 | 0.632 |
| Age at onset of NS (years) | 1.2 | 1 | 1.37 | 0.043* |
| Duration of NS (years) | 1.1 | 1.03 | 1.12 | 0.0001* |
| Non-Remission Status of SRNS | 1.7 | 1.12 | 3.55 | 0.007* |

**Table : 3 Correlation between TS Hand laboratory parameters of SRNS patients.**

| TSH Level | Correlation coefficient(r) | p-value |
|---|---|---|
| Serum Creatinine | 0.010 | 0.871 |
| Serum Albumin | -0.217 | 0.0001* |
| SerumCholesterol | 0.253 | 0.00 |
| eGFR | 0.052 | 0.632 |

## DISCUSSION

Non-autoimmune hypothyroidism is a common, potentially reversible and treatable complication of Steroid Resistant Nephrotic Syndrome(SRNS) among children. Despite three decades of research, the mechanistic link and directionality of association between hypothyroid and kidney disease remain largely unknown. To search for risk factors, predictors and pathophysiology of development of hypothyroidism among patients with SRNS have

encouraged the paediatric nephrologist to explore further[8].

In our study, hypothyroidism was detected in 29.4% of patients, significantly higher than controls (p=0.0006). Among cases overt and subclinical hypothyroidism was found in 8 (9.4%), and 17 (20%) patients respectively. The subclinical hypothyroidism grade 1,2, and 3 forms were present in 4 (4.7%), 2 (2.35%) and 11(13%) patients respectively. All the controls with hypothyroidism had .subclinical form. Marimuthu et al[9] in a study found the prevalence of hypothyroidism (subclinical or overt) among the cases and controls as 33.3% and 3.3% (n=1), respectively. Prevalence in other studies was 30% and 20 % [10,11]. Roughly one third patients of SRNS are at risk of developing hypothyroidism.

The mean value of free T4 in cases was 1.2±0.4and 1.8±0.7 in controls (p=0.0001).Whereas TSH value was significantly higher (5.6±3.1)in cases than TSH value (1.8±1.0) in controls (p=0.0001). Marimuthu et al.[9] observed similar finding where mean(TSH- 4.55 Miu/L) was significantly (p<0.01) higher in cases in SRNS than controls. McLean et al7 reported significantly decreased level of serum T4, T3 in untreated SRNS patient[11]. Our observation of significantly higher level of TSH were also similar to otherstudies[10, 12, 13,] No statistically significant difference were observed for either of resistance pattern or histopathological profile between cases of SRNS with and without hypothyroidism in the present study as was similarly observed by Marimuthu et al[9].

In the present study, an increased risk of hypothyroidism was observed with early age of onset (OR =1.2;95% CI:1.00-1.37 ; P=0.045), duration of nephrotic syndrome (OR= 1.195 %CI: 1.03-1.12;P=0.001), low serum albumin (OR=1.9% CI:0.89-3.81;P=0.001) and non-remission status of disease(OR=1.7;95%CI:1.12-3.35;p=0.007). An increased risk was also observed with low serum albumin (OR=1.9% CI:0.89-3.81;P=0.001) in the study by Marimuthu et al[9] and non-remission status of disease(OR=1.7;95%CI:1.12-3.35;p=0.007) in study by Kapoor et al.[10] Sharma et al[11] found that TSH levels were significantly elevated in children with relapse (p= 0.042). However, no association of hypothyroidism with age of onset and duration of illness were seen in the study by Marimuthu et al[9].

A significant positive correlation of concentration of TSH with Serum cholesterol (r= 0.253, P=0.0001), and negative correlation with serum. Albumin (r = -0.253, P=0.00010.8711) was observed in the present study. It indicates that proteinuria for long duration causes more tubular damage and increase in loss of thyroid hormone binding protein. Similar observation were made by other studies[9,12,13,14]. With decreasing level of albumin a surge in TSH level is seen attributed to increase in protein loss leading to decreased serum level of T3, T4 and compensatory increase in TSH level by pituitary.

The study design was limited by small sample size and inability to estimate the 24 hour urinary free T3, free T4 and Thyroid binding globulin. Lack of follow up and causal relationship mechanism between SRNS and hypothyroidism were other limiting factors.

## CONCLUSION :

The prevalence of both overt and subclinical form of hypothyroidism of non-autoimmune origin seems to be higher in idiopathic steroid resistant nephrotic syndrome.

An early age of onset, long duration of nephrotic syndrome, low serum albumin and non-remission status of SRNS are importantly associated risk factors. Hypothyroid state may improve with remission, whereas early treatment with thyrid hormone may be considered in younger subjects.

The study recommends routine thyroid function tests to be performed in steroid resistant nephrotic syndrome patients. Also, overt and subclinical hypothyroidism should be treated with thyroid replacement therapy.

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