Original Research Paper

Volume - 11 | Issue - 09 | September - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

THYROID PROFILE IN CHILDREN WITH NEPHROTIC SYNDROME

Dr. Meiyappan Kavitha — Assistant professor, Department of Biochemistry, Government Sivagangai Medical College, Sivagangai, Tamil Nadu, India.

Dr. Mallaiyan Manonmani* — Associate professor, Department of Biochemistry, Government Sivagangai Medical College, Sivagangai, Tamil Nadu, India. *Corresponding Author

ABSTRACT

Objectives: Nephrotic syndrome is a common renal disorder seen in children, with proteinuria as the hallmark. Growth retardation is a known feature of nephrotic syndrome, either due to the disease or treatment with steroids. Thyroid hormone strongly influences growth of the body. So, the present study was undertaken with the objective to assess the thyroid profile in children with nephrotic syndrome

Methods: The study involved 41 cases of nephrotic syndrome and 41 age and sex matched controls. Serum total triiodothyronine (T3), total thyroxine (T4), free triiodothyronine (T3), free thyroxine (T4) and thyroid stimulating hormone (TSH) were assessed in these subjects. The thyroid hormones were correlated with urinary protein creatinine ratio. The cases were followed up after one month and the levels of thyroid hormones were reassessed.

Results: Total T3, total T4, free T3 and free T4 are significantly decreased and TSH significantly increased among cases when compared to controls. TSH is positively correlating with urinary protein creatinine ratio in cases. After one month of treatment, total T3 and total T4 are significantly increased in cases.

Conclusions: The thyroid hormone levels are altered in children with nephrotic syndrome during the episode. A state of subclinical hypothyroidism exists during the nephrotic stage. The alteration is normalized with remission and does not require treatment.

KEYWORDS : Triiodothyronine, thyroxine, nephrotic syndrome, proteinuria, hypothyroidism

INTRODUCTION

Nephrotic syndrome is a common renal disorder seen in children. It is 15 times more common in children when compared to adults. The annual incidence of nephrotic syndrome is 2-3/10000 children. Nephrotic syndrome is characterized by massive proteinuria (>40 mg/m^2/hr), hypoalbuminemia (<2.5mg/dl), edema and hyperlipidemia[1]. Nephrotic syndrome may be primary (Idiopathic) or secondary. The most common form of nephrotic syndrome is idiopathic which includes minimal change disease (85%), focal segmental glomerular sclerosis (10%), and mesangial proliferative glomerulopathy (5%). Secondary causes of nephrotic syndrome are rare and include amyloidosis, Henoch Schonlein purpura, systemic lupus erythematosis, diabetes mellitus, certain infections and malignancies[2]. Proteinuria is the hallmark of nephrotic syndrome. Heavy proteinuria, the primary abnormality in nephrotic syndrome occurs due to structural and functional defects in the glomerular filtration barrier [3]. There is a loss of negative charges along the glomerular basement membrane resulting in the loss of proteins in urine. Albumin is the major protein excreted in urine, resulting in hypoalbuminemia. As with albumin, the concentration of other plasma proteins such as coagulation inhibitors, transcortin, thyroxine binding globulin and vitamin D binding globulin are also decreased. This is because of the urinary loss of these proteins [4].

Growth is an essential feature of childhood, which depends on genetic, nutritional, social and emotional factors. It is also affected by chronic systemic diseases. Growth follows a sigma shaped curve with a high velocity in the early postnatal period and during puberty, but a steady rate during mid childhood. Nephrotic syndrome occurs most commonly in the age group of 2- 8 years when the growth rate is at a steady rate [5]. Even more, steroids form the mainstay of the treatment of nephrotic syndrome. Growth retardation is a well known feature seen in patients with frequent relapses, and requiring repeated course of steroids.

Thyroid hormone strongly influences body growth. Thyroid hormones influence growth hormone and somatomedin production, stimulate growth factor production and also influences the number of growth hormone receptors [6]. There is a curious association between thyroid hormones and growth hormone. So, the present study was undertaken to assess the levels of thyroid hormones in South Indian children with nephrotic syndrome, with the view that correction of thyroid abnormality if any might correct the growth failure in these children.

MATERIALS AND METHODS

The study involved 41 cases of nephrotic syndrome in the age group of 3-12 years who were admitted in the Pediatrics ward of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER). Of the 41 cases, 19 had first episode of nephrotic syndrome and 22 cases presented with relapse. Children with any co-morbid illness such as thyroid diseases, diabetes mellitus, hypothalamo-pituitary disorders, liver diseases, tuberculosis and seizure disorders were excluded from the study. Children on drugs that interfere with the functioning of the thyroid gland (such as carbamazepine, furosemide) were not included in the study. Patients with secondary causes of nephrotic syndrome were also excluded. The results were compared with 41 age and sex matched controls. Children attending Pediatric OPD with minor ailments like headache and healthy children accompanying the patients were recruited as controls.

The ethical clearance for the study was obtained from the Institute Ethics Committee. A written informed consent was obtained from the parents of both the cases and controls. On admission of the cases in the Pediatric ward, a detailed history was taken and physical examination was done. The anthropometric parameters (body weight and height) and vital signs including basal heart rate were assessed. Five ml of fasting blood and 100 ml of spot urine were collected from the patient. The samples were analyzed immediately for various biochemical parameters (Serum thyroid hormones, urea, creatinine, total proteins, albumin, cholesterol and urinary protein creatinine ratio).The same was repeated at the end of one month.

Total and free triiodothyronine (T_3), thyroxine (T_4) and thyroid stimulating hormone (TSH) in the sera were measured by Chemiluminescence method (ADVIA Centaur CP, Germany). The kits were procured from Siemens Medical Solutions Diagnostics, USA. Urine protein was measured spectrophotometrically by turbidimetric method[7]. Urine creatinine was estimated by modified Jaffe's method using Randox Imola, UK and the protein creatinine ratio was thus obtained.

Table 1: Routine Parameters In Controls And Nephrotic Syndrome Cases (At Admission)

Parameter	Controls (n =41)	Cases (n = 41)	p value
Age, mean (SD), yrs	8.17 (2.64)	7.8 (2.83)	0.5464
Weight for age (Z Score)	-0.16±0.84	-0.73±0.86	0.0111
Height for age (Z Score)	-0.37±0.58	-1.54±1.19	<0.0001

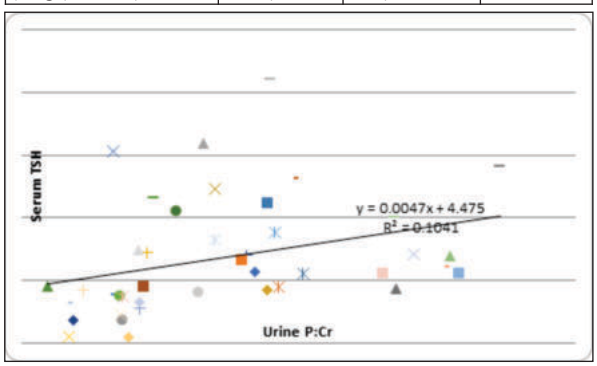
Blood urea, mean (SD), mmol/L	6.89 (1.85)	7.96 (2.8)	0.0435
Serum creatinine, mean (SD), µmol/L	43.39 (16.82)	54.76 (25.87)	0.0212
Serum total protein, mean (SD), g/L	76.78 (6.29)	40.71 (6.17)	<0.0001
Serum albumin, mean (SD), g/L	46.68 (4.49)	19.76 (4.23)	<0.0001
Serum cholesterol, mean (SD), mmol/L	3.56 (0.54)	11.12 (2.95)	<0.0001
Urine protein-creatinine ratio, median (range), mg/mmol	2.26 (0.23 – 15.16)	459.27 (64.48 – 1210.4)	<0.0001

Table 2: Thyroid Profile In Controls And Cases (At Admission)

Parameter	Controls (n=41)	Cases (n=41)	p value
Total T_3, mean(SD), nmol/L	2.78 (0.48)	1.28 (0.52)	<0.0001
Total T_4, mean(SD), nmol/L	124.93 (24.49)	65.76 (23.71)	<0.0001
Free T_3, mean(SD), pmol/L	6.26 (1.64)	3.53 (0.99)	<0.0001
Free T_4, median (range), pmol/L	16 (9.8 – 55.5)	11.7 (2.6 – 26.6)	<0.0001
TSH, mean(SD), mIU/L	2.88 (1.66)	6.86 (4.54)	<0.0001

Table 3: Comparison Of Thyroid Profile In Cases At Admission And After One Month Of Treatment

Parameter	At admission (n=41)	After one month (n=34)	p value
Total T_3, Median (range),	1.2 (0.17-2.97)	1.91 (1.11-3.65)	<0.0001
Total T_4, Mean (SD), nmol/L	65.76 (23.71)	121.94 (25.14)	<0.0001
FreeT_3,Median (range), pmol/L	3.5 (1.2 – 5.5)	3.6 (2.2 – 6.3)	0.1367
Free T_4, Median (range),pmol/L	11.7 (2.6 – 26.6)	11.75(3.5 – 28.1)	0.139
TSH, Median (range),mIU/L)	5.61 (0.44 - 21.01)	4.76 (0.6 – 15.4)	0.151



(r value: 0.515 ; p value : 0.0006)

Figure 1: Correlation Between Serum TSH (MIU/L) And Urinary Protein Creatinine Ratio(MG/MMOL) In Cases

Serum total protein, albumin, urea, creatinine and total cholesterol were estimated using a well calibrated random access discrete analyzer, Randox Imola with different methodologies. . Total protein and albumin were estimated in serum by direct Biuret method and Bromocresol green method respectively. The kits were procured from Agappe diagnostics

Urea was measured in serum by urease /GLDH methodology using kits procured from Agappe diagnostics. Serum creatinine was estimated by modified Jaffe's method with kits procured from Agappe diagnostics. Serum total cholesterol was measured by Trinders method using kits procured from ERBA diagnostics.

Normal Levels

Normal serum total T_3 levels in children:
1-5 years: 1.62 – 4.14 nmol/L
6-10 years: 1.45– 3.71 nmol/L
11-15 years: 1.26 – 3.28 nmol/L

Normal serum total T_4 levels in children:
1 – 5 years: 94 – 194 nmol/L
6– 10 years: 83 – 172 nmol/L
11 – 15 years: 72 – 151 nmol/L

Normal serum free T_3 levels in children: 3.2 – 6.8 pmol/L
Normal serum free T_4 in children: 10.3 – 25.8 pmol/L
Normal serum TSH level in children: 0.7 – 6.4 mIU/L

Statistical Analysis

Data was analyzed using the SPSS software programme version 16. Results were expressed as mean (standard deviation) and median (range) for parametric and non-parametric data respectively. Unpaired t test or Mann Whitney U test were used for comparing data between cases and controls. Paired t test or Wilcoxon matched pairs test was used to compare data among cases at admission and after one month. Spearman correlation was used to correlate the thyroid hormones and urinary protein creatinine ratio. 'p' value of less than 0.05 was considered as significant.

RESULTS

Table 1 shows the routine parameters in the study subjects. As far as the age is concerned, there was no significant difference between the cases and controls. The cases had significantly altered Z score for weight and height as compared to the controls. As expected, the serum total protein level was decreased and the serum cholesterol level was increased in the cases. The urinary protein creatinine ratio was significantly higher among the cases when compared to controls.

Thyroid profile among controls and cases at admission are shown in Table 2. The serum total T_3, total T_4, free T_3 and free T_4 are significantly decreased among cases when compared to controls. On the other hand, serum TSH is significantly increased among cases. Though there is a statistical difference, the values of free T_3 and free T_4 are within the normal range in both groups. All the patients were clinically euthyroid. On correlating the thyroid parameters with urinary protein creatinine ratio, it is found that TSH is positively correlating with urinary protein creatinine ratio in cases. Figure 1 shows the correlation between serum TSH (mIU/L) and urinary protein creatinine ratio (mg/mmol) in cases (r value: 0.515; p value : 0.0006)

After one month of treatment, the total $T_3$and total T_4 of the study subjects had significantly risen. The free thyroid hormones were also altered but this was not statistically significant. There was no significant change in TSH levels one month after treatment. These are shown in Table 3.

DISCUSSION

Nephrotic syndrome occurs most commonly in the age group of 2-8 years when the growth is at a steady rate. In our study, both sexes were affected to the same extent.The total thyroid hormones are known to be altered in patients with nephrotic syndrome [8]. According to findings from our study, the serum total T_3 and total T_4 as expected were significantly lower in the cases than controls. This can be attributed to the urinary losses of thyroxin binding globulin (TBG), transthyretin, and albumin and subsequent loss of thyroid hormones bound to them. [9]

According to study by Ito et al [4] free T_3 and free T_4 are also massively lost in urine in untreated children with nephrotic syndrome. Their study supported the existence of mild hypothyroidism in untreated nephrotic children. This could be the reason for significant rise in serum free T_3 and free T_4 seen in cases in our study. As a result of loss of thyroid hormones in the urine, the TSH secretion is stimulated by a feedback mechanism This accounts for TSH being significantly increased in cases at admission when compared to controls.In our study, we found that the urinary protein creatinine ratio is positively correlating with the serum TSH in cases at onset. Other studies have obtained varied results. The urine protein creatinine ratio significantly correlated with serum T_3, T_4, TSH and free T_4 in patients with nephrotic syndrome in a study by Jung et al [10]. Guo et al [11] found that proteinuria correlated with total T_3, total T_4 and free T_4 but not with free T_3 and TSH in a study done on children with nephrotic syndrome.Further, in our study we found that after one month of treatment, the serum total T_3 and

total T_4 were significantly increased in cases when compared to the values at the onset. Though there was an increase in the serum free T_3 and free T_4 after one month, these did not reach statistical significance. A fall in serum TSH was also noticed but was statistically insignificant. These findings would support proteinuria as the main cause of alteration in thyroid hormones in children with nephrotic syndrome. Other mechanisms may have a role to play as well. Damage to renal tubules decreases the reabsorption of low molecular weight proteins, including free thyroid hormones. Long term use of steroids and other immunosuppressive drugs might affect the functioning of the thyroid. Disturbances in the peripheral conversion of T_4 to T_3 in nonthyroid illness are well explained by studies[12,13].

The results of our study are in line with few other similar studies done in nephrotic syndrome. Dhanjal et al studied serum free T_3, free T_4 and TSH in 30 children with nephrotic syndrome and compared the values with 30 healthy controls. They found that free T_3 and freeT_4 are significantly lowered and TSH significantly increased in cases when compared to controls. They concluded that hypothyroidism being a treatable complication should be actively sought for in patients with nephrotic syndrome [14]. Matttoo T K showed the existence of hypothyroid state in children with nephrotic syndrome and recommended routine thyroid screening and early replacement therapy in them [15]. Gilles et al studied thyroid function in 159 adult patients with proteinuria. They found that the thyroid function is altered in these patients, specifically the TSH levels are increased. Subclinical hypothyroidism was six times more common but overt hypothyroidism due to the urinary losses was rare[16]. Vinayagam et al estimated free T_4, TSH and thyroglobulin in 40 nephrotic children during the episode and compared it with remission. They found that free T_4 was not significantly altered but TSH and thyroglobulin levels were significantly elevated during nephrosis when compared to remission. However clinical hypothyroidism was not seen in any of the patients [17]. Similarly studies by Gattoo I, Sawant and Choudhury et al have also shown that transient subclinical hypothyroidism is present during nephrosis [18,19,20] Sawant et al have attributed it mainly to the increased oxidative stress seen in nephrotic syndrome as they have found in their study that lipid peroxidation and glutathione peroxidase are significantly increased among the cases when compared to controls. On the other hand, there is a significant decrease in superoxide dismutase in the cases.

CONCLUSION

The thyroid profile is altered and a state of subclinical hypothyroidism exists in nephrotic syndrome. As the situation improves with remission and the patients are clinically euthyroid, they generally do not require replacement therapy.

Limitations Of The Study

We did not measure the thyroid hormone levels in urine. So, we could not clearly explain the mechanism by which thyroid hormones are altered in nephrotic cases. Another limitation of the study is the small sample size. Since the follow up samples were collected one month later, these may not be sufficient to prove the effect of treatment on thyroid profile. Larger studies involving more number of subjects and of longer duration are needed to establish the need for treatment with replacement therapy in patients with nephrotic syndrome.

REFERENCES

1. Vogt BA and Avner ED. Nephrotic syndrome, in Nelson Textbook of Pediatrics. 18th edition, In: Kliegman RM, Jenson HB, Behrman RE and Stanton BF, editors. Philadelphia: Saunders; 2007.p 2190-2195
2. Bagga A and Mantan M. Nephrotic Syndrome in children. Indian J Med.Res. 2005; 122: 13-2
3. Eddy AA and Simons JM. Nephrotic Syndrome in childhood. Lancet 2003;362:629-39
4. Ito S, Kano K, Ando T, Ichimura T. Thyroid function in children with nephrotic syndrome. Pediatr Nephrol. 1994;8(4):412-5
5. Mohan KR and Kanitkar M. Growth in children with steroid sensitive nephrotic syndrome. Med J Armed Forces India. 2009; 65: 4-6
6. Cabello G and Wrutniak C. Thyroid function and growth: relationships with growth hormone effects and regulation. Reprod. Nutr. Dev. 1989; 387-402
7. Varley H. Practical Clinical Biochemistry.4th edition. London: Heinemann; 1988.p143-144
8. Oyemade OA, Lukanmbi FA, Osotimehin BO and Dada OA. Biochemical hypothyroidism in Nigerian children with nephrotic syndrome. Ann Trop Paediatr.1983; 3(2): 93-96.
9. Iglesias P and Diez J J. Thyroid dysfunction and kidney disease. Eur J Endocrinol.2009; 160: 503-515
10. Jung SH, Lee JE, Chung WY. Changes in the thyroid hormone profiles in children with nephrotic syndrome Korean J Pediatr 2019;62(3):85-89
11. Guo QY, Zhu QJ, Liu YF, Zhang HJ, Ding Y, Zhai WS, Ren XQ, Zhang J, Zhang X, Yang M. Steroids combined with levothyroxine to treat children with idiopathic nephrotic syndrome: a retrospective single-center study. Pediatric Nephrology. 2014;29(6):1033-8.
12. Chopra IJ, Huang TS, Beredo A. Evidence for an inhibitor of extrathyroidal conversion of thyroxine to k3,5,3' triiodothyronine in sera of patients with nonthyroidal illness. J Clin Endocrinol Metab 1985; 60: 666
13. Abo-Zenah HA, Shoeb SA, Sabry AA and Ismail HA. Relating circulating thyroid hormone concentrations to serum interleukins-6 and -10 in association with nonthyroidal illness including chronic renal insufficiency. BMC Endocr Disord. 2008; 8(1): 21-27
14. Dhanjal GS, Garg M. Thyroid function studies in children of nephrotic syndrome. Int J Contemp Pediatr 2019;6(3):1190-3.
15. Mattoo TK. Hypothyroidism in infants with nephrotic syndrome. Pediatric Nephrology. 1994;8(6):657-9.
16. Gilles R, Heijer MD, Ross AH, Sweep FCGJ, Hermus ARMM and Wetzels JFM. Thyroid function in patients with proteinuria. Neth J Med. 2008; 66(11): 483-485
17. Vinayagam V, Susan Uthup, Geetha Saradakutty, Radhika Chemmanganattu Radhakrishnan, Liji Ramakrishnan, Lalitha Kailas. Thyroid function in childhood nephrotic syndrome. Sch J App Med Sci. 2019;7(9): 3143-3148
18. Gattoo I, Aziz A, Latief M, Najar BA. Thyroid Function in Pediatric Nephrotic Syndrome: A Hospital Based Observational Study. Int J Adv Res. 2015; 3(5):500-5
19. Sawant SU, Chandran S, Almeida AF, Rajan MGR. Correlation between oxidative stress and thyroid function in patients with nephrotic syndrome. Int J Nephrol. 2011; 2011: 256420
20. Choudhury J. A study on thyroid function test in children with nephrotic syndrome. Int J Contemp Pediatr 2016;3 (3):752-4.