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Hypothyroidism in infants with nephrotic syndrome

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Abstract. Thyroid function indices were studied in five children with nephrotic syndrome in the 1st year of life. Four had primary hypothyroidism as defined by low serum free tri-iodothyronine (FT_3) and free thyroxine (FT_4), and high serum thyroid-stimulating hormone (TSH) levels. One patient with low serum FT_3 and FT_4 had a normal TSH level. T_4 replacement therapy lowered TSH to normal levels in all four patients and normalized FT_4 in three of them. There were no significant changes in serum FT_3 levels. Adrenal function was studied in three patients, none had adrenal calcification or hypoadrenocorticism. This study supports the existence of a hypothyroid state in some infants with nephrotic syndrome. Routine thyroid screening and early replacement therapy is recommended.

Key words: Nephrotic syndrome – Hypothyroidism

Introduction

Abnormal thyroid function indices have been reported in some adults and children with nephrotic syndrome (NS). These include low serum thyroxine (T_4) with high thyroid-stimulating hormone (TSH) [1–3], low serum tri-iodothyronine (T_3) with normal TSH [4], and high free T_4 (FT_4) and normal total T_4 and TSH levels [5]. Opinions differ on the true thyroid status in these patients: according to some they are euthyroid [4, 5], whereas others believe they suffer from hypothyroidism [1, 3]. The exact aetiology of low serum hormone levels is not known. Low binding globulin levels in the serum and an increased urinary loss in the presence of a heavy proteinuria are favourite explanations [4–8]. Whether or not T_4 replacement therapy is necessary is also controversial.

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Patients and methods

Five infants with NS were admitted to our renal service over a period of 30 months. NS was diagnosed by the presence of generalized oedema associated with proteinuria of more than 2 g/24 h and hypoalbuminaemia of less than 25 g/l. Patients were screened for toxoplasmosis, cytomegalovirus, syphilis (VDRL) and hepatitis B infection. Ultrasound examination of the kidneys and isotope scans were performed to confirm the presence of two kidneys with equal function. Kidney biopsy was performed percutaneously or by an open surgical approach. Patients received supportive therapy in the form of a high-protein, high-calorie diet, albumin transfusions, diuretics, aspirin, dipyridamole, benzathine penicillin and gamma globulins, in different combinations. Four patients received oral L-T_4 at a starting dose of 25 μg/day; this was subsequently increased according to the serum TSH level.

FT_3 was measured by radioimmunoassay (Kodak, UK) and free T_4 and TSH were assayed by enzyme-linked immunosorbent assay, a fully automated non-radioactive system, ES-600, Boehringer Mannheim, Germany. Serum cortisol was measured before and 30 min after intramuscular administration of 0.125 mg Cortrosyn (cosyntropin, Organon), a synthetic adrenocorticotropic hormone (ACTH).

Results

The study includes five patients with NS in the 1st year of life. Kidney biopsy revealed diffuse mesangial proliferative glomerulonephritis in two patients (nos. 1, 4) and Finnish microcystic disease (FMD) in one patient (no. 3). A sibling (patient no. 2) of the patient with FMD did not have a kidney biopsy and the result of the biopsy was inconclusive in one patient (no. 5).

The follow-up period ranged from 6 to 37 months (median 8 months). Patients 1 and 2 died of sepsis at the ages of 18 and 8 months, respectively. Patients 3, 4, and 5 were alive at the ages of 38, 17 and 8 months, respectively (Table 1). Patients 1, 3, and 4 had unilateral nephrectomy at the ages of 3, 17 and 9 months, respectively. This was performed in order to alleviate the problems related to heavy proteinuria [9]. Urine protein excretion and creatinine clearance at the time of diagnosis and at the last follow-up are shown in Table 1.

Table 1. Patients with nephrotic syndrome in the 1st year of life

Patient number (sex)	1 (M)	2 (M)[a]	3 (F)[a]	4 (F)	5 (M)
Age at clinical diagnosis (months)	10	1.3	1	2	1
Renal histology	MesPGN	ND	FMD	MesPGN	IC
Follow-up period (months)	8	6	37	15	7
Urine protein excretion (g/l)					
At diagnosis	20	18	13	8.1	8.9
Last follow-up	NA	16	7.5	3.3	18
Serum creatinine (μmol/l)					
At diagnosis	40	40	6	17	6
Last follow-up	4	5	383	49	12
Creatinine clearance (ml/min per 1.73 m^2)					
At diagnosis	NA	62	54	76	38
Last follow-up	NA	NA	6	24	53
Serum albumin on diagnosis (g/l)	<6	6	3	3	<6
Outcome	Died	Died	Alive	Alive	Alive

ND, Not done; NA, not available; IC, inconclusive; MesPGN, diffuse mesangial proliferative glomerulonephritis; FMD, Finnish microcystic disease
[a] Siblings

Table 2. Endocrine function tests in infants with nephrotic syndrome

Patient no.	1[a]	2	3	4	5
Age at initial TFT (months)	10	2	14	3	2
FT_3 (normal = 2.9–8.9 pmol/l)					
Before treatment	1.0	<0.5	0.5	0.6	0.5
On treatment	–	<0.5	2.2	0.5	0.5
FT_4 (normal = 8–22 pmol/l)					
Before treatment	3.0	5.5	6.8	9.7	4.3
On treatment	–	6.2	11	12.2	9.1
TSH (normal = 0.3–5 mIU/l)					
Before treatment	2.4	11.5	24.5	41.5	22.2
On treatment	–	5.4	4.1	1.2	3
Serum cortisol (normal = 140–690 nmol/l)					
Before and	ND	ND	586	438	145
30 min after ACTH	ND	ND	793	689	724
CT scan of adrenal glands	ND	ND	N	N	N

TFT, Tyhroid function tests; N, normal; TSH, thyroid-stimulating hormone; T_3, tri-iodothyronine; T_4, thyroxine; ACTH, adrenocorticotropic hormone; CT, computed tomography
[a] Patient 1 did not receive T_4

As shown in Table 2, serum FT_3 and FT_4 levels were low in all patients. Four patients had elevated serum TSH levels which returned to normal with 50 (patient 2) to 75 (patients 3, 4, 5) μg/day of L-T_4. FT_4 increased to normal levels in three patients, whereas there was no significant change in FT_3 levels. Adrenal gland function was studied in three patients (nos. 3, 4, 5). All had a normal serum cortisol level and a normal response to ACTH stimulation. No adrenal calcification was seen on computed tomography (CT).

Discussion

Some patients with NS have abnormal thyroid function tests, and whether or not these indicate hypothyroidism is controversial. This is because of conflicting interpretation of thyroid indices, exacerbated by the unavailability (until recently) of sensitive assays for measuring serum unbound thyroid hormone levels. In the present study, four infants with NS had high serum TSH and low FT_3 and FT_4 levels. These changes are consistent with primary hypothyrodism in a partially compensated form as a result of the hypothalamic-pituitary axis response to low serum thyroid hormone levels. McLean et al. [1] and Wilschanski et al. [3] reached a similar conclusion on the basis of low T_4 and high TSH levels in the serum. FT_3 levels in the former study were normal in three of the four patients and no free thyroid hormone levels were measured in the latter.

The exact aetiology of hypothyroidism in NS is unknown. The absence of thyroid antibodies, normal thyroid scans and autopsy examination exclude morphological changes or an immune-mediated pathology in the thyroid gland [1, 8]. A decrease in serum thyroid hormone level is

attributed to its diminished binding by low serum levels of albumin, prealbumin and thyroid (T_4)-binding globulin [4, 6, 7], and an increase in the urinary excretion of bound and FT_4 [8]. This is supported by positive correlations between serum albumin and T_4 levels [6], the degree of proteinuria and the urinary loss of T_4 [5], and normalization of thyroid indices with the onset of remission of NS [8] or anuria [10]. It does not, however, explain the presence of normal TSH in one of our patients. A significant decrease in renal function and proteinuria did not resolve hypothyroidism in two of our patients. The T_4 requirement did not decrease even after the onset of terminal renal failure in one patient.

All our patients who received T_4 responded by lowering serum TSH to normal levels, as has been reported previously by others [1, 3]. FT_4 increased to normal levels in three patients, whereas there was no improvement in FT_3 levels. The clinical response to treatment could not be evaluated because of the multifactorial aetiology and the complex management of failure to thrive in infants with NS.

Some patients with congenital nephrosis have adrenal calcification and diminished adrenal function [10, 11]. Three of our patients screened for the purpose had normal adrenal CT scans, normal serum cortisol levels and a normal response to ACTH stimulation. T_4 is important for normal somatic and mental development, and in no other age group is the diagnosis of hypothyroidism as important as during infancy. It is therefore suggested that all infants with NS be screened and those proven to be hypothyroid with low FT_3 and FT_4 and an elevated TSH receive replacement therapy and adequate follow-up.

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Announcement

The 6th International Workshop on Developmental Nephrology will be held on August 23–25, 1995 at Airlie House in Airlie, Virginia. The Workshop is intended to provide a comprehensive review of renal developmental physiology and cell and molecular biology and renal growth. Topics will include renal embryogenesis and differentiation, receptors and cell signaling, cell effecters, vasoactive agents, growth factors, renal maldevelopment and developmental pathophysiology will be included. For further information, please contact Robert L. Chevalier, M.D., Department of Pediatrics, Box 386, University of Virginia School of Medicine, Charlottesville, Virginia, 22908 USA. Telephone (804) 924-5093. Fax (804) 982-3561.