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THYROID FUNCTION IN PEDIATRIC NEPHROTIC SYNDROME: A HOSPITAL BASED OBSERVATIONAL STUDY

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ABSTRACT

Background: Nephrotic syndrome is a condition which is characterised by proteinurea, hypoprotenemia, hyperchlolesterolemia and significant edema. In children with nephrotic syndrome, it is probable to determine a hypothyroid state because of significant loss of thyroxine (T4), tri-iodothyronine (T3) and thyroid-binding globulin in presence of proteinuria. **Objectives:** To determine the thyroid function test in pediatric cases of nephrotic syndrome, and to find any association and impact on thyroid harmone levels in these patients. **Methods:** It was a prospective observational study from march 2012 to march 2014, thyroid function tests were performed in 208 patients which included both indoor and outdoor patients in the department of paediatrics Government Medical College, A tertiary care Pediatric Hospital. **Results:** 122 cases identified as hypothyroid patients. There were 82 (67.2%) males and 40(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 TSH (Thyroid-stimulating hormone) was 11.65±6.71 Micu/ml and 2.82±0.82 in the hypothyroid and euthyroid patients respectively. In *al*, TSH was negatively correlated with the total urinary protein content. **Conclusions**: 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. It is proposed to systematic*al*y search hypothyroidism by measuring TSH and free T4 in these patients particularly when proteinuria is prolonged.

INTRODUCTION

Nephrotic syndrome is a glomerular disorder characterized by proteinuria greater than 40 miligrams per m^2 per hour , 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 (Karen *et al*., ?). Possibility of hypothyroidism in patients with nephrotic syndrome was reported by Epsteinin 1917. However, symptoms of hypothyroidism with increased Thyroid-stimulating hormone (TSH) in children with nephrotic syndrome were discovered about 30 years later (Trouillier *et al*., 2008). Renal albumin excretion is not compensated by increased liver albumin production in patients with nephrotic syndrome that leads to decreased blood albumin level.

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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 nephrotic syndrome (Afrasiabi *et al*., 1979 and Fonseca *et al*., 1991). 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 tri-iodothyronine (T3) and Free thyroxine (T4) levels are remained normal. In some patients with sustained nephrotic syndrome and prolonged proteinuria, continuos excretions of TBG can reduce levels of free thyroid hormones and increase TSH (Hoffman *et al*., 1988). 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 (Kelly, 2005 and Sawant *et al*., 2011). 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

This study included 208 children both indoor and outdoor patients who presented to our hospital, Department of Pediatrics Government Medical College Srinagar and were subsequently diagnosed as nephrotic syndrome. *Al* children had First episode of nephrotic syndrome, Patients with remession or having multiple episodes in past wetre excluded. Patients 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. The present study has been approved by the ethics committee of the hospital. Informed consent was obtained from parents prior to inclusion in the study. Parents of children who did not consent to participate in this study, patients who had repeated episodes as well as cases of children who had defects in documentation were excluded. After data collection, the data was analyzed by statistical software SPSS V.17. Qualitative data is demonstrated by frequency and quantitative data were reported as mean±SD. In our study Chi-Square test was used to assess the relationship between qualitative variables.

RESULTS

In this study, 208 patients with nephrotic syndrome were studied. 130 cases (62.5%) were male and 78 (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. 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 uthyroidism patient 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 1. Distribution of the incidence of hypothyroidismin patients with nephrotic syndrome according to their age

Age	Total		Hypothyroidism			
			No		Yes	
	%	n	%	n	%	n
	37.5	78	23.2	20	47.5	58
0.25-0	1	2	0	0	1.6	2
1-0.25	11.5	24	2.3	2	18	22
3-1	25	52	20.9	18	27.9	34
6-3	33.7	70	34.9	30	32.8	40
Over 6 years	28.9	60	41.8	36	19.7	24
12-6	26	54	39.5	34	16.4	20
12<	2.9	6	2.3	2	3.3	4
Total	100	208	100	86	100	122

Table 2. Distribution thyroid function test results in patients

Hypothyroid patients (n = 61)	Minimum	Maximum	Mean	Standard deviation
(Micu/ml) *TSH	4.31	34.40	11.6551	6.71980
(Ng/dl) ‡T3	1.50	168.00	83.9262	35.54151
(Mg/dl) †T4	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-stimulatinghormone; ‡T3,tri-iodothyronine; †T4, thyroxine

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 *et al*. (2011), it was demonstrated that patients with mild or subclinical hypothyroidisms were clinic*al*y euthyroid. In the study by Mattoo (1994), was shown hypothyroidism requiring treatment in 4 of 5 cases of subjects with nephrotic syndrome. McLean *et al*. (1982) reported that disturbance in height-weight regression of a child with congenital nephrotic syndrome 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 nephrotic syndrome signs and clinical symptoms of hypothyroidism are not well known (Trouillier *et al*., 2008).

It seems that the main reason for the difference in results in previous study (Afroz *et al*., 2011) is based on evaluation according to clinical features of hypothyroidism than laboratory findings in hypothyroidism cases. In our study of total 121 patients with hypothyroidism, 82 were boys while 40 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 (Ghadiri *et al*., 2012). Saif Ali Hashemi *et al*. (2006) showed hypothyroidism is more common in boys than girls. This study showed the highest incidence of hypothyroidism in children aged. According to the results of McLean *et al*. (1982) 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 nephrotic syndrome. In 58.6 % of patients with nephrotic syndrome, thyroid test results indicate greater than normal values. The results of study by Mattoo (1994), Ito *et al*. (1994) and Harton *et al*. (1984) are consistent of our data. These changes are due to primary hypothyroidism in relative compensate form cause the response of hypothalamic-hypophysis of low levels of thyroid hormones. McLean *et al*. (1982) and Wilschanski *et al*. (1992) 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 (Afroz *et al*., 2011; Ito *et al*., 1994 and Kapoor *et al*., 2013). 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 (Afroz *et al*., 2011; Ito *et al*., 1994 and Burke and Shakespear, 1976). Gilles in his study showed that TSH levels in patients with impaired renal protein excretion was higher than control group (Afroz *et al*., 2011). Some researchers beleive that the adault 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 (Fonseca *et al*., 1991 and Mattoo, 1994).

Although increase in TSH level is seen in the end stage of massive proteinuria (Mattoo, 1994 and Abid *et al*., 2012). Some researchers beleive that proteinuria and urine excretion of hormones and binding proteins compared to body weight is heigher in children than adults that caused of heigher prevalence of hypothyroidism in children with nephrotic syndrome (McLean *et al*., 1982). 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*. (1991) 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 *et al*. (1984) 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 nephrotic syndrome. In some cases that we observed low levels of T3 it does not have significant relation with renal disorders. In the study by Afrasiabi *et al*. (1979) and Gavin *et al*. (1978), it was shown decreased T3 level in nephrotic syndrome. This obvious difference could be explained by increased T3 production and peripheral conversion of T4 to T3 (Harton *et al*., 1984 and Basiratnia *et al*., 2013). 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 (Harton *et al*., 1984). 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 (Afrasiabi *et al*., 1979; Fonseca *et al*., 1991 and Wilschanski *et al*., 1992). On the other hand, this study showed that *al* 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 (Wilschanski *et al*., 1992).

This issue is congruent with other studies (Trouillier *et al*., 2008; Mattoo, 1994 and Harton *et al*., 1984). Decreased in thyroid hormones levels due to low level of albumin, prealbumin, thyroxin binding globulin and high renal excretion of T4, FT4 (Fonseca *et al*., 1991 and Burke and Shakespear, 1976). 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 nephrotic syndrome symptoms or developing anuria confirmed this matter (Fonseca *et al*., 1991; Burke and Shakespear, 1976; Gavin *et al*., 1978 and Feinstein *et al*., 1982). Probably treatment with levothyroxin can cause the stronger effect of corticosteroid (Guo *et al*., 2014; Liu *et al*., 2014 and Kapoor *et al*., 2014). 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 nephrotic syndrome 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 systematic *aly* search hypothyroidism by measuring TSH and free T4 in these patients particularly when proteinuria is prolonged.

Conflict of interest

The authors have no conflicts of interest.

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