

Research Article

Study of thyroid dysfunction in cases of nephrotic syndrome

Nida Muzaffar, Amna Muzafar
and M. Azam Rush

¹Ex-House Officer, Mayo Hospital, Lahore

²woman medical officer, Lahore General Hospital, Lahore

³DHQ Hospital, Chilas

[Received: 25/04/2019; Accepted: 03/07/19; Published: 07/07/2019]

ABSTRACT

Objective: To study the thyroid dysfunction in cases of nephrotic syndrome.

Material and methods: This cross sectional study was conducted at Department of Medicine Mayo Hospital, Lahore from March 2018 to September 2018 over the period of 6 months. Total 39 patients with nephrotic syndrome having age >18 years either male or female were selected for this study. Thyroid dysfunction was assessed in selected patients.

Results: The study included 39 patients with newly diagnosed nephrotic syndrome and 39 controls. When compared to the control group, patients with nephrotic syndrome had significantly higher thyroid stimulating hormone and significantly lower total thyroxine, total triiodothyronine, free thyroxine and free triiodothyronine levels.

Conclusion: The study confirms that significant number of adult patients with NS have abnormalities in thyroid function tests. Most of these abnormalities improve with remission of NS. Anti-TPO antibodies tend to be more common in adult NS patients than control group and those with elevated anti-TPO are more likely to progress to overt hypothyroidism. Hence, all patients with NS who have elevated TSH should be evaluated for anti-TPO and those with elevated anti-TPO should be closely followed-up or replaced with LT4.

Keywords: Nephrotic syndrome, Proteinuria, Hypothyroidism, Anti thyroperoxidase antibodies

INTRODUCTION

Nephrotic syndrome (NS) is a common cause of massive proteinuria and is associated with loss of multiple binding proteins like thyroid binding globulin (TBG), corticosteroid binding globulin and vitamin D binding globulin.^{1,2} Urinary loss of thyroid binding globulin is accompanied with loss of thyroxine (T4) and triiodothyronine (T3).³⁻⁶ This leads to decrease in serum total thyroxine (TT4) and serum total triiodothyronine (TT4) concentrations and increases the demand on thyroid gland to produce more T4. This increased demand is reflected by increase in the elevation of thyroid stimulating hormone (TSH), although not always above the upper limit of normal.^{4,5}

Many studies have documented thyroid abnormalities in children with NS.^{4,7} In children, association of thyroid abnormalities with NS may help to identify the latter condition at an earlier stage. Elevation of TSH in new-born screening programs often leads to diagnosis of congenital NS.^{8,9} However, there is limited data on thyroid abnormalities in adults with NS. More importantly, the natural history of thyroid abnormalities in adult patients with NS is not well studied. It has been documented that abnormalities in thyroid functions could be normalised by LT4 replacement. On the other hand, few studies have

concluded that thyroid abnormalities are transient and does not require replacement with LT4.^{4,11}

Hence, it is not clear whether patients with NS with subclinical hypothyroidism should receive replacement with L-thyroxine. It would be important to know the course of thyroid functions in adult patients with NS and identify any predictors of persistence of hypothyroidism in them. Hence, we have studied the thyroid function abnormalities and predictors of persistence of thyroid abnormalities in adults with NS.

Operational definition:

Nephrotic syndrome:

Nephrotic syndrome was defined as 24-h urinary protein excretion $>3.5 \text{ g}/1.73\text{m}^2$ or spot urinary protein creatinine ratio >2.0 .

MATERIAL AND METHODS

This cross sectional study was conducted at Department of Medicine Mayo Hospital, Lahore from March 2018 to September 2018 over the period of 6 months. Total 39 patients with nephrotic syndrome having age >18 years either male or female were selected for this study. The study was approved by institutional ethics committee and a written informed consent was obtained by all participants. Patients with acute sickness, pregnancy, lactation, diabetes mellitus and previously diagnosed patients with hypothyroidism were excluded from the study. Age and sex matched healthy volunteers constituted the control group.

At diagnosis of NS, all participants were subjected for serum total protein, albumin and globulin, 24-h urinary protein excretion, spot urinary protein creatinine ratio, thyroid function tests including TSH, TT4, TT3, FT3, FT4 and anti-thyroperoxidase antibody (anti-TPO) level. Additional investigations such as renal biopsy, serum complement 3, antinuclear antibody, HBsAg, anti HCV and anti HIV etc were performed as per the standard protocol at our institution to evaluate an adult with new onset NS. All patients received treatment with immunosuppressive drugs as per the standard

protocols. Patients were followed up every 1-3 monthly with spot urinary protein creatinine ratio, serum creatinine and serum albumin and 2-3 monthly with thyroid function tests.

Thyroid function tests, serum creatinine, serum albumin, urinary protein, urinary creatinine were analysed using UnicelDxC 600 Synchron®, Beckman Coulter Ireland Inc. Normal reference range for TSH, TT4, TT3, FT3, FT4 and anti TPO were $0.4\text{-}4.2 \mu\text{IU}/\text{ml}$, $5.5\text{-}11.0 \mu\text{g}/\text{dl}$, $0.94\text{-}180 \text{ ng}/\text{ml}$, $2.5\text{-}3.9 \text{ pg}/\text{ml}$, $0.61\text{-}1.12 \text{ ng}/\text{dl}$ and $9 \text{ IU}/\text{ml}$. All the collected was entered in SPSS version 18 and analyzed. Mean and SD was calculated for numerical data and frequency and percentage was calculated for categorical data.

RESULTS

Thirty nine patients presented with newly diagnosed NS. The mean age of the study population was 34.89 ± 9.14 years and was not significantly different from that of controls ($n=39$).

When compared to the age and sex matched control group, patients with NS had significantly higher TSH and significantly lower TT4, TT3, FT3 and FT4 (Table 1). In NS group, sixteen (41.02%) patients had normal TSH ($0.4\text{-}4.2 \mu\text{IU}/\text{ml}$), four (10.25%) had more than $10 \mu\text{IU}/\text{ml}$ whereas the rest (19, 48.71%) had TSH between 4.2 and $10 \mu\text{IU}/\text{ml}$. Fourteen (35.89%) patients had a low TT4 and nine (23.07%) had low TT3 whereas FT3 was low in four (10.25%) and FT4 was low in three (7.6%) at presentation. In healthy volunteer group, none of the patients had abnormal thyroid function tests. Among NS group, eight patients had elevated anti-TPO whereas only two subjects in the control group had positive anti-TPO ($p=0.3$). None of the patients had TSH $>15 \mu\text{IU}/\text{ml}$ and none were replaced with thyroxine.

Patients with NS were followed-up over a period of 18.3 ± 3.4 months. Eighteen patients had remission of NS at last follow-up whereas the rest had persistence of NS. At last follow-up, TSH was significantly lower whereas TT4, TT3, FT3 and

FT4 were significantly higher when compared to that at diagnosis of NS. There was significant reduction in serum creatinine and spot urinary

protein to creatinine ratio and significant increase in serum albumin in patients with remission of NS (Table 2).

Table 1: Comparison of thyroid function tests between patients with nephrotic syndrome at diagnosis and healthy volunteers.

Variable	Nephrotic syndrome	Controls	P value
Thyroid stimulating hormone (μIU/ml)	7.03±4.21	2.58±0.98	<0.001
Total triiodothyronine (ng/dl)	97.46±10.89	141.28±18.63	<0.001
Total thyroxine (μg/dl)	7.37±1.26	10.09±1.42	<0.001
Free triiodothyronine (pg/ml)	2.69±0.32	3.29±0.36	<0.001
Free thyroxine (ng/dl)	0.85±0.21	1.07±0.12	<0.001
Age (years)	34.89±9.14	34.97±8.31	0.9
Male: Female	18:21	19:20	0.5

Table 2: Comparison of patient characteristics at diagnosis of nephrotic syndrome and at last follow-up.

Variable	At diagnosis of nephrotic syndrome	At last follow-up	P value
Total triiodothyronine (ng/dl)	97.46±10.89	125.33±15.62	<0.0001
Total thyroxine (μg/dl)	7.37±1.26	8.54±1.93	0.002
Free triiodothyronine (pg/ml)	2.69±0.32	2.89±0.37	0.01
Free thyroxine (ng/dl)	0.85±0.21	0.94±0.25	0.01
Thyroid stimulating hormone (μIU/ml)	7.03±4.21	4.34±3.68	0.003
Spot urinary protein/creatinine	7.25±3.23	3.38±3.12	<0.0001
Serum albumin (g/dl)	2.02±0.48	3.11±0.8	<0.0001
Serum creatinine (mg/dl)	1.61±0.38	1.18±0.41	<0.0001
Serum sodium (mEq/l)	133.66±8.27	135.11±7.72	0.42

DISCUSSION

This study reports significantly lower concentration of serum TT4, TT3, FT3 and FT4 and significantly higher concentration of serum TSH in patients with NS when compared with age and sex matched healthy volunteers. Previous studies have demonstrated similar findings.⁴⁻⁷ Studies have also documented significant reduction in serum TBG levels.¹² Decrease in concentration of serum TT4, TT3, FT3, FT4 and TBG levels in patients with NS is due to excessive urinary loss of these substances.³⁻⁶

Urinary loss of serum T4, T3 and TBG levels in turn lead to significant decrease in serum TT3 and TT4 and demands increased production of T4 from the thyroid gland to compensate for the urinary loss of T4 and T3.^{4,5} This in turn increases serum TSH level. In milder cases, increase in TSH compensates to maintain serum FT3 and FT4 level. However, in severe urinary T4 loss, thyroid

gland may not be able to meet for the increasing demand and FT4 level may fall below the normal range. In agreement with this, 58.97% of our patients had elevated TSH whereas only 7.6% of patients had low FT4. However, a larger number of patients demonstrate low serum TT4 level. Compared to 7.2% patients who had lower FT4, higher number (35.89%) of patients had low serum TT4, which is due to concomitant loss of TBG.

The study also evaluated the thyroid functions at last follow-up in all patients and demonstrated that the abnormalities in thyroid function improved in most of the patients with remission of NS. Similar effect of remission of NS on thyroid functions has been reported previously.^{3-5,10} Improvement in thyroid functions of NS patients has also been documented with bilateral nephrectomy which provides a cure for proteinuria and prevents loss of TBG and T4 in urine.¹³

Anti-TPO antibodies tended to be more common in NS patients than in control group. It may be a reflection of underlying autoimmune etiology of NS in these patients. Coexistence of autoimmune hypothyroidism has been described previously with various histological types of nephrotic syndrome, especially with membranous nephropathy.¹⁴⁻¹⁸ In our study, four of 15 patients with membranous nephropathy had elevated anti-TPO antibodies.

Among patients with remission elevated anti-TPO antibody was associated with persistence of hypothyroidism at last follow-up and these patients were initiated on LT4 replacement. Higher rate of progression to overt hypothyroidism in patients with positive anti-microsomal antibodies has been proven previously.¹⁹ Hence, patients with elevated anti-TPO should be closely followed-up for progression of hypothyroidism or initiated on LT4 replacement.

CONCLUSION

The study confirms that significant number of adult patients with NS have abnormalities in thyroid function tests. Most of these abnormalities improve with remission of NS. Anti-TPO antibodies tend to be more common in adult NS patients than control group and those with elevated anti-TPO are more likely to progress to overt hypothyroidism. Hence, all patients with NS who have elevated TSH should be evaluated for anti-TPO and those with elevated anti-TPO should be closely followed-up or replaced with LT4.

REFERENCES

1. Musa BU, Seal US, Doe RP. Excretion of corticosteroid-binding globulin, thyroxine-binding globulin and total protein in adult males with nephrosis: effects of sex hormones. *J ClinEndocrinolMetab.* 1967;27(6):768-74.
2. Grymonprez A, Proesmans W, Van Dyck M, Jans I, Goos G, Bouillon R. Vitamin D metabolites in childhood nephrotic syndrome. *PediatrNephrol.* 1995;9(3):278-81.
3. Fonseca V, Thomas M, Katrak A, Sweny P, Moorhead JF. Can urinary thyroid hormone loss cause hypothyroidism? *Lancet.* 1991;338(8765):475-6.
4. Afroz S, Khan AH, Roy DK. Thyroid function in children with nephrotic syndrome. *Mymensingh Med J.* 2011 Jul;20(3):407-11.
5. Ito S, Kano K, Ando T, Ichimura T. Thyroid function in children with nephrotic syndrome. *PediatrNephrol.* 1994;8(4):412-5.
6. Afrasiabi MA, Vaziri ND, Gwinup G, Mays DM, Barton CH, Ness RL, et al. Thyroid function studies in the nephrotic syndrome. *Ann Intern Med.* 1979;90(3):335-8.
7. Oyemade OA, Lukanmbi FA, Osotimehin BO, Dada OA. Biochemical hypothyroidism in Nigerian children with nephrotic syndrome. *Ann Trop Paediatr.* 1983;3(2):93-6.
8. Finnegan JT, Slosberg EJ, Postellon DC, Primack WA. Congenital nephrotic syndrome detected by hypothyroid screening. *ActaPaediatr Scand.* 1980;69(5):705-6.
9. Dluholucký S, Hornová V, Hudec P, Bucek M, Fukal J, Lukác P. A case of congenital nephrotic syndrome detected during screening for congenital hypothyroidism. *CeskPediatr.* 1982;37(4):203-5.
10. Etling N, Fouque F. Effect of prednisone on serum and urinary thyroid hormone levels in children during the nephrotic syndrome. *HelvPaediatrActa.* 1982;37(3):257-65.
11. Mattoo TK. Hypothyroidism in infants with nephrotic syndrome. *PediatrNephrol.* 1994;8(6):657-9.
12. Trouillier S, Delèvaux I, Rancé N, André M, Voinchet H, Aumaître O. Nephrotic syndrome: don't forget to search for hypothyroidism. *Rev Med Interne.* 2008;29(2):139-44.
13. Chadha V, Alon US. Bilateral nephrectomy reverses hypothyroidism in congenital

- nephrotic syndrome. *PediatrNephrol.* 1999;13(3):209-11.
14. Nishimoto A, Tomiyoshi Y, Sakemi T, Kanegae F, Nakamura M, Ikeda Y, et al. Simultaneous occurrence of minimal change glomerular disease, sarcoidosis and Hashimoto's thyroiditis. *Am J Nephrol.* 2000;20(5):425-8.
 15. Thajudeen B, John SG, Ossai NO, Riaz IB, Bracamonte E, Sussman AN. Membranous nephropathy with crescents in a patient with Hashimoto's thyroiditis: a case report. *Medicine (Baltimore).* 2014;93(8):e63.
 16. Ruiz-Zorrilla LC, Gómez GB, Rodrigo PA, Molina MA. Membranous glomerulonephritis secondary to Hashimoto's thyroiditis. *Nefrologia.* 2010;30(5):595-6.
 17. Akikusa B, Kondo Y, Iemoto Y, Iesato K, Wakashin M. Hashimoto's thyroiditis and membranous nephropathy developed in progressive systemic sclerosis (PSS). *Am J ClinPathol.* 1984;81(2):260-3.
 18. Illies F, Wingen AM, Bald M, Hoyer PF. Autoimmune thyroiditis in association with membranous nephropathy. *J PediatrEndocrinolMetab.* 2004;17(1):99-104.
 19. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly: microsomal antibodies as discriminant for therapy. *JAMA.* 1987;258:209-13.