

Examine of Thyroid Function in Pediatric Nephrotic Syndrome; Tehran-Iran

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Abstract

Introduction

In children with Nephrotic Syndrome (NS), it is probable to determine a hypothyroid state because of Thyroxine (T4), Triiodothyronine (T3) and Thyroid-binding globulin loss in presence of proteinuria. The aim of this study was to examine thyroid function in pediatric cases of nephrotic syndrome.

Materials and Methods

In a cross-sectional study, from march 2010 to march 2012, thyroid function tests were performed in 104 patients referred to the Nephrology Department of Children's Medical Center, Tehran-Iran; because of nephrotic syndrome. Collected data analyzed with SPSS 17 software and $p < 0.05$ used to denote statistical significance.

Results

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. 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.

Conclusions

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.

Key Words: Children, Hypothyroidism, Nephrotic syndrome, Thyroid function.

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Introduction

Nephrotic syndrome is a glomerular disorder characterized by proteinuria greater than 2 grams per m² per day, low level of serum albumin (less than 2.5 g per dL), edema and hypercholesterolemia (serum total cholesterol level greater than 250 mg per dL). It seems that age, ethnicity and geographical distribution have effect on incidence of nephrotic syndrome (1). Possibility of hypothyroidism in patients with nephrotic syndrome was reported by Epstein in 1917. However, symptoms of hypothyroidism with increased Thyroid-stimulating hormone (TSH) in children with nephrotic syndrome were discovered about 30 years later (2). Renal albumin excretion is not compensated by increased liver albumin production in patients with nephrotic syndrome that leads to decreased blood albumin level. Beside albumin, other proteins such as some hormones is excreted in the urine. Several studies have shown renal excretion of thyroid hormones and Thyroxine-binding Globulin (TBG) in subjects with nephritic syndrome (3,4). According to TBG excretion in nephrotic syndrome, total amounts of hormones bonded to TBG are diminished, but any metabolic disorder is not expected since TSH, free Triiodothyronine (T3) and free Thyroxine (T4) levels are remained normal. In some patients with sustained nephrotic syndrome and prolonged proteinuria, continuous excretions of TBG can reduce levels of free thyroid hormones and increase TSH (5). Although in literatures this complication is uncommon, in practice by routine thyroid function test in children with nephrotic syndrome higher number of patients is observed. On the other hand, it should be considered that kidney function and metabolism of thyroid hormones had mutual relationship. In consequence of thyroid dysfunction significant changes in fluid and electrolytes hemostasis, tubular and

glomerular function is expected. In fact hypothyroidism is accompanied by reduced glomerular infiltration, hyponatremia and changes in urine osmolarity (6,7). Early diagnosis of hypothyroidism in children can prevent mental and physical retardation. To the best of our knowledge, there is no comprehensive study that evaluates thyroid function in pediatric cases of nephrotic syndrome in Iran. Therefore, we decided to assay prevalence of hypothyroidism in children with nephrotic syndrome.

Materials and Methods

In this study, all patients, who had referred to the Department of Nephrology of Tehran Children's Medical Center Hospital were evaluated during January 2010 to December 2012. Children with nephrotic syndrome were examined about levels of thyroid function tests. Child's age, onset date of kidney disease and the type of treatment, urine protein excretion (24-hour) or protein-creatinine ratio, albumin, cholesterol, T3, T4 and TSH levels had been evaluated. We treated the patients with enalapril, prednisolone, cyclosporine, CellCept and treatment of hypothyroidism with levothyroxine. The present study has been approved by the Ethics Committee of Tehran University of Medical Sciences. Informed consent was obtained from parents prior to inclusion in the study. Parents of children who did not consent to participate in this study, as well as cases of children who had defects in documentation were excluded.

After data collection, the data was analyzed by statistical software SPSS software, version 17. Qualitative data is demonstrated by frequency and quantitative data were reported as Mean \pm SD. In our study Chi-Square test was used to assess the relationship between qualitative variables. P value < 0.05 was considered significant.

Results

In this study, 104 patients with nephrotic syndrome were studied. 65 cases (62.5%) were male and 39 (37.5%) were female. 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). It should be noted that this complication was seen in 12 patients less than one year old. Table.1 is shown the frequency of occurrence of hypothyroidism in patients with nephrotic syndrome according their age.

Table 1 : Distribution of the incidence of hypothyroidism in patients with NS according their age

Hypothyroidism Age	Total		No		Yes	
	%	n	%	n	%	n
3 years>	37.5	39	23.2	10	47.5	29
0.25-0	1	1	0	0	1.6	1
1-0.25	11.5	12	2.3	1	18	11
3-1	25	26	20.9	9	27.9	17
6-3	33.7	35	34.9	15	32.8	20
Over 6 years	28.9	30	41.8	18	19.7	12
12-6	26	27	39.5	17	16.4	10
12<	2.9	3	2.3	1	3.3	2
Total	100	104	100	43	100	61

Increased TSH level was seen in 50.8% of patients who had urinary protein excretion between 1 to 10 times more than normal values and increased TSH level was seen in 72.1% of patients with urinary protein excretion more than 10 times of normal values. Increasing the amount of proteinuria (more than 10 times than normal) and increasing the TSH level had significant relationship. Based on the results of tests, TSH in hypothyroidism patients was 4.31 Micu/ml to 34.40 micU/ml (Mean± SD: 11.65 ± 6.71

micU/ml). low levels of T3 and T4 was observed in 68.3 % and 64.4 % of patients, respectively. However, the mean of T3 was (83.92 ±35.54) and the mean of T4 was (4.73 ±2.71), there were some patients who had normal T3 and T4 values despite of having hypothyroidism.

On the other hand, the TSH level in euthyroid patients was 0.80 micU/ml to 4.12 Micu/ml (Mean± SD 2.82 ± 0.82 micU/ml). Table. 2 shows distribution of thyroid function test results in patients with hypothyroidism and euthyroidism.

Table 2 : Distribution thyroid function test results in patients

Hypothyroid patients (n = 61)	Minimum	Maximum	Mean	SD
TSH* (Micu/ml)	4.31	34.40	11.6551	6.71980
T3 [‡] (Ng/dl)	1.50	168.00	83.9262	35.54151
T4 [†] (Mg/dl)	1.10	14.00	4.7328	2.71494
Control group of patients (n = 43)				
TSH	.80	4.12	2.8202	.82847
T3	41.00	148.00	94.2093	25.88211
T4	1.30	12.00	6.2605	2.94102

*TSH: Thyroid-stimulating hormone; [‡]T3: Tri-iodothyronine; [†]T4: Thyroxine

This study demonstrated that all patients with serum albumin levels <1.5 were suffered from hypothyroidism. Increasing the level of serum albumin leads to decreased number of hypothyroidism. Sixty-four percent and 58.1% of patients, who had serum albumin between 1.5 to 2 and between 2 to 2.5, had experienced hypothyroidism, respectively. In 63.2% of patients who had Serum albumin level more than 2.5, all thyroid function tests were normal range. However, the relationship between level of serum albumin and incidence of hypothyroidism was not statically significant ($P=0.068$). Based on our study increasing the level of proteinuria results in increasing the level of TSH.

Discussion

In this study, thyroid functions were evaluated in children with nephrotic syndrome. So, 58.6 % of patients experienced hypothyroidism. However, in the study by Afroz (8), it was demonstrated that patients with mild or subclinical hypothyroidisms were clinically euthyroid. In the study by Mattoo (9), was shown hypothyroidism requiring treatment in 4 of 5 cases of subjects with nephrotic syndrome. McLean (10) reported that disturbance in height-weight regression of a child with congenital NS was sub-sequenced of reduction in TSH level and need for using thyroid hormone replacement therapy. Given that it is difficult to differentiate between clinical signs and laboratory findings data about hypothyroidism, so association between NS signs and clinical symptoms of hypothyroidism are not well known (2). It seems that the main reason for the difference in results in previous study (8) is based on evaluation according to clinical features of hypothyroidism than laboratory findings in hypothyroidism cases. In our study of total 61 patients with hypothyroidism, 41 were boys while 20

were girls. The statistics show that the incidence of hypothyroidism in boys patients is about 1.2 times more than girls. However, other studies on primary hypothyroidism showed that hypothyroidism was more common in girls than boys in the neonates (11). Saif Ali Hashemi (12) showed hypothyroidism is more common in boys than girls. This study showed the highest incidence of hypothyroidism in children aged <3 years old who were suffered from NS. It should be noted that this condition is more common in age less than one year (12 patients). With getting older reduction in incidence of hypothyroidism was observed. Hypothyroidism was seen 32.8 % in 3 to 6 years, and 19.7% after 6 years in patients with NS, so younger children with NS experienced higher rate of hypothyroidism. According to the results of McLean (10) the rate of urinary excretion of hormones and proteins compared to body weight is effective on rate of thyroid hormones excretion. This issue explains the higher incidence of hypothyroidism in children with NS. In 58.6 % of patients with NS, thyroid test results indicate greater than normal values. The results of study by Mattoo (9), Ito (13) and Harton (14) are consistent of our data. hese changes are due to primary hypothyroidism in relative compensate form cause the response of hypothalamic-hypophysis of low levels of thyroid hormones. McLean (10) and Wilschanski (15) also found similar results in their studies based on low levels of T4 and high levels of TSH in similar cases. In fact, thyroid hormone levels decline during nephrosis period. In contrast, the level of TSH is increased in untreated patients (8, 13, 16). Our study showed that there is a direct relationship between the protein excretion in urine and increased in serum TSH levels. Many studies suggest the relationship between proteinuria and serum TSH levels (8, 13,17). Gilles in his study showed that TSH levels in patients with

impaired renal protein excretion was higher than control group (18). Some researchers believe that the adult thyroid gland can compensate the urine excretion of hormones and binding proteins (2) and the urine excretion is not a significant reason for increase TSH and true hypothyroidism (4,9). Although increase in TSH level is seen in the end stage of massive proteinuria (9, 19). Some researchers believe that proteinuria and urine excretion of hormones and binding proteins compared to body weight is higher in children than adults that caused of higher prevalence of hypothyroidism in children with NS (10). TSH level in hypothyroid patients was 4.31 micU/ml to 34.40 micU/ml and average of TSH level was 11.65 ± 6.71 micU/ml. Trouillier (2) showed that the average of TSH level was 5.26 micU/ml (5.63-4.89 micU/ml) and maximum of measured TSH level was 10.38 micU/ml (5.90-16.20 micU/ml) which is lower than our patients' values. However, in the study by Fonseca et al. (4) the mean of TSH level (12.15 Micu/ml, between 8.60 to 26 Micu/ml) had been reported higher than our study. However, the mean T3 was 83.92 ± 35.54 and the mean T4 was 4.73 ± 2.71 . In the study by Harton (14), T3 and T4 levels in patients with primary glomerular nephropathy was 124 ± 54 and 4.84 ± 2.11 , respectively. Although average of T4 levels in both mentioned studies are similar, in our study this average was significantly lower than normal. The maximum values of the two hormones indicate that a number of patients, who had diagnosis of hypothyroidism despite of normal levels of thyroid hormones (T3 and T4). Since majority of T4 is bonded to proteins in blood, decreasing in level of proteins due to excretion in urine leads to decline in T4 blood level. We showed that T3 blood level probably because of low bindings to proteins is not affected by NS. In some cases that we observed low levels of T3 it does not have significant relation with

renal disorders. In the study by Afrasiabi (3) and Gavin (20), it was shown decreased T3 level in Ns. This obvious difference could be explained by increased T3 production and peripheral conversion of T4 to T3 (14, 21). In this study the maximum values of T3 and T4 indicated a number of patients, who had diagnosis of hypothyroidism despite of normal levels of thyroid hormones levels (T3 and T4). However, as already mentioned, high or even normal levels of T3, did not rule out hypothyroidism (14).

This study showed that an increased rate of proteinuria can be reduced the normal thyroid function. These facts are consist with the reports of urine excretion of thyroid hormones in patients with proteinuria (3, 4, 15). On the other hand, this study showed that all patients with serum albumin levels less than 1.5 were suffered from hypothyroidism. In 63.2% of patients with serum albumin higher than 2.5 thyroid function tests were normal. The role of proteinuria in this issue is cleared by opposite relation between TSH and serum albumin (15). This issue is congruent with other studies (2, 9, 14). Decreased in thyroid hormones levels due to low level of albumin, prealbumin, thyroxin binding globulin and high renal excretion of free T4 (fT4). The positive relationship between serum albumin, level of T4, rate of proteinuria, T4 urine excretion and also return of thyroid function tests to normal by remission of NS symptoms or developing anuria confirmed this matter (4, 17, 20, 22). Probably treatment with levothyroxine can cause the stronger effect of corticosteroid (23-25). Because in patients with hypothyroidism the receptor of glucocorticoid is reduced (13) so it decreases drug effect on kidney. Glucocorticoids have important role in treatment of NS beside of decrease in glucocorticoid receptors the treatment of hypothyroidism must be noted.

Conclusion

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.

Conflict of interest: None.

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