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Nephrotic Syndrome As A Cause Of Transient Clinical Hypothyroidism

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Abstract
Nephrotic syndrome may trigger the onset of hypothyroidism, promoting massive urinary protein losses including thyroxine (T4) and triiodothyronine (T3) along with their binding proteins. However, in patients with prolonged and severe proteinuria, especially with concomitant low thyroid reserve, urinary losses of free and protein-bound thyroid hormones are sufficiently pronounced to induce a subclinical or overt hypothyroidism.
We reported a case of a 25-year-old man with previous normal thyroid function who developed overt hypothyroidism due to a severe nephrotic syndrome, requiring supplementation with levothyroxine (LT).

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I. Introduction

Nephrotic syndrome (NS) is one of the most common glomerular diseases and is classically characterized by massive proteinuria (>3.5 g/24 hours), hypoalbuminemia, edema, and hyperlipidemia. Associated excessive urinary protein excretion, justified by marked increase in the glomerular permeability to macromolecules, results in urinary losses of thyroid hormone-binding proteins (thyroxine binding globulin (TBG), transthyretin, and albumin), as well as thyroid hormones (thyroxine (T4) and triiodothyronine (T3) usually bound to them. Additionally, injury of renal tubules can coexist and compromise the reabsorption of free thyroid hormones.(5)

In early stages of the disease, especially when there is no prior history of thyroid disorder, levels of physiologically crucial free T3 (fT3) and T4 (fT4) remain normal and a clinical and biochemical euthyroid state is expected. However, in patients with prolonged and severe proteinuria and with low thyroid reserve, urinary losses of free and protein-bound thyroid hormones are sufficiently pronounced to induce an increase in thyroid-stimulating hormone (TSH) values resulting in subclinical or overt hypothyroidism.(1, 2, 3)

II. Case Report

A 25-year-old man was evaluated for mild asthenia and generalized edema with swelling of the face, abdomen, and lower limbs over the preceding two weeks.The physical examination showed the presence of an exuberant edema of the legs and abdominal wall. His weight was 60 kg, corresponding to a weight gain of 13% in a 3-month period. No evidence of heart failure was noted.

Urinalysis was positive for proteinuria of 1860 mg/dL (reference range (RR): 0-14 mg/dL), with a protein-to-creatinine ratio of 560 mg/mg (RR: 15-68 mg/mg). Blood tests revealed hypoproteinemia of 3.4 g/dL (RR: 6.4–8.3 g/dL), hypoalbuminemia of 1.6 g/dL (RR: 3.5–5.5 g/dL), and hyperlipidemia (triglycerides: 686 mg/dL (RR: 40–160 mg/dL) and total cholesterol: 400 mg/dL (RR: 0–200 mg/dl). Liver function tests were normal, and renal depuration was preserved (serum creatinine: 0.8 mg/dL (RR: 0.6–1.3 mg/dL); an estimated glomerular filtration rate of 56 mL/min/1.73 m2, according CKD-EPI equation). At this point, the serum TSH level was 9.06 µUI/mL (RR: 0.30–5.0) T3 was 0.7 ng/mL (RR: 0.6-1.8 ng/mL) and T4 was 2.32 ug/dL (RR: 4.5-12.6 ug/dL). Renal ultrasound (US) showed grade 1 bilateral renal parenchymal disease.

A high dose of glucocorticoid (prednisolone) was initiated, with cyclophosphamide being added to the therapy strategy and patient recovered with generalised swelling.

The diagnosis of clinical hypothyroidism secondary to nephrotic syndrome was assumed, although a possible contribution of euthyroid sick syndrome on thyroid hormone levels was considered. The patient was started on oral LT treatment 50 µg daily.

After 3 months of starting the treatment, swelling decreased and thyroxine (LT) dose was decreased to 25 µg. T3 was 1.6 ng/mL, T4 was 7.6 ng/mL and TSH was 6.2 µUI/mL. Cyclophosphamide was stopped and prednisolone was decreased. After follow up for another 2 months, thyroxine (LT) was stopped.

III. Discussion

Thyroid hormones, T3 and T4, are both poorly soluble in water, and more than 99.5% circulate in the blood bound to proteins: approximately 70% bound to TBG, 20% to albumin, and 10% to prealbumin. However, only the low levels of free hormones are metabolically active at the tissues and responsible for all thyroid functions.(6)

Under normal conditions, urinary protein losses are insignificant. In NS, on the other hand, there is massive urinary protein losses, including T3 and T4 along with their binding proteins and, to a lesser extent, the free fractions fT3 and fT4 (1, 2, 3). In early stages of the disease or in milder clinical conditions, serum free hormone levels remain normal and the patient is in euthyroid state. In more prolonged situations with worsening of proteinuria and hypoalbuminemia, and especially when associated with a low thyroid reserve, fT3 and fT4 are also significantly reduced and overt hypothyroidism may occur.(2)

In a study with 317 patients who had been definitively diagnosed with NS, it was proved that high levels of urinary proteins and serum creatinine were independent risk factors for predicting thyroid dysfunction, while a higher level of plasmatic albumin was an independent protective factor.(3) Likewise, some published clinical cases have shown that NS may be the cause behind the increased requirements of LT in patients previously diagnosed with hypothyroidism.(5)

The clinical hypothyroidism was triggered by significant urinary losses of hormones and their binding proteins, requiring LT replacement. Corticosteroids could promote thyroid dysfunction by their suppressive effect on serum TSH levels, impairment of peripheral conversion of T4 in T3, and the decrease of TBG production.(4)

In addition to NS, cases of reversible proteinuria and biopsy-proven glomerulonephritis (GN) including membranous nephropathy, minimal change, membranoproliferative GN, amyloidosis, and IgA nephropathy have been reported in association with hypothyroidism, mainly if autoimmune thyroiditis has been present.(1)

Consent

Informed written consent was obtained from the patient, although no patient identifiable data were included in this case report.

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