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ORIGINAL ARTICLE

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Bilateral nephrectomy reverses hypothyroidism in congenital nephrotic syndrome

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Abstract A state of biochemical hypothyroidism is commonly seen in infants with congenital nephrotic syndrome (NS) and therefore the current recommendation is to place all patients with congenital NS on supplemental thyroid preparations. We report our experience in five children with congenital NS in whom thyroid supplementation was discontinued following bilateral nephrectomy and initiation of renal replacement therapy. Immediately after nephrectomy, thyroid function tests normalized, except serum thyroid-stimulating hormone (TSH) concentration, which initially rose, but normalized later. This observation supports the hypothesis that hypothyroidism in these patients is secondary to the chronic massive proteinuria and is not the result of a defect intrinsic to the thyroid gland itself. Abatement of massive proteinuria enables discontinuation of thyroid supplementation, and a transient rise in TSH in the early post-nephrectomy stage should be potentially expected.

Key words Congenital nephrotic syndrome · Hypothyroidism · Nephrectomy · Thyroid function tests

Introduction

Patients with nephrotic syndrome (NS) usually demonstrate alterations of their thyroid hormone indices [1–7]. Most of the studies have observed a reduction in serum concentrations of thyroid-binding globulin (TBG), total thyroxine (T_4), total tri-iodothyronine (T_3), and an increase in T_3 resin uptake; however the basal thyroid-stimulating hormone (TSH) concentration and the peak TSH response to thyrotropin-releasing hormone were within normal range [3]. The free thyroxine (FT_4) concentrations were either normal or elevated [1, 3]. These disturbances have been attributed to the increased urinary losses of T_3, T_4, TBG, and FT_4, which positively correlate with the degree of proteinuria [1, 6, 7]. It is likely that these patients remain euthyroid, despite the evidence of biochemical thyroid disease, due to the fact that the normal thyroid gland is able to compensate for these excessive urinary losses and maintain normal serum FT_4 and TSH concentrations.

McLean et al. [4] reported elevated serum TSH and low T_4 in four of five patients with congenital NS, and a positive response to T_4 substitution. They speculated a combination of urinary losses, malnutrition, and depleted iodine state as possible causes of hypothyroidism in these patients. Their findings were later corroborated by Mattoo [5]. Consequently, as recommended by Holmberg et al. [8], the current standard of care is to treat all newly diagnosed patients with congenital NS with supplemental thyroid preparation. With current advances in nutrition and renal replacement therapy, most children with congenital NS can anticipate an expanded life span. However, the outcome of their thyroid function status following nephrectomy, dialysis, and transplantation has not been yet defined, as four of the five patients reported by McLean et al. [4] died by the age of 16 months. We report our experience on the thyroid function of five patients with congenital NS, who underwent nephrectomy and were placed on renal replacement therapy.

Case reports

The clinical data of the five patients [four with Finnish type NS and one with Drash syndrome (male pseudohermaphroditism, nephropathy, and Wilms tumor)] are summarized in Table 1. All patients had massive proteinuria, hypoalbuminemia, and edema. Except for the patient with Drash syndrome, who was nephrectomized shortly after his diagnosis, the other four children were treated according to the protocol recommended by Holmberg et al. [8], with daily intravenous albumin infusion, high protein and calorie intake, anticoagulants, and numerous nutritional supplements and medications. All patients received levo-thyroxine (25–62.5 μg/day); the dose was adjusted according to the TSH levels and discontinued after bilateral nephrectomy. Following bilateral nephrectomy all patients were placed on peritoneal dialysis, except for patient no. 3, who received a pre-emptive living-related (LR) kidney transplant. Currently all but patient no. 1 have well-

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Table 1 Summary of case histories of five children with congenital nephrotic syndrome

Patient no.	Current age	Sex	Diagnosis	Presenting age	Age at nephrectomy	Summary
1	6 years 10 months	M	Finnish type	6 weeks	11 months	Two LR transplants at ages 23 and 32 months, rejected both. Currently on hemodialysis
2	5 years 2 months	F	Finnish type	6 weeks	17 months	LR renal transplant at age 22 months. Current SCr 0.8 mg/dl. Urine protein negative
3	4 years 11 months	M	Finnish type	2 weeks	32 months	LR renal transplant at time of bilateral nephrectomy. Current SCr 1.0 mg/dl. Urine protein negative
4	2 years 1 month	F	Finnish type	2 days	14 months	LR renal transplant at age 23 months. SCr 0.7 mg/dl. Urine protein negative
5	3 years 8 months	M	Drash syndrome	10 months	10 months	LR renal transplant at age 22 months. Current SCr 0.7 mg/dl. Urine protein negative

LR, Living-related; SCr, serum creatinine

Table 2 Thyroid function tests before and during treatment with thyroid supplementation, and after discontinuation of therapy upon bilateral nephrectomy[a]

Patient. no.		TSH (0.4–5.5 μIU/ml)	T_4[b]	FT_4 (0.8–1.9 ng/dl)	FTI (1.1–3.9)
1	Presupplement	11.6	3.3	–	0.8
	On levo-thyroxine	4.3	0.6	–	0.2
	Postnephrectomy	9.9	9.4	–	2.7
	Later (5 years)	3.8	10.1	–	–
2	Presupplement	8.8	2.0	–	0.8
	On levo-thyroxine	2.4	2.9	–	1.37
	Postnephrectomy	9.2	9.4	–	3.2
	Later (2 months)	3.3	10.5	–	3.0
3	Presupplement	5.0	3.34	–	1.5
	On levo-thyroxine	2.1	6.3	–	2.0
	Postnephrectomy	11.0	–	–	1.5
	Later (2 years)	0.51	6.79	–	–
4	Presupplement	24.0	4.1	–	–
	On levo-thyroxine	4.46	2.0	1.0	–
	Postnephrectomy	24.7	6.8	1.2	–
	Later (3 months)	4.3	12.7	1.4	–
5	Presupplement	6.5	–	–	–
	On levo-thyroxine	–	–	–	–
	Postnephrectomy	8.6	6.9		2.4
	Later (6 months)	3.2	12.7	1.6	3.8

TSH, Thyroid-stimulating hormone; T4, total thyroxine; FT4, free thyroxine; FTI, free thyroxine index

[a] Reference values in parentheses

[b] Reference values for T_4 (μg/dl): 0–3 days, 8.2–19.9; 3 days to 1 month, 6.0–15.9; 1–12 months, 6.1–14.9; 1–3 years, 6.8–13.5; 3–10 years, 5.5–12.8

functioning LR kidney transplants. In all patients diagnosis was confirmed by histological examination of renal tissue.

Analyses of TSH, T_4, and FT_4 were performed using Immulite (Diagnostic Products, Los Angeles, Calif., USA) on an automated, random-access immunoassay analyzer with a solid-phase washing process and a chemiluminescent detection system. Thyroid studies before starting treatment with levo-thyroxine, while on therapy, after nephrectomy (1–6 weeks), and later (2 months to 5 years) are shown in Table 2. All five infants had an elevated initial TSH value and four had decreased T_4 levels (not measured in patient no. 5). The free thyroxine index (FTI), which is an indirect estimate of FT_4, was low in two (nos. 1 and 2) of the three infants in whom it was measured. Following institution of levo-thyroxine therapy, the TSH levels returned to and remained within the normal range. The T_4 values were still low (patients 1, 2 and 4), but FT_4 (or FTI) levels were mostly normal during this period (patients 2, 3, and 4). As patient 5 received T_4 therapy only for a few days before undergoing bilateral nephrectomy, thyroid studies were not performed while he was receiving T_4.

In the immediate post-nephrectomy period, T_4 and FT_4 (or FTI) normalized, but TSH levels increased before decreasing into the normal range after a few weeks to months. During the subsequent follow-up, the thyroid hormone indices of these patients have all remained normal.

Discussion

In addition to its four classic components of massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia, NS is often associated with other perturbations in body

homeostasis. Those may include depletion of serum IgG, antithrombin III, transferrin, TBG, and other proteins lost in the urine concomitantly with albumin [9]. Although the loss of TBG causes some alterations in biochemical markers of thyroid function, it usually does not cause a true state of hypothyroidism, as serum FT_4 concentration remains normal and consequently so does TSH [1, 3]. However, in infants with congenital NS who already have severe on-going massive proteinuria in utero, urinary losses of FT_4 are so extensive that they result in stimulation of the hypothalamic-pituitary axis with an elevation of TSH values. Our findings confirm those of McLean et al. [4] and Mattoo [5] of uniformly elevated TSH levels in infants with congenital NS, in some of whom we detected the abnormality at a very young age (Table 1). The elevation of TSH levels seen in the face of normal serum FT_4 concentrations are indicative of early thyroid failure and, therefore, by themselves indicate the need for treatment [10]. Treatment of these infants with thyroid supplement normalized FT_4 and TSH levels may have contributed to their normal development when combined with the rest of the protocol outlined by Holmberg et al. [8]. Interestingly, following discontinuation of thyroid supplementation our patients demonstrated a transient, but significant elevation of their serum TSH concentration, despite normal concentrations of T_4 and FT_4 (or FTI) (Table 2). This can possibly be attributed to suppression of the thyroid gland by levo-thyroxine, with the thyroid gland requiring several weeks to fully recover its function [10].

The condition of the thyroid gland in patients with NS in general, and in those with congenital NS in particular, somewhat resembles the situation of mineral homeostasis in NS. It is now well established that vitamin D-binding protein is lost in the urine and with it significant amounts of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$] [11, 12]. However, serum ionized calcium and parathyroid hormone (PTH) concentrations are normal due to maintenance of a normal concentration of serum free $1,25(OH)_2D_3$. Some patients, and especially those with more-severe and prolonged proteinuria, develop hypocalcemia, hyperparathyroidism, and metabolic bone disease after their free $1,25(OH)_2D_3$ is depleted. These patients, when treated with vitamin D, normalize their serum ionized calcium and PTH concentrations [13], similar to the observed normalization of thyroid function tests following thyroid supplementation in those nephrotic patients with elevated TSH. Although no information is currently available regarding the status of mineral metabolism in infants with congenital NS, the protocol of Holmberg et al. [8] calls for supplementation with vitamin D and calcium.

The fact that both T_4 and FT_4 levels returned to and remained within the normal range after the kidneys were removed supports the notion that hypothyroidism in congenital NS is secondary to urinary losses of the hormone, and is not due to a primary abnormality of the thyroid gland itself. Pomeranz et al. [14] recently reported success in diminishing proteinuria in two patients with congenital NS by the use of captopril and indomethacin. It will be of importance to learn whether this maneuver might also normalize thyroid function tests.

In summary, we confirm that infants with congenital NS are usually hypothyroid and benefit from thyroid supplement therapy. Our new observation is that following bilateral nephrectomy thyroid supplementation can be discontinued, as the underlying cause for the hypothyroidism is reversed. In the first few weeks after nephrectomy a transient elevation of TSH should be anticipated.

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