Hypothyroid myopathy with periodic paralysis as the main symptom: a case report and literature review

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Abstract: Hypothyroid myopathy is a skeletal muscle disease caused by hypothyroidism. However, patients with hypothyroidism are often misdiagnosed as polymyositis if they do not have a clear history of thyroid gland or obvious hypometabolic symptoms, but with myasthenia and myalgia as the main symptoms or the first symptoms. Moreover, hypothyroid myopathy with periodic paralysis as the first symptom is rare in clinic. In this study, we summarized the clinical data of 1 case of hypothyroid myopathy with periodic paralysis as the first symptom in our clinical diagnosis and treatment. A 27-year-old male patient with recurrent periodic paralysis was found with hypothyroidism during a most recent attack of myasthenia and was diagnosed with hypothyroid myopathy, which was relieved after oral administration of levothyroxine. We also found 13 similar cases reported internationally, and summarized their clinical characteristics, diagnosis, and treatment methods to provide reference for the clinical diagnosis and treatment of such cases. In general, periodic paralysis may be the main symptom or even the first symptom of hypothyroid myopathy, which is easy to be confused with renal tubular acidosis (RTA) or other autoimmune diseases. The diagnosis is mainly based on the detection of thyroid function and thyroid autoantibodies. Timely supplement of thyroxine and correction of electrolyte disorders are the key to treatment.

Keywords: Hypothyroid myopathy; periodic paralysis; diagnosis; case report

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the true prevalence of neuromuscular complications during hypothyroidism is not easy to determine and may be underestimated. So, it is not difficult to diagnose hypothyroid myopathy if the patients have a clear history of hypothyroidism (primary hypothyroidism, secondary hypopituitarism hypothyroidism, autoimmune thyroiditis, post-thyroidectomy status, antithyroid drug prescription, etc.), or muscle lesions diagnosed according to the typical clinical symptoms of hypothyroidism (low basal metabolism syndrome, myxedema face, cardiovascular system, digestive system changes, etc.) (8). However, it is easy to misdiagnose hypothyroidism patients if they have no clear history of thyroid disease or no significant hypometabolism symptoms, but do have myasthenia and myalgia as the main symptoms or the first symptom (9). The condition most commonly confused with hypothyroid myopathy in clinic is polymyositis (10). However, hypothyroid myopathy with periodic paralysis as the first symptom is rare in clinic, and is mostly only known through case reports. This study summarized the clinical data of 1 case of hypothyroid myopathy with periodic paralysis as the first symptom in our clinical diagnosis and treatment. In the study, we also found 13 similar cases reported internationally, and summarized their clinical characteristics, diagnosis, and treatment methods to provide reference for the clinical diagnosis and treatment of such cases. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1578).

Case presentation

The patient was a 27-year-old male from Tianmen City, Hubei Province, and was admitted on September 23, 2017. Beginning 8 years prior, the patient had lower limb weakness and difficulty in walking. The examination in hospital found low serum potassium, so the patient was given potassium supplement for treatment with the symptoms being relieved after rest. On September 21, 2017, after exerting himself, the patient relapsed with lower limbs weakness and difficulty in walking but without loss of energy, fear of cold, lethargy, poor appetite, constipation, weight gain, or other symptoms. Consequently, the patient visited our emergency department for treatment. The examination results were as follows: serum potassium, 3.2 mmol/L; muscle enzyme, serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were normal. The symptoms were not significantly relieved after intravenous drip of potassium aspartate and oral administration of potassium chloride solution. On September 22, the serum potassium was 2.98 mmol/L, and intravenous and oral potassium supplement was continued. On the night of September 22, the serum potassium was 3.64 mmol/L, and the patient still felt weakness of the lower limbs, and so was admitted with periodic paralysis. The patient was previously healthy and denied any history of hypertension, thyroid dysfunction, or other diseases. His vital signs were normal: body temperature, 36.2 °C; pulse, 72/min; blood pressure 120/84, mmHg. The patient had no obvious thyroid enlargement, and no obvious abnormalities in the heart, lung, or abdomen. His muscle strength and upper limb muscle tension were generally normal, and he exhibited no obvious muscle atrophy or hypertrophy of the lower limbs, and no muscle tenderness. The muscle strength was grade 4, muscle tension decreased, and knee reflex and Achilles tendon reflex had weakened. Laboratory results during hospitalization, including blood biochemistry, urine biochemistry, and blood gas analysis, are shown in Table 1. Blood cortisol, aldosterone, and other examinations showed no abnormality. Electrocardiogram (ECG) revealed sinus rhythm and ST segment elevation. Chest X-ray showed no obvious abnormality. Abdominal color Doppler ultrasound showed fatty liver, with both kidneys and urinary bladder showing no obvious abnormality. Electromyography (EMG) showed no definite neurogenic or myogenic injury. The patient was diagnosed with HOPP, and continued oral and intravenous potassium supplement. Serum potassium on multiple retests was generally normal, while creatine kinase (CK) on multiple retests was elevated (Table 1). After 5 days, the subjective symptoms of the patient had improved with normal serum potassium. He refused further diagnosis and treatment due to personal reasons and was discharged.

On July 31, 2018, the patient again experienced weakness with pain in the lower limbs after exertion. Outpatient blood biochemistry and thyroid function detection are shown in Table 1. Liver enzymes were elevated: alanine aminotransferase (ALT), 81 U/L (reference value 0–50 U/L); aspartate transaminase (AST), 67 U/L (reference value 0–50 U/L). Twelve items of anti-ENA antibody were all negative. Thyroid color Doppler ultrasound showed diffused thyroid enlargement and abundant blood supply. EMG revealed no clear neurogenic or myogenic injury. According to these indicators, the patient was diagnosed with autoimmune thyroiditis complicated with hypothyroid myopathy, and was given levothyroxine sodium tablets 25 μg, 1 tablet/day orally. After 4 weeks, the patient indicated by
telephone follow-up that the weakness and myalgia of the lower limbs had disappeared.

We searched all relevant literature and found 13 cases with complete clinical diagnosis and treatment reports of hypothyroidism with periodic paralysis (Table 2). Of these, 5 cases with hypothyroid myopathy were previously relatively healthy without history of thyroid diseases or other underlying diseases. Periodic paralysis was their first symptom, and the course of periodic paralysis ranged from 2 weeks to 2 years. The main symptom was limb weakness, especially lower limb weakness, without respiratory muscle or sphincter involvement. The other 8 cases of hypothyroid myopathy with periodic paralysis were complicated with other clinical conditions (Table 3). The treatment of all cases is summarized in the discussion section. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Table 1 Laboratory results in the patient with hypothyroid myopathy with hypokalemic periodic paralysis as the first symptom

<table>
<thead>
<tr>
<th>Date</th>
<th>Na+ (mmol/L)</th>
<th>K+ (mmol/L)</th>
<th>CL− (mmol/L)</th>
<th>CK (U/L)</th>
<th>Urine K+ (mmol/24 h)</th>
<th>Urine PH</th>
<th>Blood PH</th>
<th>AnGap (mmol/L)</th>
<th>TSH (uIU/L)</th>
<th>FT4 (pmol/L)</th>
<th>aTPO (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-9-21</td>
<td>142</td>
<td>3.2</td>
<td>96</td>
<td>164</td>
<td>5.4</td>
<td>15.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017-9-22</td>
<td>141</td>
<td>2.98</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017-9-23</td>
<td>137</td>
<td>4.27</td>
<td>98.2</td>
<td>619</td>
<td>8</td>
<td>7.3</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017-9-27</td>
<td>142</td>
<td>3.8</td>
<td>103.7</td>
<td>977</td>
<td>83.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018-7-31</td>
<td>142</td>
<td>3.67</td>
<td>100.4</td>
<td>142</td>
<td>10.58</td>
<td>13.58</td>
<td>85.59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference value: Na+ 137–147 mmol/L, K+ 3.5–5.3 mmol/L, CL− 99.0–110.0 mmol/L, CK 26–218 U/L, AnGap 5.0–8.0 mmol/L, TSH 7.3–7.45 μIU/mL, FT4 8–16 pmol/L, aTPO 0.35–5.5 U/mL.

CK, creatine kinase; TSH, thyroid stimulating hormone; FT4, free thyroxine.

Table 2 Clinical data of 5 previously healthy cases of hypothyroid myopathy with periodic paralysis as the first symptom

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (year)</th>
<th>K+</th>
<th>CK</th>
<th>FT4</th>
<th>TSH</th>
<th>TPOAb (IU/mL)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>China (11)</td>
<td>Female</td>
<td>36</td>
<td>3.37 mmol/L</td>
<td>380 U/L</td>
<td>0.32 μg/dL</td>
<td>288.8 IU/mL</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>2.</td>
<td>India (12)</td>
<td>Female</td>
<td>38</td>
<td>1.8 mmol/L</td>
<td>241 U/L</td>
<td>–</td>
<td>&gt;100 mIU/mL</td>
<td>287</td>
</tr>
<tr>
<td>3.</td>
<td>UK (13)</td>
<td>Female</td>
<td>8</td>
<td>Normal</td>
<td>Normal</td>
<td>11.1 (8.5–24) pmol/L</td>
<td>10.9 (0.35–4) mU/mL</td>
<td>132</td>
</tr>
<tr>
<td>4.</td>
<td>India (14)</td>
<td>Female</td>
<td>30</td>
<td>Fluctuation 1.6–3.2 meq/L</td>
<td>1,067 mg/dL</td>
<td>Low level, no specific values</td>
<td>&gt;100</td>
<td>386.4</td>
</tr>
<tr>
<td>5.</td>
<td>Sri Lanka (15)</td>
<td>Male</td>
<td>30</td>
<td>2.2 mmol/L</td>
<td>234 (24–195) μL</td>
<td>Normal</td>
<td>16.5 (0.3–4.2) mU/L</td>
<td>324</td>
</tr>
</tbody>
</table>

–, the results not reported; (), a range of reference values. CK, creatine kinase; TSH, thyroid stimulating hormone; FT4, free thyroxine; EMG, electromyography.

Discussion

We found a total of 14 relevant cases: 13 cases from literature review and 1 case from our study. Eleven cases (78.6%) were from Asian countries, of which 6 (42.9%) were from the South Asian countries of India and Sri Lanka, which is consistent with the epidemiological characteristics of sporadic HOPP being more common in Asian populations (23). However, in this study, the female-to-male ratio was 10:4 (71.43% in females and 28.57% in males), which is the opposite trend to the gender difference reported in the incidence of primary HOPP (about 38% in females and 62% in males) (24). This may be due to
the fact that primary diseases such as chronic lymphocytic thyroiditis and hypothyroidism have a higher incidence in the female population.

Renal tubular acidosis (RTA) is a chronic metabolic acidosis caused by distal renal tubular secretion of hydrogen ions and/or proximal bicarbonate reabsorption disorder, and is often accompanied by hypokalemia, and disorders of calcium and phosphate metabolism. It is also a common cause of HOPP. RTA is also common in autoimmune diseases such as Sjogren’s syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), and chronic lymphocytic thyroiditis. Chronic lymphatic thyroiditis, in turn, is the most common cause of hypothyroidism, which explains why as many as 6 of 14 hypothyroidism cases (42.9%) had RTA. In addition to cases 11 and 13, which were definitely diagnosed with Sjogren’s syndrome, RTA in other cases was likely due to chronic lymphocytic thyroiditis (20, 22). Renal secretion of H+ depends on the transport of distal convoluted tubule cells through the hydrogen-potassium ATP pump. In the state of hypothyroidism, the number and function of the hydrogen-potassium ATP pump are decreased, and there is a higher risk of acidosis and hypokalemia (25). HOPP is more likely to occur when combined with other factors affecting acid-base balance and water-electrolyte balance, such as taking diuretics, alcohol abuse, or diabetes (16, 18). RTA is diagnosed based on clinical symptoms and some auxiliary examinations. Clinical symptoms include hyperchloremic metabolic acidosis with normal anion gap, urine pH persistently >5.5, susceptibility to renal calculi, while auxiliary examinations include sodium chloride load test and furosemide test. In September 2017, during the onset of periodic paralysis, our patient experienced hypokalemia with acidosis (arterial blood PH 7.30), and alkaline urine (urine PH 8.0). The possibility of RTA was considered, but it was not confirmed because of the normal blood chloride level and increased anion gap, and the patient refused further examination.

Table 3 Clinical data of 8 cases of hypothyroid myopathy with periodic paralysis complicated with other clinical conditions

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (year)</th>
<th>K+</th>
<th>CK</th>
<th>TSH</th>
<th>TPOAb</th>
<th>Other clinical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Japan (16)</td>
<td>Female</td>
<td>69</td>
<td>1.3 meq/L</td>
<td>8,522 mU/mL</td>
<td>25.1 µU/mL</td>
<td>&gt;1,000 IU/mL</td>
<td>Hypertension; taking thiazide diuretics</td>
</tr>
<tr>
<td>2. Peru (17)</td>
<td>Male</td>
<td>17</td>
<td>1.44 mmol/L</td>
<td>–</td>
<td>5.5 (0.27–4.2) mIU/mL</td>
<td>48.2 IU/mL</td>
<td>Distal renal tubular acidosis; growth retardation</td>
</tr>
<tr>
<td>3. India (18)</td>
<td>Male</td>
<td>56</td>
<td>1.7 mmol/L</td>
<td>2.33 (0.66–4.0) µkat/L</td>
<td>12.06 (0.5–5.5) mIU/mL</td>
<td>–</td>
<td>Distal renal tubular acidosis; alcohol abuse</td>
</tr>
<tr>
<td>4. India (18)</td>
<td>Female</td>
<td>55</td>
<td>2.4 mmol/L</td>
<td>23.43 µkat/L (0.66–4.0)</td>
<td>36.08 (0.5–5.5) mIU/mL</td>
<td>–</td>
<td>Vomiting with fever; hypokalemia; hypomagnesemia; metabolic alkalosis; diabetes mellitus</td>
</tr>
<tr>
<td>5. Saudi Arabia (19)</td>
<td>Female</td>
<td>23</td>
<td>2.7 (3.6–5.0) meq/L</td>
<td>350 (39–117) U/L</td>
<td>Normal</td>
<td>443 (0–35) IU/mL</td>
<td>Distal renal tubular acidosis; pathological fracture; short stature</td>
</tr>
<tr>
<td>11. Peru (20)</td>
<td>Female</td>
<td>45</td>
<td>1.4 meq/L</td>
<td>246 U/L</td>
<td>Increased</td>
<td>High titer</td>
<td>Systemic lupus erythematosus; Sjogren’s syndrome; distal renal tubular acidosis</td>
</tr>
<tr>
<td>12. India (21)</td>
<td>Female</td>
<td>40</td>
<td>1.8 meq/L</td>
<td>Normal</td>
<td>31.6 (0.5–5.5) mcU/mL</td>
<td>39.86 (0–18) IU/mL</td>
<td>Distal renal tubular acidosis</td>
</tr>
<tr>
<td>13. China (22)</td>
<td>Female</td>
<td>38</td>
<td>3.0 mmol/L</td>
<td>–</td>
<td>28.95 (0.55–4.78) µU/mL</td>
<td>&gt;1,300 (&lt;60) IU/mL</td>
<td>Primary Sjogren’s syndrome; renal tubular acidosis</td>
</tr>
</tbody>
</table>

–, the results not reported; (), a range of reference values; CK, creatine kinase; TSH, thyroid stimulating hormone.

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in 70–90% of polymyositis cases, while EMG shows no specificity in hypothyroid myopathy, which can be neurogenic, myotonic, or normal. The typical symptoms of muscle biopsy in polymyositis indicate muscle fiber necrosis, inflammatory cell infiltration, and perifascicular muscle atrophy, while muscle biopsy in hypothyroid myopathy is mostly normal or shows slight uncharacteristic muscle pathological changes. However, EMG and muscle biopsy are difficult to use as routine examinations in clinic due to the limitation of objective conditions. Therefore, thyroid function examination and thyroid autoantibody examination are important for the diagnosis of patients with clinical symptoms of unexplained muscle weakness, hypokalemia, and elevated muscle enzymes. For patients with recurrent periodic paralysis, a single normal result in a thyroid function test cannot rule out the possibility of hypothyroid myopathy (as the case reported here). If the patient experiences recurrent muscle weakness, thyroid function should be reexamined in time.

In terms of treatment, 13 of 14 patients were treated with a potassium supplement (intravenous or oral). In case 3 (13), the patient had normal serum potassium at the onset of periodic paralysis, and limb weakness did not recur after thyroxine supplement. In the 13 patients with hypokalemia, the time for serum potassium to return to normal levels after potassium supplementation varied from hours to weeks, with 3–7 days being the most common duration. In a few cases (18,20), serum potassium levels decreased in the initial phase of potassium supplement. In this condition, patients required more potassium supplement, and hypokalemia was relieved even a few hours after receiving continuous intravenous pumping of potassium (20). A total of 13 patients were treated with exogenous thyroxine supplement at a dose of 25–150 μg/day, and thyroid function spontaneously returned to normal in case 6 (16) at 36 days after onset (without thyroxine supplementation). Of note, in some cases, after thyroxine therapy was started, hypokalemia could not be quickly relieved (12,14), and serum potassium levels returned to normal after continued potassium supplement for 4 weeks after starting oral levothyroxine. In case 13, long-term oral potassium citrate was still required after discharge. The reason for this “delayed” correction of hypokalemia may be related to the diuretic effect and increased potassium excretion during the initial phase of thyroxine administration (15). In addition to potassium and/or thyroxine supplement, patients with other clinical conditions (Table 3) were also given alkali, magnesium, antihypertensive, hypoglycemic, immunosuppressive, anti-osteoporosis, and other treatments according to the primary disease type. All patient symptoms were controlled after timely treatment. Among these patients, case 7 stopped taking levothyroxine without authorization 3 weeks after initial treatment, and developed more severe muscle weakness with hypokalemia 1 week after drug withdrawal. The patient was readmitted for potassium, alkali, and thyroxine supplementation, and the symptoms were relieved (17).

In summary, hypothyroid myopathy characterized by periodic paralysis is uncommon in clinic, but periodic paralysis has the potential to be the first symptom of hypothyroid myopathy. For patients with recurrent skeletal muscle flaccid paralysis, a comprehensive thyroid disease laboratory examination [thyroid function and antibodies like autoantibodies to thyroid peroxidase (TPOAb)] is recommended to exclude thyroid dysfunction (hyperthyroidism or hypothyroidism), regardless of serum potassium level abnormalities or obvious basic metabolic abnormalities. For patients of HOPP with RTA, chronic lymphocytic thyroiditis needs to be screened for, along with connective tissue diseases, such as Sjogren’s syndrome and SLE. Correction of abnormal serum potassium level and supplementation of an appropriate amount of thyroxine can effectively control periodic paralysis caused by hypothyroidism. However, it should be noted that clinical conditions such as the diuretic effects of thyroxine supplementation and combined acidosis may lead to a slow increase of serum potassium in patients with hypokalemia. Thus the route, dose, and course of potassium supplementation may vary from person to person.

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Footnote

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Ethical Statement: The authors are accountable for all
aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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