Hypothyroidism due to nephrotic syndrome: a notable clinical entity

Shuji Fukata, Mitsuru Ito, Mitsushige Nishikawa, Toshihiko Kasahara, Eijun Nishihara, Takashi Akamiuzu and Akira Miyauchi

Center for Excellence in Thyroid Care, Kuma Hospital, Kobe 650-0011, Japan

Abstract. Nephrotic syndrome (NS) is characterized by massive urinary protein leakage and associated hypoproteinemia due to increased protein permeability caused by impaired renal glomerular connections. Although there have been several sporadic reports regarding the relationship between NS and thyroid dysfunction, a consensus has yet to be reached. The mechanism of hypothyroidism in NS is attributed to the loss of protein-bound thyroid hormones, such as thyroxine-binding globulin, transthyretin, and albumin, into the urine. Herein, we report four adults with hypothyroidism that developed or worsened due to the onset of NS. The patients’ underlying thyroid status was post-total thyroidectomy with supplemental levothyroxine (L-T4) in two patients, hypothyroidism with supplemental L-T4 due to Hashimoto’s disease in one patient, and Hashimoto’s disease with normal thyroid function in one patient. Our results suggest that the presence of a reduced thyroid reserve may predispose patients to hypothyroidism in NS. We conclude that NS may cause or exacerbate hypothyroidism. In such cases, an NS assessment, including a urine test, is required.

Key words: Nephrotic syndrome, Hypothyroidism, Hashimoto’s disease

NPHROTIC SYNDROME (NS) is characterized by massive urinary protein leakage and associated hypoproteinemia due to increased protein permeability caused by impaired renal glomerular connections. Besides renal dysfunction, NS is associated with various complications, such as edema, dyslipidemia, coagulopathy, immunodeficiency, and susceptibility to infection [1]. Although there have been several sporadic reports regarding the relationship between NS and thyroid dysfunction, a consensus has yet to be reached. Herein, we report four adult cases in which hypothyroidism developed or worsened with the onset of NS. We discuss the pathogenesis of NS and the need for awareness of this notable clinical entity.

Case Presentation

Case 1: 68 years old female

At 62 years old, the patient underwent total thyroidectomy for papillary thyroid carcinoma. Thereafter, she took levothyroxine (L-T4) 125 μg/day, and her serum TSH level was under normal control with semi-annual follow-up. At the age of 68, her serum TSH level increased to 56.40 μU/mL (ECLusys; Roche Diagnostics GmbH, Mannheim, Germany, reference value, 0.5–5.0) despite good adherence to medication. Thereafter, the L-T4 dose was increased to 150 μg/day, but the patient’s serum TSH level remained elevated at 42.30 μU/mL, and the dose was further increased to 200 μg/day. Eight months later, her serum TSH level recovered to its original value. Upon examination, the patient had significant indented edema of the lower legs, and thyroid function with L-T4 200 μg/day was as follows: TSH, 0.411 μU/mL; free thyroxine (FT4), 1.45 ng/dL (ECLusys; Roche Diagnostics GmbH, Mannheim, Germany, reference value, 0.9–1.7); and free triiodothyronine (FT3), 1.93 pg/mL (ECLusys; Roche Diagnostics GmbH, Mannheim, Germany; reference value, 2.3–4.0). Serum albumin level decreased, and serum total cholesterol level increased [2.9 g/dL (3.8–5.2) and 266 mg/dL (120–220), respectively] (Fig. 1A). Renal function was mildly deteriorated (serum creatinine, 1.65 mg/dL [0.5–1.3] mg/dL, estimated glomerular filtration rate [eGFR]: 24.6 [>60] mL/min/1.73 m²), and HbA1c was markedly elevated at 10.2% (4.6–6.2). Furthermore, urinary protein significantly increased to 21.1 g/g Cr (<0.15). Therefore, we diagnosed NS secondary to diabetic nephropathy. In this case, urinary thyroid hormone and thyroxine binding
globulin (TBG) levels were measured. Urinary $T_4$ (ECLusys; Roche Diagnostics GmbH, Mannheim, Germany) was 5.09 μg/dL and $T_3$ (ECLusys; Roche Diagnostics GmbH, Mannheim, Germany) was 2.24 ng/mL. The urine creatinine concentration was 99.8 mg/dL, and the creatinine index, corrected by creatinine, was 51 μg/g Cr for $T_4$ and 2.2 μg/g Cr for $T_3$. The urinary TBG was 8.0 μg/mL (Immulite 2000 XPi; Siemens, Tarrytown, NY, USA).

**Case 2: 64 years old male**

Since the age of 52, the patient had been treated with L-T$_4$ for hypothyroidism caused by Hashimoto’s disease; his thyroid function was stable for 11 years with L-T$_4$ 175μg/day. At the age of 64, he visited our clinic because of weight gain and swelling of the lower limbs that appeared in approximately 10 days. The serum TSH level was 58.0 μU/mL, the serum FT$_4$ was 0.79 ng/dL, indicating exacerbation of hypothyroidism, and the serum total cholesterol level was markedly elevated at 463 mg/dL, and the serum albumin level was markedly low at 1.1 g/dL. Urinary protein was 4+ in the qualitative test, and the patient was diagnosed with NS and referred to the Department of Nephrology at another hospital. Urine protein quantification increased to 9.85 g/g Cr, and renal biopsy revealed primary NS due to focal segmental glomerulosclerosis. Steroid pulse therapy was initiated, followed by administration of immunosuppressive drugs. After remission of NS, the patient revisited our outpatient clinic; L-T$_4$ was continued at 250 μg/day, and the thyroid function was thyrotoxic: TSH 0.038 μU/mL, FT$_4$ 3.68 ng/dL, and FT$_3$ 1.43 pg/mL. The dose of L-T$_4$ was reduced to 150 μg/day, and thyroid function normalized after one month (Fig. 1B).

**Case 3: 43 years old female**

The patient underwent total thyroidectomy at 20 years old due to multiple endocrine neoplasia type 2A (MEN 2A). She was given supplemental LT$_4$ 100 μg/day and
remained euthyroid. At the age of 43, edema of the face and lower limbs appeared; 2 weeks later, the patient was admitted to a local hospital. At the time of admission, her serum albumin level was markedly low at 0.9 g/dL, and her urinary protein level increased significantly to 6.8 g/gCr. Renal biopsy confirmed the diagnosis of minimal change in NS. At the time of admission, thyroid function was deteriorating with TSH 239.7 μU/mL and FT₄ 0.57 ng/dL, and the L-T₄ dose was increased to 150 μg/day. NS remitted with steroid pulse therapy, and thyroid function gradually improved with recovery from NS. The dose of L-T₄ was reduced to 100 μg/day, and thyroid function normalized (Fig. 1C).

**Case 4: 37 years old female**

The patient was diagnosed with chronic thyroiditis with normal thyroid function at 31 years old, and had since been undergoing follow-up examinations at our clinic once a year. At the age of 37, she was diagnosed with edema in the dorsum of both feet for two weeks, and visited a local doctor, who determined that she had hypothyroidism and referred her to our hospital. Thyroid function tests were performed, and the patient was found to be hypothyroid: TSH 61.700 μU/mL (ARCHTECT i2000; Abbott Japan, Tokyo, reference value 0.3–5.0), FT₄ 0.57 ng/dL (0.7–1.6). Although 50 μg/day of L-T₄ was initially prescribed, the edema did not improve, and the patient returned to our clinic one month later. Thyroid function improved slightly to TSH 14.60 μU/mL and FT₄ 0.85 ng/dL, but there was significant indented edema in the lower leg. Serum total cholesterol level was elevated to 286 mg/dL, and serum albumin level was markedly low at 1.2 g/dL. A qualitative test for urinary protein was 4+, indicating NS, and the patient was admitted to the nephrology department the following day. The daily proteinuria was 3.87 g/day. A renal biopsy showed NS secondary to lupus nephritis. Steroid therapy was initiated, the NS went into remission, L-T₄ medication was stopped, and thyroid function returned to normal (Fig. 1D).

**Discussion**

There have been several sporadic reports regarding the relationship between NS and thyroid dysfunction. In 1979, Afrasiabi et al. assessed thyroid function in seven adult patients with NS and reported no difference in serum TSH and FT₄ levels compared with controls [2]. Feinstein et al. also studied thyroid function in 15 adult patients with primary NS with normal GFR and without thyroid disease, and found that approximately half had decreased serum total T₃ and total T₄ levels, presumably due to urinary loss of thyroid hormone binding proteins, such as TBG, transthyretin (TTR), and albumin; however, serum FT₄ and TSH levels were normal and there was no need for treatment with thyroid hormones [3]. Additionally, several reports have documented worsening thyroid function with the onset of NS in children [4] and adults [5]; however, few studies have reported an association between proteinuria and elevated TSH in NS patients [6].

Approximately 75% of serum T₄ is bound to TBG, 20% to TTR, and the remaining 5% to albumin [7]. Since the molecular weight of TBG is 54 kDa, smaller than that of albumin (66.5 kDa), it is rational to assume that thyroid hormones can be lost into urine together with TBG when urinary protein increases in NS. In the present case 1, urinary T₄ was 51 μg/g Cr and urinary T₃ was 2.2 μg/g Cr, suggesting that a significant amount of T₄ and T₃ was lost into urine daily. Considering that the daily production of thyroid hormones in normal subjects is 85 μg/day for T₄ and 6.5 μg/day for T₃ [8], it is believed that hypothyroidism can be easily exacerbated by NS in a state where the thyroid gland has no or limited reserve of hormones. Regarding the mechanism of urinary excretion, TBG in urine was 14.8 nmol/dL in case 1. There is only one T₄ binding site in one TBG molecule, and approximately 20% of TBG binding sites in the blood are occupied by T₄ [7]. Therefore, the amount of T₄ excreted into urine with TBG in case 1 was calculated to be 2.3 μg/dL (14.8 nmol × 0.2 × 777 (molecular weight of T₄) ÷ 1.000 = 2.3 μg). The actual urinary T₄ level was 5.09 μg/dL, thus it is estimated that approximately 45% of the T₄ was excreted in the urine with TBG excretion, and the rest was excreted bound to TTR and/or albumin. However, such differences in the excretory mechanism with the type of binding proteins may depend on differences in renal tissue changes in individual NS patients.

With regards to the relationship between renal diseases, such as NS with high protein excretion in urine and thyroid function, thyroid function has been reported to worsen when urinary protein levels increase. Gilles et al. studied 159 thyroid peroxidase-negative patients who excreted large amounts of protein in their urine [9]. Serum TSH levels were elevated compared to controls, but serum FT₄ levels did not differ from those in the controls. Recently, a large cohort study reported that the risk of hypothyroidism was directly related to the amount of urinary protein excreted in patients with proteinuria [10]. However, the details regarding underlying thyroid disease and the presence of anti-thyroid autoantibodies were not examined in that study [11].

There have been some reports on the development and exacerbation of hypothyroidism in adult patients with NS [3, 12-15]. In most of these reports, hypothyroidism, due to Hashimoto’s disease, total thyroidectomy for Graves’
disease, radioiodine treatment for Graves’ disease, or lobectomy for benign nodules, existed as an underlying disease before the onset of NS. In the present report, the underlying thyroid diseases were post-total thyroidectomy, hypothyroidism due to Hashimoto’s disease, and Hashimoto’s disease with normal thyroid function.

Considering the changes in thyroid function when $T_4$ and $T_3$ are excreted in the urine together with TBG, TTR, and albumin, if the loss of $T_3$ is relatively mild, it can be offset by the decrease in serum total $T_4$ to maintain a stable level of $FT_4$. This leads to a decrease in the $T_4$ content and, therefore, leads to a decrease in the requirement for the whole body, and thyroid function can remain normal. When the $T_3$ loss becomes more severe, it becomes subclinical hypothyroidism in which serum $FT_4$ levels remain normal due to the compensatory mechanism of elevated serum TSH levels. In even more severe cases of NS, the compensatory mechanism of TSH is no longer effective, resulting in overt hypothyroidism. In this instance, hypothyroidism is more likely to occur when the thyroid reserve is decreased due to underlying diseases, such as Hashimoto’s thyroiditis. Moreover, this change is particularly important in patients undergoing radiiodine therapy for Graves’ disease or after total thyroidectomy, as thyroid tissue is abolished and $L-T_4$ replacement is essential. Hypothyroidism, if present, can have a significant negative impact on the pathogenesis of NS, leading to more severe complications and increased mortality. Therefore, in such cases, appropriate measures, such as increasing the dose of $L-T_4$, should be taken after diagnosis by rapid examination, including urinalysis, along with thyroid function [16-18].

Thus, although there is a close relationship between NS and hypothyroidism, the American Thyroid Association’s guidelines for the treatment of hypothyroidism provides only the statement accessory to “Weak recommendation, low-quality evidence” that “In patients with NS, increased $L-T_4$ requirements can occur due to massive thyroid hormone loss along with massive amounts of protein, including TBG, TTR, and albumin,” and does not provide clear medical guidelines [19]. Furthermore, recent NS guidelines in Japan mention little regarding thyroid function [1].

Generally, if hypothyroidism is exacerbated in hypothyroid patients treated with $L-T_4$, nonadherence to medication and impaired absorption are the most common causes, but it should be noted that the onset of NS may also be the cause. Particularly in patients with absent or reduced thyroid autoregulation, such as in patients who underwent total thyroidectomy or patients taking thyroid hormones for hypothyroidism, NS should be considered as one of the causes; which should be tested with a simple urinalysis. In future, it will be necessary to study this condition in more detail and formulate guidelines regarding its treatment.

In this case report, there are certain limitations. Urinary thyroid hormone and TBG levels were measured in only one case. Such a detailed study needs to be performed in the future in $L-T_4$-treated patients with reduced or absent thyroid reserve, such as those with Hashimoto’s thyroiditis or after total thyroidectomy.

In conclusion, we report four adult cases of hypothyroidism that appeared or worsened with the onset of NS in patients with underlying thyroid diseases. It is important to note that NS is one of the causes of hypothyroidism, as it can cause or exacerbate hypothyroidism due to the loss of thyroid hormones in the urine. Moreover, if hypothyroidism worsens in a patient who is stable and on replacement therapy with $L-T_4$ for hypothyroidism, it is necessary to investigate for the presence of NS and other causes, such as medication adherence and malabsorption, before increasing the dose of $L-T_4$. This is especially crucial in patients who lack the hormone-producing capacity of the thyroid gland after total thyroidectomy or radioiodine treatment.

**Informed Consent**

The present case report was approved by the Ethical Committee at Kuma Hospital, and all patients provided informed consent.

**Acknowledgments**

We would like to thank Dr. Shiro Shakutsui, Tomotaka Naka, Yuuki Yokoyama, and Midori Kitayama for the treatment of NS patients.

**Disclosure Statement**

None of the authors have any potential conflicts of interest associated with this research.

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