Reversal deterioration of renal function accompanied with primary hypothyroidism

Reverzibilno akutno smanjenje bubrežne funkcije udruženo sa primarnom hipotireozom

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Abstract

Introduction. Thyroid hormones are necessary for growth and development of the kidney. They are also involved in maintenance of water and electrolyte homeostasis in different organs and tissue departments. Hypothyroidism is often accompanied with decline of kidney function, or inability to maintain electrolyte balance. These changes are very subtle and usually overlooked in everyday clinical practice. Case report. Two patients with elevated serum creatinine levels due to primary autoimmune hypothyroidism, with complete recovery of creatinine clearance after thyroid hormone substitution therapy are presented. The first patient was a young male whose laboratory tests suggested acute renal failure, and the delicate clinical presentation of reduced thyroid function. The second patient was an elderly woman with a history of long-term signs and symptoms attributed to ageing, including the deterioration of renal function, with consequently delayed diagnosis of hypothyroidism. Conclusion. Serum thyrotropin and thyroxin levels measurement should be done in all cases of renal failure with undefined renal disease, or in all patients with chronic kidney disease whose kidney function is rapidly worsening.

Key words: hypothyroidism; renal insufficiency; diagnosis; thyrotropin; thyroxin; treatment outcome.

Introduction

Thyroid hormones are necessary for growth and development of the kidney. They are also involved in maintenance of water and electrolyte homeostasis in different organs and tissue departments. Hypothyroidism is often accompanied with decline of kidney function, or failure of electrolyte balance. These changes are very subtle and usually overlooked in everyday clinical practice. We described two patients with impaired renal function due to primary hypothyroidism, and complete recovery of creatinine clearance after thyroid hormone replacement therapy.

Case reports

Case 1

A 23-year-old male was referred to the outpatient department for elevated serum creatinine levels with the history of the mild muscle weakness and tiredness over the few months. Physical examination revealed normal anthropomet-
ric parameters, body mass index (BMI) of 24 kg/m², body temperature of 36.5°C, dry skin with no edema. He was normotensive with pulse rate of 64 beats per minute, and showed no hepatomegaly.

Laboratory blood tests revealed an elevated serum creatinine level of 168 mmol/L (normal range: 50–75 mmol/L), creatine kinase (CK) level of 430 U/L (normal range 21–294 U/L) and serum total cholesterol level: 8.4 mmol/L (normal range < 5.2 mmol/L), while serum liver enzymes levels were slightly elevated: aspartate aminotransferase (AST) 44 U/L (normal range 0–34 U/L), alanine aminotransferase (ALT) 63 U/L (normal range 7–49 U/L) and lactate dehydrogenase (LDH) 420 U/L (normal range 208–378 U/L). Biochemistry data included normal concentration of serum urea, triglyceride, bilirubine, albumin, potassium, sodium, glucose, hemoglobin, platelet and white blood count. Urine tests showed no proteinuria or hematuria. There were no casts in the urine sediment. Serum and urine myoglobin levels were not determined. Creatinine clearance estimated using the Cockcroft-Gault formula was reduced to the value of 68 mL/min (normal range for males 97–137 mL/min), suggesting renal failure. An abdominal ultrasonography showed normal morphology and volumes of both kidneys. Due to the constant presence of muscle weakness, the thyroid function test were performed. Thyroid stimulating hormone or thyrotoxin (TSH) level was elevated: 56 mIU/L (normal range 0.35–5.5 mIU/L), serum free thyroxine (FT4) level was lower: 9.5 pmol/L (normal range 11.5–22.7 pmol/L) and free triiodothyronine (T3) level was at the lower limit of the normal range: 3.6 pmol/L (normal range 3.5–6.5 pmol/L). The thyroperoxidase antibodies titer were elevated, 1: > 1 300 (normal range 0–60.0), while antithyroglobulin antibodies titer were not determined. The ultrasonography of the thyroid showed a slight enlargement of the gland with the heterogenous texture suggesting autoimmune thyroiditis.

After the primary hypothyroidism was detected, the patient was recommended to take levothyroxine replacement therapy at 100 mcg daily dose (1.6 mcg/kg). One week after starting the levothyroxine therapy, the patient felt better. After two months of hormone substitution, all biochemical parameters returned to the normal levels: TSH level was 3.5 mIU/L, serum creatinine level was 94 mmol/L and the creatinine clearance was 117 mL/min (Table 1). The patients went back to his everyday activities.

### Table 1

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>At diagnosis</th>
<th>Two weeks later</th>
<th>Two months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>56</td>
<td>0.35</td>
<td>3.5</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>9.5</td>
<td>12</td>
<td>17.5</td>
</tr>
<tr>
<td>Free T3 (pmol/L)</td>
<td>3.6</td>
<td>4.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>168</td>
<td>130</td>
<td>94</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>8.4</td>
<td>6.1</td>
<td>5.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.9</td>
<td>3.5</td>
<td>2.95</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>430</td>
<td>300</td>
<td>115</td>
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<tr>
<td>LDH (U/L)</td>
<td>420</td>
<td>305</td>
<td>277</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>44</td>
<td>/</td>
<td>20</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>63</td>
<td>/</td>
<td>34</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>68</td>
<td>/</td>
<td>117</td>
</tr>
</tbody>
</table>

TSH – thyrotoxin; T4 – thyroxine; T3 – triiodothyronine; LDL – low density lipoprotein; CK – creatine kinase; LDH – lactate dehydrogenase; AST – aspartate aminotransferase; ALT – alanine aminotransferase

Case 2

An 81-year-old female patient was referred to our department for the presence of clinical and humoral parameters suggesting primary hypothyroidism. The patient complained about tiredness, muscle pain, dry skin and the presence of elastic edema of the lower limbs and ankles, not responsive to furosemid therapy over the last eight months. The patient also had the history of arterial hypertension and ischemic heart disease, ordinarily treated with adequate therapy recommended by the cardiologist. Physical examination revealed bradycardia (heart rate of 55 beats per minute), increased blood pressure of 160/100 mmHg, dry skin, palor, elastic edema of the ankles, with no hepatomegaly or other signs of cardiac failure. The patient had slightly enlarged palpable thyroid with hard consistency. Laboratory data noted mild normochromic and normocytic anemia with hemoglobin levels of 105 g/L (normal range 130–180 g/L); serum glycemia was 7 mmol/L (normal range 4.1–5.9 mmol/L) with elevated level of total cholesterol 9.6 mmol/L (normal range < 5.0 mmol/L) and CK 480 U/L (normal range 21–294 U/L). Serum biochemistry included high levels of serum creatinine of 180 mmol/L (normal range 80–124 mmol/L) and slightly elevated serum urea levels of 11.6 mmol/L (normal range 3.2–8.2 mmol/L). Serum levels of other liver enzymes, triglyceride, albumin and bilirubine were normal. Creatinine clearance, assessed using the Cockcroft-Gault formula, was reduced to the value of 35 mL/min (normal values for female 88–128 mL/min) suggesting renal failure. Ultrasonography of the kidneys or other abdominal organs were not performed.

Diagnosis of primary hypothyroidism was based on the elevated TSH levels: 65.6 mIU/L (normal range 0.35–5.5 mIU/L), decreased FT4: 10.4 pmol/L (normal range 11.5–22.7 pmol/L) and FT3 levels: 0.9 pmol/L (normal range 3.5–6.5 pmol/L). The thyroperoxidase antibodies titer were elevated (1 : 600). The ultrasonography of the thyroid gland showed that its volume was at the lower limit of normal values with heterogenous structure suggesting autoimmune thyroiditis. Levothyroxine replacement therapy started with the dose of 100 mcg daily (gradually increasing dose by 25 mcg weekly). Two months after starting the substitution therapy, the patient’s edema retreated following the decrease of plasma TSH levels. After four months of the therapy, thy-
Hypothyroidism might happen. Decrease in GFR produces a diminished clearance. Consequently, elevation of plasma creatinine levels resulted in free water overload and decrease in creatinine clearance. The patient continued to feel well.

**Discussion**

The functional association between hypothyroidism and kidney failure has been described many times in the literature, and it seems to be reversible after hormone substitution therapy. Montenegro et al. showed a decrease in glomerular filtration rate (GFR) in all of their hypothyroid patients, whereas only 55% had an increase in serum creatinine levels. A few years later, Villabona et al. described the decrease in effective renal blood flow and GFR in hypothyroid patients with chronic renal disease. Karanikas et al. performed isotopic renal function studies in thyroidectomized patients showing that the hemodynamic changes in severe hypothyroidism mainly affect the glomerular function.

The most common kidney derangements associated with hypothyroidism are an increase in serum creatinine levels, reduction in GFR and renal plasma flow, decreased capacity of free water excretion and hypernatremia. About one half of patients with autoimmune thyroid disease have positive circulating immunocomplexes that are in correlation with the presence of thyroid peroxidase antibodies, but not with their titer. Immunocomplexes deposits in the basement membrane of the glomeruli have been also reported in patients with Hashimoto thyroiditis; still, no casual relationship between the presence of immunocomplexes and antibodies has been proved so far.

Although the exact mechanism of these changes has not been defined yet, it seems that kidney failure secondary to hypothyroidism involves heterogeneous processes based on the direct or indirect effects of thyroid hormones on renal hemodynamics. Thyroid hormone deficiency decreases myocardial contractility and cardiac output. On the other hand, an impaired endothelial-mediated vasodilatation in hypothyroidism increases peripheral and renal vascular resistance. These effects reduce renal plasma flow and GFR, resulting in free water overload and decrease in creatinine clearance. Consequently, elevation of plasma creatinine levels might happen. Decrease in GFR produces a diminished water delivery to distal tubular segments that is partly responsible for the hyponatremia. Hyponatremia appears in 45% of hypothyroid patients who have elevated serum creatinine levels and in about 21% of those with normal creatinine levels. Thyroid hormones also have a hold upon tubular transport of sodium via their actions on the sodium-potassium adenosine triphosphate pump (Na/K ATP-ase) and on the potassium permeability in the membrane of the proximal tubules.

Levothyroxine is a synthetic product identical to natural thyroxine, produced by the thyroid gland. After the normalisation of serum thyroxine levels, cardiac output and myocardial contractility recover, leading to the increase in renal plasma flow and creatinine clearance.

Systemic manifestations of hypothyroidism vary considerably, depending on the duration and severity of the hypothyroid state. Gradual and imperceptible onset somethimes account for the inconclusive clinical diagnosis of hypothyroiditis. We described two patients with autoimmune hypothyroidism presented with elevated serum creatinine levels and reverse deterioration of renal function.

The first patient was a young male with a delicate clinical presentation of reduced thyroid function. Due to nonspecific symptoms and signs associated with laboratory parameters suggesting acute renal failure, clinical findings were not easy to interprete. Our examination results could not reveal any kidney disease.

Hypothyroidism is known to be associated with elevated serum CK levels along with other muscle enzymes (LDH). Due to the myopathy, hypercholesterolemia and elevated levels of CK in this young patient, we performed thyroid hormone testing. High serum thyrotropin and decreased serum free thyrotropin levels, accompanied with elevated titer of antiperoxidase antibodies were adequate to define primary autoimmune hypothyroidism. After the beginning of thyroid replacement therapy, thyroid status improved and kidney function progressively recovered. This observation is consistent with the previously published data.

In elderly patients with various illnesses, symptoms and signs of hypothyroidism could be easily confused with the usual signs or effects of aging such as cold intolerance, dry, pale, thick and rough skin, intestinal constipation, non-depressive edema, mental slowness or increased body weight. In the
second case, we described the elderly patient with the history of long-term edema and symptoms similar to aging. Deterioration of renal function, followed with moderate renal atrophy and elevated serum creatinine levels are not unusual in an 81-year-old patient with the history of arterial hypertension or ischemic heart disease. Creatinine clearance appears to decrease with age (each decade corresponds to a decrease of about 6.5 mL/min/1.73 m²). After establishing the diagnosis of primary hypothyroidism, hormonal treatment with levothyroxin was started. After four months of the treatment, adequate control of hypothyroidism was seen with progressive recovery of kidney function and restore of serum creatinine levels, that was somewhat unexpected. Still, similar findings has been observed by other authors: in older patients with various illnesses, even with the moderate renal atrophy on ultrasound images, thyroid replacement therapy recovered renal creatinine clearance to physiological values.4,5,12

Hyponatremia, as the commonest electrolyte derangement in hypothyroidism, did not appear in any of our patients. Because of the mild elevation of serum CK levels and the mild form of myalgia, we did not find it necessary to perform measurement of serum and urinary myoglobin levels. Both of our patients were presented with elevated CK and cholesterol levels. A deficit in the expression of the hepatic low density lipoprotein (LDL) receptor gene in hypothyroidism diminishes LDL cholesterol clearance which results in hypercholesterolemia. A degree of metabolic dysfunction in skeletal muscle was seen even in subclinical hypothyroidism.13 Similary to kidney disfunction, this could be reversed with thyroid hormone treatment. In the presented cases, a few months after the introduction of thyroxine replacement therapy and normalisation of serum TSH levels, creatinine clearance, serum cholesterol and serum CK levels recovered to the normal vaelues, no matter of the clinical presentation of hypothyroid state, or the age of the patients.

There are some published clinical case reports confirming stabilisation of kidney function in patients with chronic kidney disease after correction of thyroid function.3,14 There are also described cases of acute deterioration of kidney function in patients with chronic kidney disease and unrecognised hypothyroidism.15 We therefore recommends measurement of serum thyrotropin and thyroxin levels in all cases of renal failure with undefined renal desease, even if the typical clinical presentation of hypothyroidism is absent. We also recommend that thyroid hormone assays should be performed in all patients with chronic kidney disease whose kidney function is rapidly worsening.

Conclusion

The presence of reversal renal failure as the consequence of hypothyroidisms is usually subtle and frequently overlooked. Knowledge of the association between hypothyroidism and deterioration of renal function is very important in clinical practice.

This association must be recognized in time, avoiding the unnecessary diagnostic procedures that postpone adequate treatment.

REFERENCES


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