NDT Plus (2008) 6: 440–441
doi: 10.1093/ndtplus/sfn158
Advance Access publication 13 October 2008

NDT PLUS
Nephrology Dialysis Transplantation

Teaching Point
(Section Editor: A Meyrier)

Renal impairment resulting from hypothyroidism

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Keywords: hypothyroidism; renal impairment

Introduction

We describe two cases of reversible renal impairment secondary to hypothyroidism. We suggest that patients with renal impairment of unknown cause have thyroid function tests undertaken as part of routine investigation.

Case one

A 37-year-old woman presented with recent constitutional upset and a year-long history of swelling of her face and hands. Her past medical history included pre-eclampsia. Her father had suffered from focal segmental glomerulosclerosis and her brother underwent renal transplantation for reflux nephropathy. Examination revealed peri-orbital oedema and hypertension (140/100 mmHg). Her pulse rate was 58 beats/min.

Investigations included haemoglobin 11.6 g/l, white cell count 6.2 $\times$ 10^9/l, sodium 137 mmol/l, potassium 3.6 mmol/l, creatinine 148 μmol/l, estimated glomerular filtration rate (GFR) 37 ml/min/1.73 m^2, urea 7.6 mmol/l, cholesterol 9.8 mmol/l, alkaline transferase 97 IU/l, alanine transaminase 45 IU/l, alkaline phosphatase 89 IU/l, albumin 45 g/l, calcium 2.37 mmol/l and glucose 4.9 mmol/l. Hepatitis, Epstein-Barr and cytomegalovirus serologies were negative.

Urinalysis was normal. A 24-h urine collection identified 0.30 g of protein and a creatinine clearance of 58 ml/min. Ultrasonography revealed her kidneys to measure 11 cm on the left and 10 cm on the right. A small pericardial effusion was evident on echocardiography, with no left ventricular hypertrophy. Magnetic resonance angiography revealed patent renal arteries.

A renal biopsy was undertaken. Twenty-two glomeruli were available for analysis, with no evidence of focal lesion or glomerulonephritis. Further, light microscopy, immunohistochemistry and electron microscopy were unremarkable.

At this point the patient described myalgias. Thyroid function tests showed a free thyroxine (FT_4) concentration of <3 pmol/l and a thyroid stimulating hormone (TSH) concentration of >75 mu/l, consistent with severe hypothyroidism. Creatine kinase was elevated to 3454 IU/l, but urinary myoglobin was not detected. She was commenced on levothyroxine 100 mcg. Her blood pressure (110/70 mmHg), serum creatinine (94 μmol/l), creatine kinase and cholesterol (4.2 mmol/l) all normalized.

Case two

A 50-year-old man presented with indigestion, abdominal bloating, weight gain, dry skin and lethargy. His past medical history included laminectomy and longstanding tobacco use. He was hypertensive (156/102 mmHg) and overweight (126 kg), with dry skin, peripheral oedema and slow-relaxing reflexes.

Investigations included haemoglobin 149 g/l, white cell count 7.4 $\times$ 10^9/l, sodium 138 mmol/l, potassium 4.2 mmol/l, serum creatinine 135 μmol/l, estimated GFR 52 ml/min/1.73 m^2, urea 7.2 mmol/l, calcium 2.23 mmol/l, cholesterol 6.6 mmol/l, alkaline transferase 94 IU/l, alkaline phosphatase 72 IU/l, bilirubin 7 μmol/l, albumin 43 g/l and glucose 7.8 mmol/l. Urinalysis showed 1+ protein. A 24-h urine collection revealed 0.16 g of protein. Renal tract ultrasonography was normal. A glomerulonephritis screen was normal, but he too was found to be hypothyroid (FT_4 <4 pmol/l, TSH >75 mu/l).

His thyroid function (TSH 2.7 mu/l, FT_4 19 pmol/l) was controlled with levothyroxine 225 mcg daily. His blood pressure (124/84 mmHg), peripheral oedema, proteinuria (dipstick negative) and serum creatinine (110 μmol/l) all normalized.

Discussion

We describe two cases in which the initial finding of renal impairment guided further investigations, leading to the

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diagnosis of hypothyroidism. In both cases, thyroid hormone replacement therapy brought about complete recovery of renal function.

Most reports documenting hypothyroidism with renal impairment have described patients with unexplained worsening of pre-existing renal disease of an alternative aetiology; descriptions of renal impairment solely attributable to hypothyroidism, as in our cases, are less common.

Although aspects of our second patient's presentation were clearly suggestive of hypothyroidism, our first case illustrates that the classical clinical signs and symptoms may be subtle or absent, even in severe hypothyroidism. Furthermore, when renal impairment coexists, these signs and symptoms may be attributed to uraemia. In hindsight, the anaemia (more pronounced than might have been expected given the degree of renal impairment), hypercholesterolaemia and raised transaminases were perhaps clues to the underlying diagnosis in our first patient.

Recent epidemiological studies, identifying a high prevalence of thyroid dysfunction amongst patients with renal impairment, lend a new importance to the phenomenon of reversible hypothyroidism-induced renal impairment. Subclinical hypothyroidism (elevated TSH levels with normal FT_4 levels) and clinically-apparent hypothyroidism occur in ∼18–20% of patients with chronic kidney disease not requiring renal replacement therapy, with the prevalence rising as the degree of renal impairment worsens [1,2]. The benefits of thyroid hormone replacement therapy, including its effects on renal function, in patients with subclinical hypothyroidism remain unclear.

Whilst the pathophysiology of impaired renal function in hypothyroidism is multifactorial, the reduction in GFR due to the lower cardiac output and renal blood flow is likely to be the predominant mechanism [3]. It has also been suggested that thyroxine may mediate tubular secretion of creatinine [4]. Furthermore, hypothyroidism may increase creatinine release from muscle [5]. Although freely filtered, additional tubular secretion of creatinine renders it a poor marker of GFR. In patients with hypothyroidism, clarification of whether an elevated serum creatinine represents true renal impairment (i.e. reduced GFR) or simply increased generation, and tubular secretion, of creatinine therefore requires further analysis by the way of isotope GFR studies.

Although hypothyroid myopathy is usually limited to myalgias, rhabdomyolysis leading to acute kidney injury is a rare complication of hypothyroidism [6]. Treatment with thyroid hormone replacement therapy reverses rhabdomyolysis and improves renal function [6]. Although creatine kinase was elevated in our first patient, the absence of urinary myoglobin and the normal biopsy findings excluded rhabdomyolysis.

Although end-stage renal disease secondary to hypothyroidism has been reported [7], changes in serum creatinine resulting from hypothyroidism are commonly subtle. Histological findings (including glomerular and tubular basement membrane thickening, mesangial enlargement and epithelial and interstitial cell inclusions) have all been described in patients with hypothyroidism [8]. These have proven both reversible and irreversible with treatment [8,9].

Hypothyroidism has also been described as the consequence, rather than the cause, of renal dysfunction; thyroxine is heavily protein bound and is lost via the urine in nephrotic syndrome [10]. Undiagnosed nephrotic syndrome should therefore be considered in cases of refractory hypothyroidism, whilst thyroid function should be monitored in cases of severe, prolonged nephrotic syndrome.

Our first patient underwent a renal biopsy prior to diagnosis. To prevent unnecessary and hazardous investigations, we recommend that thyroid function be assessed early in patients with renal impairment.

Teaching points

1. Hypothyroidism is an under-appreciated cause of renal impairment.
2. Thyroid function should be assessed in patients with deteriorating renal function, including those with known renal impairment in whom the deterioration is unexpected.
3. The classical clinical signs and symptoms may be subtle or absent, even in severe hypothyroidism.

Conflict of interest statement. None declared.

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Received for publication: 14.9.08
Accepted in revised form: 17.9.08