Thyrotoxic myopathy: research status, diagnosis, and treatment

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Abstract

Thyrotoxic myopathy is hyperthyroidism accompanied by muscle lesions. It is recognized as the general term for a group of symptoms with several main manifestations of several hyperthyroidism patients in the course (e.g. muscle weakness, muscle paralysis, or pain). From the clinical perspective, it may only be manifested as muscle-related symptoms. The symptoms of high metabolic syndrome (e.g. thyrotoxicosis) are absent, obscured, or relatively delayed, so it can be easily misdiagnosed. Accordingly, patients experiencing the first symptom of myopathy should concentrate on the possibility of thyrotoxic myopathy. Given the clinical characteristics, thyrotoxic myopathy can be devided into chronic thyrotoxic myopathy, thyrotoxicosis with periodic paralysis, hyperthyroidism with myasthenia gravis, as well as infiltrating exophthalmos with ophthalmoplegia. In this paper, we review thyrotoxic myopathy research status, diagnoses, and treatments. (Endokrynol Pol 2022; 73 (1): 157–162)

Key words: thyrotoxic myopathy; thyrotoxicosis; periodic paralysis; hyperthyroidism; myasthenia gravis

Introduction

Thyrotoxic myopathy (TM) is a complication of hyperthyroidism [1]. In the clinical field, given the characteristics exhibited by the disease and the different parts involved, TM can be devided into chronic thyrotoxic myopathy (CTM), thyrotoxicosis with periodic paralysis (TPP), acute thyrotoxic myopathy (ATM), hyperthyroidism accompanied by myasthenia gravis, as well as infiltrating exophthalmos accompanied by ophthalmoplegia [1]. Among the mentioned categories, CTM and TPP are considered as the most common [2, 3]. Some TM patients experience hyperthyroidism symptoms that are not typical. The mentioned symptoms are difficult to diagnose early and are easily confused with primary myopathy, thereby causing the rate of misdiagnosis to be high. To present more insights for physicians into TM, increase the diagnostic accuracy, and elucidate the characteristics and pathogenesis of the disease, we review the existing progress of TM research.

Chronic thyrotoxic myopathy

Chronic thyrotoxic myopathy is a common TM that occurs before or after hyperthyroidism. It shows an insidious onset and slow progress. CTM has general initial symptoms (e.g. proximal muscle involvement, distal muscle rarely affected, as well as rare bulbar paralysis respiratory and muscle involvement). The symptoms are primarily manifested as symmetrical limb weakness, and a single limb is involved [4], with the manifestation of progressive muscle weakness, wasting, and even atrophy, without muscle paralysis and sensory disturbance. Muscle weakness first involves the proximal muscle group of the body, the scapular girdle muscle is more involved than the pelvic girdle muscle, and extension is involved more than flexion. Overall, patients often complain about difficulties in climbing stairs, standing up from a squatting position, as well as combing their hair. In most patients, serum potassium, creatine kinase (CK), and myoglobin levels are normal.

For the pathogenesis of CTM, excessive thyroid hormone can reduce CK activity and the contents of creatine and phosphate in skeletal muscle [6]. Also, thyroid hormone exerts an impact on mitochondria in muscle cells, which causes swelling and degeneration, thereby causing energy metabolism disorder in muscle cells [7, 8]. As a result, muscle weakness and muscle atrophy are induced. On the whole, the proximal muscle group of the human body covers muscle red fibres that are abundant in mitochondria [7, 9]. For this reason, myopathy usually involves the proximal muscle group first. Pathological variations are largely characterized...
Thyrotoxic myopathy

Thyrotoxic myopathy Han Cui, Xiuwei Zhang

by degeneration of muscle fibres and infiltration of lymphocytes and plasma cells [10].

Through the control of hyperthyroidism, CTM can be effectively cured. After the hyperthyroidism is controlled, symptoms (e.g. muscle weakness and atrophy) can be recovered. Electromyography (EMG) recovery cannot keep abreast with the occurrence of clinical symptoms, and the improvement of muscle atrophy is time-consuming. From the clinical perspective, CTM is easy to diagnose if the patient experiences muscle weakness after a definite diagnosis of hyperthyroidism. However, some patients first experience the symptoms of muscle weakness, muscle atrophy, and other CTM symptoms, so it can be easily misdiagnosed in the department of neurology or rheumatology. In addition, some patients do not show obvious symptoms of muscle weakness and muscle atrophy at the early stage of CTM. They can be easily diagnosed as hyperthyroidism, whereas the possibility of CTM is ignored. Thus, in clinical studies, patients with paroxysmal muscle weakness and pain should be rigorous about the possibility of CTM. Furthermore, thyroid function and EMG should be examined to confirm the diagnosis. Hyperthyroidism patients should receive routine EMG to prevent missed diagnoses.

Thyrotoxicosis with periodic paralysis

Thyrotoxicosis with periodic paralysis is correlated with abnormal potassium metabolism, immune factors, mental factors, etc. In addition, it shows significant ethnic differences [11, 12]. Asians most commonly have significant TPP, followed by Latinos and Caucasians [13]. It is therefore demonstrated that TPP is correlated with genetic susceptibility. Male-to-female ratio = 20:1–26:1, and the age of onset mostly ranges from 20 to 40 years. It is capable of occurring before hyperthyroidism, during hyperthyroidism, or after remission of hyperthyroidism. TPP has been commonly diagnosed in China, mostly among young males (TPP occurs in 13% of males) [13], which may be correlated with the fact that young male patients are more engaged in strenuous exercise and heavy physical work when stressed. Furthermore, TPP may be correlated with inattention to dietary habits, accelerated metabolism attributed to overeating, accelerated glycogen synthesis, facilitated intracellular transfer of potassium, as well as abnormal androgen metabolism.

Overall, hypokalaemia occurs in the attack of TPP without increasing urinary potassium; laboratory examination shows that the transtubular potassium concentration gradient (TTKG) decreases. The intracellular potassium concentration in muscle cells is normal or elevated. The symptoms can be mitigated after potassium supplement treatment is performed. Accordingly, its occurrence may display a tight relationship to abnormal glucose metabolism and potassium metabolism. Activation of Na⁺, K⁺-ATPase in TPP patients exerts the dual effects of an increase in potassium ion influx, as well as a decrease in potassium efflux, which is primarily attributed to functional defects in inwardly rectifying potassium (Kir) channels. On that basis, hypokalaemia is precipitated, cell membrane polarity and muscle excitability are disturbed, hyperpolarization of the myocyte membrane is formed, the neuromuscular junction becomes unresponsive to normal nerve impulses, and muscle atony is induced, thereby largely triggering TPP symptoms [14–16]. Furthermore, TPP is generally accompanied by hypophosphataemia and hypomagnesaemia, capable of aggravating the symptoms of muscle weakness. It was reported that in specific Kir channels on skeletal muscle cell membranes, the C-terminal mutation D252N in the KCNJ18 gene encoding Kir2.6 channels and 17q loss-of-function mutations that are involved in the expression of Kir2.1 gene can both cause susceptibility to TPP [4, 5, 17–19]. Through the C-terminal mutation D252N in the KCNJ18 gene, the Kir channel membrane density can be downregulated, and the K⁺ current density efflux can be reduced by 34%. Nevertheless, the mentioned mutation only takes place in 25–33% of TPP patients in the United States, France, Singapore, and Belgium, and no such gene mutations are found in China and Thailand [17, 20].

The main clinical manifestations of TPP consist of paroxysmal muscle weakness, flaccid paralysis, bilateral symmetry, common involvement of the lower limb muscles, and rare involvement of the muscles above the neck. If TPP induces intercostal and diaphragmatic paralysis, dyspnoea may occur, which can be life-threatening if it is severe. TPP attacks more frequently at night, ranging from several hours to 2–3 days, and the frequency of attacks can be several times a day or once a few years. During attacks, muscle tension is eased, and tendon reflexes are diminished or absent, whereas paraesthesia is not caused. Blood potassium is decreased, electrocardiogram may undergo hypokalaemic variations, more significant arrhythmia is induced, urine potassium is normal, and some patients suffer from hypophosphataemia and hypomagnesaemia. Moreover, TPP is inconsistent with general hypokalaemic paralysis, the frequency of attacks is high, and symptoms of muscle weakness are also induced during the interictal period and progress to muscle atrophy. It should be differentiated from familial periodic paralysis, and TPP is commonly correlated with hypophosphataemia and hypomagnesaemia besides thyroid dysfunction, so myasthenic symptoms can be
obvious muscle atrophy is identified in patients, and binocular diplopia and hyperreflexia [28]. Overall, no Moreover, it can be manifested as bulbar paralysis with weakness of limbs, and even lethargy and coma [27].

induces chewing difficulties, dysphagia, dysphonia, primarily weakens the pharyngeal muscles and then tion is rapidly advanced to severe muscle weakness. In clinical manifestation is capable of mitigating symptoms during attacks, whereas it fails to prevent attacks. Avoiding predisposing factors and antithyroid can critically achieve TPP treatment. Several factors (e.g. massive intake of carbohydrates, excessive exercise, mental stress, infection, and trauma) can induce TPP, while drugs (e.g. insulin, potassium-depleting diuretics, epinephrine, physostigmine, and pilocarpine) are capable of triggering TPP attacks and should be avoided. Moreover, potassium supplementation cannot mitigate the onset of symptoms of some patients, when β-blockers can reverse Na+, K+-ATPase overactivation, and intravenous propranolol 1 mg per 10 min at a maximum dose of 3 mg is capable of reversing muscle weakness and hypokalaemia. Whether combined potassium supplementation is used or not, oral β-blockers can lead to a decline in the frequency of TPP attacks, as well as reduce the severity of the attack. The duration of using β-blockers continues until thyroid function returns to normal [24–26].

**Acute thyrotoxic myopathy**

Acute thyrotoxic myopathy has been relatively rare, which can be rapidly developed into bulbar paralysis. For this reason, it is known as acute hyperthyroid encephalopathy and acute hyperthyroid bulbar paralysis. It is also a rare and serious complication. In addition, it has a high mortality, and its cases have been rarely reported. Some patients may experience the complication of CTM, which is the end-stage manifestation of the disease. However, some patients have no CTM, and the disease can advance rapidly.

Acute thyrotoxic myopathy has an obscure onset, and the symptoms are atypical. The clinical manifestation is rapidly advanced to severe muscle weakness. In general, flaccid paralysis occurs in a few days, which primarily weakens the pharyngeal muscles and then induces chewing difficulties, dysphagia, dysphonia, weakness of limbs, and even lethargy and coma [27]. Moreover, it can be manifested as bulbar paralysis with binocular diplopia and hyperreflexia [28]. Overall, no obvious muscle atrophy is identified in patients, and only nonspecific changes can be observed in muscle biopsy. Sometimes the hyperthyroidism crisis may be merged, and then the respiratory muscle may cause respiratory muscle paralysis.

The treatment should be treated as hyperthyroidism crisis. If the treatment is not timely, or if the disease progresses rapidly, the risk of death will be raised. The cause of death is respiratory failure. It has been reported that the treatment of hyperthyroidism crisis (e.g. active control of hyperthyroidism, the use of glucocorticoids, β-blockers and Lugol’s solution, nutritional support, mechanical ventilation when breathing stops) can lead to better results [29].

In order to clarify the general situation of CTM, ATM, and TPP, we listed the comparison in Table 1, hoping to help physicians better distinguish and identify them.

**Supplementary contents: hyperthyroidism combined with myasthenia gravis**

Hyperthyroidism and myasthenia gravis (MG) are autoimmune diseases, but hyperthyroidism does not directly cause MG. Myasthenia gravis is commonly correlated with various autoimmune diseases (e.g. hyperthyroidism, Guillain-Barré syndrome, periodic paralysis, thymic disease, rheumatoid arthritis, Hashimoto’s thyroiditis, systemic lupus erythematosus, Sjogren’s syndrome, multiple sclerosis, and neuromyelitis optica), in which meta-analysis provides reliable evidence that thyroid disorders are prevalent in MG [32]. Therefore, the following is a supplementary description of hyperthyroidism combined with myasthenia gravis.

Some patients have predisposing factors, including catching a cold, exertion, cold, diarrhoea, and trauma, while most patients have no obvious inducement. The mechanism of the disease is still unclear. The mechanism might be that acetylcholinesterase and thyroglobulin display similarities in molecular sequence and spatial structure, and they may have common antigenic determinants [33]; besides, MG patients may be correlated with thymic abnormalities [34], thymic myoid cells express abundant acetylcholine receptor AChR [35], and TSH receptors are also presented in thymic tissue [36]. It is therefore demonstrated that the thymus may provide common autoantigens and initiate cross-autoimmune reactions in the pathogenesis of MG with hyperthyroidism [37]. Moreover, thyroid hormone is capable of affecting the function of the motor end-plate, even causing its morphological changes, as well as affecting acetylcholine synthesis and metabolism in nerve terminal mitochondria, which can reduce the binding force of acetylcholine and cholinergic receptors [33]. Furthermore, the proliferation of thymocytes

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**Table 1: Comparison of CTM, ATM, and TPP**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CTM</th>
<th>ATM</th>
<th>TPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Manifestations</td>
<td>Weakness of limbs</td>
<td>Weakness of limbs</td>
<td>Weakness of limbs</td>
</tr>
<tr>
<td>Differences</td>
<td>CTM includes a variety of symptoms</td>
<td>ATM includes a variety of symptoms</td>
<td>TPP includes a variety of symptoms</td>
</tr>
<tr>
<td>Treatment</td>
<td>CTM, ATM, and TPP</td>
<td>CTM, ATM, and TPP</td>
<td>CTM, ATM, and TPP</td>
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<tr>
<td>Prevention</td>
<td>CTM, ATM, and TPP</td>
<td>CTM, ATM, and TPP</td>
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</tbody>
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**References**

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[11] Furthermore, the proliferation of thymocytes...
induced by thyroid hormones is one of the bases of hyperthyroidism combined with MG.

When hyperthyroidism is correlated with MG, hyperthyroidism can occur before and after MG or occur simultaneously with MG. Seventy-five per cent of patients with hyperthyroidism have been reported the condition to occur before or simultaneously with MG [38]. 2–17.5% of MG patients are complicated with hyperthyroidism [39]. In the diagnosis of MG with hyperthyroidism, the clinical manifestations are the clinical features of MG, with ocular muscle weakness as the most common, with positive neostigmine test, increased AchR antibody, electromyography-heavy frequency electrical stimulation with low-frequency decrement and high-frequency decrement, accompanied by hyperthyroidism and a significant increase in thyroid hormones, and the effect is significantly promoted when the two diseases are treated simultaneously.

Antithyroid drugs are the first choice to treat hyperthyroidism, and patients with MG should undergo thyroid surgery or radioiodine therapy rigorously [40–42]. The treatment of MG mainly involves anticholinesterase drugs, immunosuppressive agents, and thymectomy. The effect of the treatment of hyperthyroidism on MG remains unclear. The symptoms of muscle weakness are mitigated in some MG patients. The hyperplastic thymus returns to normal as thyroid function returns to normal in some MG patients. Several MG patients even experience higher extent of flaccid paralysis. During the treatment of MG, the effect of thymectomy on thyroid function is also controversial, and some scholars consider that it hinders the control over hyperthyroidism, whereas it has also been reported that thymectomy can mitigate both muscle weakness and hyperthyroidism [39].

### Conclusion

Clinically, some patients that have hyperthyroidism symptoms are not typical. These patients are difficult to diagnose early, and they are easy to confuse with primary myopathy, thereby causing a high misdiagnosis rate. In the presence of the symptoms of muscle atrophy and muscle weakness on account of unknown reasons, the possibility of hyperthyroidism should be considered, and optimal effort should be made to improve the relevant examination and determine whether it is TM. The key to CTM treatment is recognized as control over hyperthyroidism. After hyperthyroidism is cured, CTM symptoms can be mitigated. Antithyroid therapy is critical to treating TPP. In the onset of TPP, oral or intravenous potassium supplement and oral triamterene can mitigate the symptoms of TPP whereas it fails to prevent the onset of TPP. When potassium supplementation does not mitigate the symptoms of TPP, β-blockers can reverse the over-activation of Na⁺, K⁺-ATPase. ATM should be treated as hyperthyroidism

| Table 1. Comparison of the basic features of chronic thyrotoxic myopathy (CTM), acute thyrotoxic myopathy (ATM), and thyrotoxicosis with periodic paralysis (TPP) |
|------------------------------------------|------------------------------------------|------------------------------------------|
| **CTM**                                  | **ATM**                                  | **TPP**                                  |
| General characteristics                   | Obscure onset, and the symptoms are atypical | Common in men aged 20–40 years            |
| Slow progress of disease                  | Rapidly developing severe muscle weakness | Periodic proximal lower limb muscle weakness or paralysis |
| Muscle weakness and atrophy               | Bulbar paralysis                          | No family history of the same disease     |
|                                           | No obvious muscle atrophy                 | The symptoms of hyperthyroidism are mild  |
|                                           | Sometimes it can be combined with hyperthyroidism crisis | High carbohydrate diet (overeating), exercise, and stress can induce TPP attack |
| Laboratory examination                    | Serum potassium, CK, and myoglobin levels were normal | During the attack, blood potassium and phosphorus decreased, accompanied by mild hypomagnesaemia |
|                                          | Only nonspecific changes were found in muscle biopsy | The acid-base balance index is normal |
|                                          |                                           | Serum TSH decreased and T4 and T3 increased. |
|                                          |                                           | Decreased urinary potassium excretion (TTKG decreased) |
|                                          |                                           | Urinary calcium-phosphorus ratio > 1.7 |
|                                          |                                           | Kir2.6 mutation combined with increased Na⁺, K⁺-ATPase activity |
| EMG                                      | Nonspecific myopathy changes              | Compound muscle action potential decrease |
|                                          | Muscle action potential has no response to adrenaline |
Crisis. To treat hypothyroidism combined with myasthenia gravis, the treatment of MG largely involves anticholinesterase, immunosuppressant, thymectomy, etc. The effect of the hypothyroidism treatment on MG remains unclear.

Conflict of interest
The authors declare that they have no conflict of interest.

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Ethical approval
This article does not contain any studies with human participants performed by any of the authors.

References
Thyrotoxic myopathy

Han Cui, Xiuwei Zhang


