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RESEARCH ARTICLE

THYROID FUNCTION STUDIES IN CHILDREN OF NEPHROTIC SYNDROME

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Abstract

Introduction:-

The possibility of hypothyroidism in nephrotic syndrome was first reported by Epstenin in 1917 Thyroid hormones are necessary for growth and development.[1,2] The thyroid hormones are transported in two forms, protein bound and free. The free hormones that is free T3 (FT3) and free T4 (FT4) which is most readily available for cellular uptake is the physiologically active fraction. The bound hormone is metabolically inactive and serves as a large, subtle reservoir of hormone and thus a constant supply of hormone is available to tissue. Thyroid hormones are bound to three plasma proteins, they are thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA) also called transthyretin and albumin. Abnormalities of the binding proteins may result in abnormal total (bound) hormone concentrations in the blood even when normal amounts of free hormones are present.[3-6] Earlier studies showed low levels of total T3, T4 compared to normal, but overt hypothyroidism features were seldom seen in patients with nephrotic syndrome. There is limited data and studies available regarding the free triiodothyronine (FT3) and free thyroxine (FT4) levels in children with nephrotic syndrome during the episode. Early diagnosis of even subclinical hypothyroidism must be made to prevent physical and mental retardation in children.

In view of all the above facts, the present study aims to evaluate the level of serum free T3, free T4, and TSH in children with nephrotic syndrome and its correlation with healthy controls.

Methods:-

This comparative study was carried out on total of 60 children (divided into two equal groups of 30 cases and 30 controls) in the age group of 1-18 years of either sex admitted to Department of Pediatrics. SreeBalaji Medical College and Hospital, Chromepet, Chennai over a from April 2018 to November 2019.

Inclusion criteria:

1. Children 1-18 years of age with first episode of nephrotic syndrome, treated with six weeks of daily steroids therapy and in remission.
2. Age and sex matched healthy controls (i.e. siblings/ school children attending the OPD for minor illness like upper respiratory infection).

Exclusion criteria:

1. Age less than 1 year and more than 18 years.
2. Children with secondary causes of nephrotic syndrome and significant renal lesions.

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3. Patients with hypothalmopituitary axis derangement or thyroid disorders.
4. Children suffering from chronic infections like tuberculosis, diabetes mellitus, cystic fibrosis.
5. Children suffering from mal-absorption (celiac disease), moderate to severe protein energy malnutrition or protein losing enteropathy.
6. Children with chronic renal or hepatic diseases.
7. Children on drugs which interfere with thyroid metabolism i.e. carbamazepine, oxcarbamazepine, furosemide, oxytocin etc.
8. Steroids resistant nephrotic syndrome.
9. Children with hyperlipidemia disorders.
10. Children with remission or having multiple episodes in past.
11. Children with first episode of nephrotic syndrome who stopped steroids before six weeks or not in remission.

Inclusion criteria for controls:
Age and sex matched healthy controls (i.e. siblings/ school children attending the OPD for minor illness like upper respiratory infection).

A written informed consent was taken from parent/guardian of each child before including them in the study. Thorough history of the cases was taken, and detailed examination done. Biochemical and other necessary investigation were done to fulfil the criteria of nephrotic syndrome. Serum free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH) were done in all 60 children.

Statistical analysis:
Data was entered in the Microsoft excel sheet and analysed with the help of SPSS version 20. Chi-square paired and unpaired t-test were applied. P value <0.05 was considered statistically significant.

Results:-

The present study included 30 cases and 30 age and sex matched healthy control, with approximately equal male to female ratio. Among cases 18 (60%) were males and 12 (40%) were females. 63.4% of the cases were in the age group 1-10 years and 36.6% were in age group 11-18 years. In the age group of 1-10 years 12 (63.2%) were males compared to 7 (36.8%) females. While from 11-18-year age group 6 (54.5%) were males and 5 (44.5%) were females.

In present study authors had taken 30 children with nephrotic syndrome and 30 healthy aged and sex matched controls. The thyroid profile of the two groups were compared. The mean ft3 and ft4 levels were significantly low in cases as compared to control whereas the TSH levels in cases were significantly higher than controls (Table 1).

Table 1:- Comparison of thyroid profile among cases and controls.

Variable	Group	Mean ± Std. Deviation	P - value
fT3	Cases	1.516±1.160	0.037
	Controls	2.087±0.898	
fT4	Cases	1.979±1.303	0.048
	Controls	3.457±2.513	
TSH	Cases	7.243±3.285	0.0001
	Controls	3.160±1.970	

Discussion:-

Nephrotic syndrome causes loss of protein in the urine which results in the changes occurring in the concentrations of thyroid hormones in the body. In present study the mean fT3 value in cases and controls were 1.516±1.16 pg/ml and 2.08±0.898 pg/ml respectively. The mean fT4 value in cases and controls was 1.979±1.303 ng/dl and 3.457±2.513 ng/dl respectively. There was statistically significant difference in the value of cases and controls. The low level of fT3 and fT4 in the cases is probably due to urinary losses of binding proteins such as thyroxine binding globulin (TBG), transthyretin or pre-albumin and albumin, TSH levels in the cases was higher in comparison to controls i.e. 7.243±3.285 mIU/ml and 3.160±1.970 mIU/ml respectively. Hypothalamus senses low circulating level of thyroid hormones T3 and T4 and responds by releasing thyrotropin releasing hormone (TRH). The TRH

stimulates the anterior pituitary to produce more thyroid stimulating hormone (TSH) resulting in increased TSH level.

Previous studies have reported low level of T3 and T4 in children with nephrotic syndrome, Ito et al in 1994 have studied thyroid hormones in seven children with untreated nephrotic syndrome. They found massive urinary losses of T4, T3, TBG, free T4 and free T3 in the untreated nephrotic children. The mean serum free T4 and free T3 concentrations were significantly lower in the untreated patients than in the same patients in remission and the mean serum TSH levels were significantly higher in the untreated patients than in the same patients in remission. These findings provide evidence of mild hypothyroidism in children with untreated nephrotic syndrome because of losses of T4, T3, free T4, free T3 and TBG into the urine.[7]

In the observational study done by Afroz S et al, in 2011, a total of 85 nephrotic children aged 2-12 years with initial attack and relapse were studied.[8] The mean value of serum T3 (0.65±0.31 ng/ml) and T4 (5.04±4.18 µg/ml) in nephrotic children during nephrosis were within normal limit. But the mean value of thyroid stimulating hormone (TSH) was higher than normal (7.1±5.8 MIU). This study concluded that nephrotic syndrome has a state of mild or subclinical hypothyroidism during proteinuria although they are clinically euthyroid.[8] Similar finding were also noted by Sahni V et al.[9]

Kapoor et al, in 2014 studied thyroid profile in 20 children with steroid resistant nephrotic syndrome compared with similar number of controls. They found an overt hypothyroidism with low FT4 and elevated serum TSH.[10]

Gatoo I et al, studied thyroid function test in 208 children with nephrotic syndrome.[11] A 122 cases identified as hypothyroid patients, of patients below 3 years, 47.5% had hypothyroidism, while hypothyroidism rate in patients between 3 and 6 years was 32.8 % and 19.7% for > 6 years, respectively. T3 level were lower in 68.3% and T4 level were lower in 64.4%. The median TSH level was 11.65±6.71 mIU/ml and 2.82±0.82 mIU/ml in the hypothyroid and euthyroid patients respectively. According to this study, there is high incidence of hypothyroidism in patients of nephrotic syndrome and thus the occurrence of hypothyroidism in such children needs to be mentioned.

In a study by Hajizadeh N et al, thyroid function tests were performed in 104 patients of nephrotic syndrome.[12] Children with nephrotic syndrome were examined about levels of thyroid function tests. Sixty-one cases identified as hypothyroid patients and were treated with supplementary levothyroxine. There were 41 (67.2%) males and 20 (32.8%) females with the mean age of 3.72±3.35 years. Of patients below 3 years old, 47.5% had hypothyroidism, while hypothyroidism rate in patients between 3 and 6 years old was 32.8% and 19.7% for >6 years, respectively (P=0.036). Our patients showed lowered T3 (68.3%) and T4 (64.4%) in comparison with normal values. Median Thyroid-stimulating hormone (TSH) was 11.65±6.71 Micu/ml and 2.82±0.82 in the hypothyroid and euthyroid patients respectively. In all, TSH was negatively correlated with the total urinary protein content. According to this study, the occurrence of hypothyroidism in any child with nephrotic syndrome needs to be mentioned. It is proposed to systematically search hypothyroidism by measuring TSH and free T4 in these patients particularly when proteinuria is prolonged.[12]

In a study by Ebadi A et al, 20 children with Nephrotic syndrome were randomly enrolled in the study to check their thyroid markers levels, authors choose two groups of children; a normal group and a group of nephrotic syndrome patients. Authors took blood samples and let it clot, then collect the serum to follow their serum T3, T4 and TSH levels by checking them every week by ELISA (Enzyme linked immunosorbent assay) for screening and to know the real situation of their thyroid function and also their urine protein to know if they develop Nephrotic syndrome or not. The T4 and T3 levels in nephrotic syndrome patients were low and TSH levels were high showing a hypothyroidism profile but the T4 levels were significantly low in nephrotic syndrome compared to normal group.[13]

Chaudhary J et al, studied the thyroid hormones in 60 children of age between 1-8 years, out of which 30 children (N group) were admitted for reason other than nephrotic syndrome (excluding known cases of thyroid disorder) and 30 children were suffering from nephrotic syndrome (NS group).[14] The T4 and T3 levels in nephrotic syndrome (NS group) patients were low. TSH level were high in NS group. Hypothyroidism was found more in younger children i.e. age less than 6 years.[14]

Mohameed S et al, carried a study which included thyroid function test in 30 hypothyroidisms was more in children with nephrotic syndrome.[15] Egyptian children with steroid responsive nephrotic syndrome in relapsing phase and

remission phase (cases) and other 30 healthy Egyptian children (control group). They found serum fT3 and fT4 was significantly lower in patients with relapse (2.84±0.74 and 3.14±1.34, respectively) in comparison to remission (8.1±2.64 and 16.75±3.69, respectively) and control group (8.97±1.95 and 18.34±4.68, respectively). However, there was significant increase of TSH in patients with relapse (6.7±2.4) in comparison to remission (2.6±1.8) and control group (2.4±1.2).[15]

Marimuthu V et al, conducted a cross-sectional study recruited 30 children (age 1-18 years) with idiopathic Steroid responsive nephrotic syndrome (SRNS) and 30 healthy controls.[16]To evaluate the frequency of non- autoimmune subclinical and overt hypothyroidism in children with idiopathic SRNS. Overt hypothyroidism was detected in 10 out of 30 children with idiopathic SRNS. Children with SRNS had a mean (SD) TSH value 4.55 (4.64) mIU/L that was higher as compared to controls (1.88 (1.04) mIU/L) (P <0.01). The study concluded that the prevalence of subclinical and overt hypothyroidism seems to be high in idiopathic SRNS, with almost one-third of children having overt or subclinical non-autoimmune hypothyroidism.

Conclusion:-

Hypothyroidism should be actively sought for in children with nephrotic syndrome as it is a treatable complication.

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