Nephrol Dial Transplant (2012) 27: 2171–2175
doi: 10.1093/ndt/gfr665
Advance Access publication 13 December 2011

Short Communication

NDT
Nephrology Dialysis Transplantation

Hypothyroidism in children with steroid-resistant nephrotic syndrome

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Abstract

Background. Non-autoimmune hypothyroidism has been reported in children with congenital nephrotic syndrome. The hypothyroid state was attributed to massive prolonged thyroid hormone loss. However, this endocrine abnormality has not been reported in steroid-resistant nephrotic syndrome (SRNS) despite similar long-standing proteinuria.

Method. We describe all the patients with SRNS in our clinic's follow-up who developed non-autoimmune hypothyroidism.

Results. Five children aged 3-11 years at diagnosis of SRNS and followed for 5-42 months developed hypothyroidism (depressed free thyroxin and elevated thyrotropin levels) without evidence of autoimmune thyroiditis. The diagnosis of hypothyroidism was not temporarily related to disease duration or renal function. The disease was resistant to all therapies, renal function deteriorated in all the patients within 1.5-14.5 years from diagnosis. Despite thyroxine treatment and a decline in renal function, thyroid hormone level normalized only after reaching end stage renal disease (ESRD) and hemodialysis start. Nephrotic syndrome recurrence after kidney transplantation (in three patients with focal segmental glomerulosclerosis) was not accompanied by recurrent hypothyroidism.

Conclusion. It is our impression that non-autoimmune hypothyroidism is a potential significant complication of SRNS, and should be actively sought for especially in cases with renal function deterioration. Hypothyroidism usually resolved when these patients reach ESRD. The incidence and pathogenesis of this condition require further study.

Keywords: hypothyroidism; nephrotic syndrome; steroid resistance

Introduction

Patients with nephrotic syndrome have a variable thyroid hormone profile. Although total T4 and T3 may be low secondary to urine loss of thyroxine-binding globulin, serum levels of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) are usually normal, so patients are considered to be euthyroid [1]. Accordingly, Feinstein *et al.* [2] reported a normal thyroid profile in 15 adults with nephrotic syndrome and normal renal function. In a study of seven children, Ito *et al.* [3] noted a decrease in FT4 and increase in TSH levels during exacerbation of nephrotic syndrome, which normalized during remission. Fonseca *et al.* [4] reported a correlation between urinary loss of T4 and low serum FT4 in 10 patients with nephrotic syndrome. Additionally, in two of the four adults with hypothyroidism requiring thyroxine replacement therapy, the hypothyroidism resolved when the nephrotic syndrome remitted.

Infants with Finnish-type congenital nephrotic syndrome, characterized by long-standing massive proteinuria, are known to acquire hypothyroidism as part of the disease [1, 5, 6]. Surprisingly, however, the thyroid status in children with long-standing proteinuria due to steroid-resistant nephrotic syndrome (SRNS) has not been examined.

Case reports

We describe five patients with SRNS who were diagnosed with hypothyroidism during the disease course. All were under follow-up within the last 10 years at a nephrology clinic of a tertiary medical center. In all cases, the SRNS progressed to end-stage renal disease (ESRD) requiring dialysis (Tables 1 and 2).

The patients are described in the order of their presentation at the clinic. Patients 1, 2 and 4 have already undergone deceased donor kidney transplantation and the others are on the waiting list and being treated with hemodialysis.

Patient 1

A 7.5-year-old girl with newly diagnosed nephrotic syndrome was treated with prednisone 60 mg/m^2/day. Two months after remission was achieved, the disease relapsed and proved resistant to the same therapy. Kidney biopsy revealed focal segmental glomerulosclerosis (FSGS). Patient complaints of fatigue, non-specific pain and hair loss prompted a complete workup including thyroid hormone profile. The results showed a high-normal TSH level of 3.8 mIU/L (normal range 0.4–4) and a depressed FT4 level of 5.7 pmol/L (normal range 11.7–28). At that time, the patient had proteinuria of 4.3 g/day

Table 1. Background data and clinical course of SRNS in five patients with a complication of non-autoimmune hypothyroidism[a]

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis of nephrotic syndrome (years)	7.5	3	3.5	11	7.5
Sex	Female	Female	Female	Male	Female
Histopathologic diagnosis	FSGS	FSGS	FSGS	DMP	FSGS
Age at dialysis (years)	11	18.5	10.5	12.5	9
Age at transplantation (years)	12	19[b]	Still on HD	15	Still on HD

[a]DMP, diffuse mesangial proliferation; HD, hemodialysis; FSGS - focal segmental glomerulosclerosis.
[b]The graft was rejected after 2 years due to poor compliance; the patient is currently on hemodialysis.

Table 2. Thyroid profile and course of hypothyroidism in five children with SRNS[a]

Thyroid hormone profile	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Thyroid hormone profile at diagnosis of nephrotic syndrome, TSH (mIU/L)/FT_4 (pmol/L)[b]	ND	ND	2.8/15.3	2.5/15.8	3.0/12.4
Time from onset of nephrotic syndrome to diagnosis of hypothyroidism (months)	4	134	6.5	12	9
Thyroid hormone profile at hypothyroidism diagnosis, TSH (mIU/L)/FT_4 (pmol/L)	3.8/5.7	9.9/9.4	5.5/9.4	6.9/8.5	6.9/7
Anti-Tg/anti-TPO/TSH-R (mIU/L)	Negative	Negative	Negative	Negative	Negative
Serum creatinine at diagnosis of hypothyroidism (mg/dL)	0.8	0.6	0.5	2.3	0.73
Proteinuria at diagnosis of hypothyroidism (g/day)	4.3	6.2	6	4	5.5
Average weekly thyroxine dose during active nephrotic syndrome (mcg)	262	425	425	325	275
Time from diagnosis of hypothyroidism to ESRD (months)	36	42	10	5	7
Average weekly thyroxine dose during dialysis (mcg)	175	175	150	150	150
Time from dialysis onset to hypothyroidism resolution (years)	2	0.4	2	0.5	0.5

[a]Tg, thyroglobulin; TPO, thyroid peroxidase; TSH-R, TSH receptor.
[b]TSH normal range, 0.4–4 mIU/L; FT_4 normal range, 10.5–25.7 pmol/L.

and normal renal function. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative. Thyroid sonogram was normal. Treatment with thyroxine at a weekly dose of 175–350 mcg led to an improvement in thyroid hormone levels (TSH, 2.5–7.2 mIU/L; FT4, 7–15 pimol/L). The proteinuria was resistant to corticosteroids, cyclosporine and angiotensin-converting enzyme (ACE) inhibitor.

Renal function began to deteriorate 2.5 years after diagnosis and progressed to ESRD 1 year later. The patient was treated with peritoneal dialysis for 1 year, during which time the thyroid hormone profile normalized under low doses of thyroxine replacement (175 mcg/week). At age 12 years, the patient underwent deceased donor kidney transplantation. FSGS recurred immediately in the graft and was treated with plasmapheresis and cyclophosphamide along with corticosteroids and cyclosporine. Despite preserved graft function, significant proteinuria (up to 2.5–4 g/day) persisted. Nevertheless, thyroid function remained normal and thyroxine therapy was slowly discontinued.

At the latest follow-up, 8 years after kidney transplantation, serum creatinine was stable at 1.2 mg%; proteinuria was 2.5 g/day and thyroid hormone profile was within normal range.

Patient 2

A 3-year-old girl presented at another pediatric nephrology clinic with nephrotic syndrome. The disease proved resistant to initial treatment with prednisone 60 mg/m^2. Subsequent kidney biopsy revealed FSGS. Eight weeks of treatment with cyclophosphamide led to remission. The parents decided to stop all therapy after 3 months, and for the next 8 years, the patient was asymptomatic. At age 11 years, nephrotic syndrome recurred during a febrile illness, and the patient was referred to our clinic.

This time, remission was achieved with prednisone 60 mg/m^2 and ACE inhibitors. The patient was steroid dependent until age 14 years, when steroid resistance developed. At that time, she began to complain of fatigue, and her thyroid status was examined. TSH measured 9.9 mIU/L (normal 0.4–4 mIU/L) and FT4, 9.4 pmol/L (normal 10.5–25.7 pmol/L). Renal function was normal (serum creatinine 0.6 mg/dL), with urine protein measuring 6.2 g/day. Findings for anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative, and the thyroid sonogram was normal. Over the next 4 years, under therapy with thyroxine 300–550 mcg/week, TSH levels ranged from 0.5 to 8 mIU/L and FT4 levels, from 7 to 17 pmol/L. The inadequate control of the hypothyroidism was attributed to the patient's non-adherence to treatment. Additional therapies for nephrotic syndrome, including methylprednisolone pulses, cyclosporine and mycophenolate mofetil, failed to lead to remission. Renal function slowly deteriorated to ESRD at age 19 years. At that time, the patient was transferred to an adult hemodialysis unit. The patient underwent hemodialysis for 6 months, during which time thyroxine was slowly discontinued and her thyroid hormone profile remained normal. She then received a kidney transplant from her

mother. FSGS recurred soon after and the patient lost the graft because of non-adherence to treatment. Currently, she is again on hemodialysis.

Patient 3

A 3.5-year-old girl was referred to our clinic with nephrotic syndrome. After multiple relapses, the disease was reclassified as steroid-dependent nephrotic syndrome. Success with cyclophosphamide and levamisole therapy was limited. Remission was achieved with cyclosporine therapy and lasted until age 9.5 years, when the disease relapsed and became steroid resistant. Renal biopsy revealed FSGS. Given our experience with Patients 1 and 2, we began to routinely check the thyroid status. Thyroid hormone levels at diagnosis of FSGS were within normal range, but 4 months later, TSH measured 5.5 mIU/L and FT4, 9.4 pmol/L. At that time, the patient had proteinuria (6 g/day) with preserved renal function. Blood tests for thyroid autoantibodies were negative. Following treatment with thyroxine supplement at a weekly dose of 150–170 mcg, the thyroid profile normalized: TSH 3.9–3 mIU/L, FT4 9–13 pmol/L. However, over the next 10 months, renal function rapidly deteriorated to ESRD requiring hemodialysis. The patient became anuric. Her thyroid hormone profile normalized, and thyroxine supplement was gradually discontinued.

The patient has been receiving hemodialysis for 2.5 years while awaiting a kidney transplant. Her thyroid profile remained normal during this time.

Patient 4

An 11-year-old boy referred to our clinic with nephrotic syndrome failed to respond to 6 weeks of therapy with prednisone, 60 mg/m^2. Renal biopsy revealed diffuse mesangial proliferation. Treatment with cyclosporine, ACE inhibitor and angiotensin receptor blocker (ARB) failed. Again, prompted by our earlier experience, we began to monitor the patient's thyroid status. Findings were normal in the first year after diagnosis, though renal function rapidly deteriorated (creatinine clearance 25 mL/min/1.73m^2; serum creatinine 1.6 mg/dL). Fourteen months after disease onset, thyroid insufficiency was noted, with TSH measuring 6.9 mIU/L (normal 0.4–4 mIU/L) and FT4, 8.5 pmol/L (normal 11.7–28). No thyroid autoantibodies were detected. Thyroxine supplement was started. At that time, serum creatinine measured 2.3 mg/dL, albumin 1.9 g/dL and urine protein 4 g/day.

At 19 months after disease onset, hemodialysis was started for ESRD. Thyroid hormone levels normalized, and thyroxine therapy was slowly tapered down and then stopped. After 3 years on hemodialysis, the patient underwent deceased donor kidney transplantation. Nephrotic range proteinuria developed a few days later, probably owing to a recurrence of FSGS in the graft. Plasmapheresis and a switch from tacrolimus- to cyclosporine-based immune suppression led to a gradual improvement. At present, 6 months after transplantation, serum creatinine is 0.7 mg/dL and urine protein is $<$0.5 g/day. The thyroid hormone profile remains in normal range.

Patient 5

A 7.5-year-old girl referred to our clinic with nephrotic syndrome failed to respond to 6 weeks of prednisone 60 mg/m^2/day. Kidney biopsy demonstrated FSGS with diffuse mesangial proliferation. Treatment with methylprednisolone pulses, cyclosporine, ACE inhibitors and ARB was unsuccessful. Genetic analysis yielded a heterozygous podocin mutation. Six months after disease onset, immunosuppression therapy was stopped. We began to monitor her thyroid status at disease onset, and after 9 months, TSH measured 6.9 mIU/L (normal 0.4–4) and FT4, 7 pmol/L (normal 10.5–25.7). Findings for thyroid autoantibodies were negative. Thyroxine therapy was started. At that time, serum creatinine was 0.73 mg% and urine protein, 5.5 g/day.

Over the next 6 months, kidney function continued to deteriorate. ESRD was diagnosed 1.5 years after disease onset. During treatment with hemodialysis, urine output was minimal but serum albumin and thyroid hormone levels normalized. The thyroxine supplement was gradually tapered off. Currently the patient is on hemodialysis awaiting kidney transplantation. Her thyroid hormone profile remains normal.

Discussion

We describe a series of five children with SRNS who acquired non-autoimmune hypothyroidism. Our review of the literature revealed no other reports on SRNS complicated by hypothyroidism in children and only one report on non-autoimmune hypothyroidism in four adult patients with nephrotic syndrome [4]. In the latter series, the hypothyroidism resolved in two patients after the nephrotic disease remitted and persisted in one patient despite disease remission; the fourth patient died. There are also a handful of case reports of thyroid abnormalities in patients with minimal change glomerular disease, but in all of them, unlike our cases, the thyroid disease had an autoimmune etiology [7, 8].

Despite the lack of reports, it is our view that non-autoimmune hypothyroidism is not an uncommon complication of SRNS in children. After the diagnosis of hypothyroidism in Patients 1 and 2 of this report, who were evaluated for non-specific complaints, we acquired a high index of suspicion and began to regularly evaluate thyroid function in children with persistent nephrotic syndrome. Consequently, three additional cases of hypothyroidism (Patients 3–5) were identified. It is noteworthy that these patients also only had non-specific complaints at the time of diagnosis of hypothyroidism, and none had the full-blown disorder. The complaints could also have been attributable to their primary disease. In all five patients, there was no temporal relationship of the diagnosis of hypothyroidism with either the duration of the nephrotic disease or renal function.

Our decision to administer thyroxine supplement was based on the important effect of thyroid hormone on growth and metabolism, the cardiovascular and central nervous system and the skeleton in health and disease

[1, 9]. Accordingly, other authors reported the administration of thyroxine in infants who with hypothyroidism secondary to congenital nephrotic syndrome [6].

In a random check of the thyroid hormone profile of four children with steroid-sensitive nephrotic syndrome (SSNS) being treated at our center, TSH level at disease onset ranged from 10 to 20 mIU/L and FT4, from 9 to 7 pimol/L (mildly low). Values normalized 1–2 weeks after disease remission. The serum level of TSH in our patients with SRNS ranged from 5 to 10 mIU/L, which is lower than expected in patients with hypothyroidism and also lower than in the patients with new-onset SSNS. We attributed this finding to the urine loss of TSH, which is a low-molecular-weight protein (LMWP) (molecular weight 28 500 Da). SRNS is associated with a greater loss of LMWP than SSNS [10, 11].

By contrast to our observation in four children with SSNS, an earlier report of a small sample of children with SSNS [4] found that although FT4 and FT3 levels were low and TSH levels were high in the majority of cases, all three values remained within normal range. All these results require further clarification in a well-controlled observational study.

Interestingly, in our patients, when the renal dysfunction deteriorated to end-stage disease, the thyroid hormone profile normalized and thyroxine supplement could be discontinued. This observation may indicate a pivotal role of proteinuria and thyroxine loss in the urine in the pathogenesis of hypothyroidism in nephrotic syndrome, in line with findings for non-autoimmune hypothyroidism in the context of congenital nephrotic syndrome [1, 2, 4, 5, 12]. Nevertheless, the proteinuria itself cannot explain why the hypothyroidism developed in only some of the patients with SRNS and why it did not develop already at disease onset, which in our experience has shown to be true for SSNS.

Normal renal handling of free thyroid hormone has been investigated in several small-scale observational studies [8, 13–16], which measured 24-h urine excretion of creatinine, FT3 and FT4. The results showed that FT4 is reabsorbed by the tubules, whereas FT3 is secreted. Nearly all the thyroid hormone in the circulation is bound to three proteins (molecular weight 50 000–70 000 daltons): mainly thyroid binding globulin and also transthyretin (prealbumin) and albumin [17]. These proteins which partially cross the glomerular membrane are absorbed in the proximal tubule by megalin and cubilin [10]. From the sparse studies available on urine excretion of total T4, total T3 and thyroxine-binding globulin in proteinuria and nephrotic syndrome, all studies reported higher excretion of total T3 and T4 during nephrosis, which normalized on remission [2–4]. Although TSH is a LMWP, there are no studies of urine loss of TSH in nephrotic syndrome.

We suggest that a difference in proteinuria selectivity and in renal handling of free and protein-bound thyroid hormones and TSH between children with SSNS or SRNS at disease onset and during disease progression may explain why hypothyroidism develops in some patients with nephrotic syndrome, whereas others have a normal thyroid profile. The difference in proteinuria selectivity will cause a different urine loss of protein-bound thyroid hormones. It may also change the amount and concentration of free T3 and T4 since proteins in the filtrate may bind free thyroid hormone. Another potential pathophysiological mechanism of the development of hypothyroidism during disease progression is an association of advanced SRNS with a functional defect in the proximal tubule, where there is active absorption of proteins that have crossed the glomerulus filtration barrier [18]. It is also possible that hypothyroidism is a consequence not only of urine loss of thyroid hormones but also of a failure of the thyroid gland to compensate for this loss. However, this mechanism is less likely given that the hypothyroidism resolved when the patients reached ESRD and required dialysis.

Studies performed in the last two decades have shown that congenital nephrotic syndrome and SRNS may be caused by a genetic defect in podocyte proteins [18]. However, we do not believe that the SRNS in our cases had a genetic basis because the disease recurred in the graft in all three patients who underwent kidney transplantation, which is more characteristic of primary SRNS [19]. In addition, the only relevant finding on genetic analysis in the other two patients was heterozygosity for podocin mutation in one. Thus, the present report is important because it adds to previous findings that hypothyroidism is a part of hereditary nephrotic syndrome [1], showing that it may also occur in patients with idiopathic SRNS.

The present report was limited by its small size and retrospective observational design, so conclusions regarding the incidence of hypothyroidism in SRNS in children cannot be reached. Furthermore, we did not perform studies to quantify the urine loss of thyroid hormone in relation to the development of hypothyroidism.

In conclusion, hypothyroidism should be actively sought and treated in patients with SRNS, especially children in whom the disease progresses to ESRD. Hypothyroidism may be more common than recognized in children with nephrotic syndrome. Prospective observational studies are needed to determine the etiology and pathogenesis of this health threatening, potentially treatable complication.

Conflict of interest statement. None declared.

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Received for publication: 22.10.10; Accepted in revised form: 19.10.11