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Thyrotoxic myopathy: research status, diagnosis, and treatment

Han Cui, Xiuwei Zhang

Department of Endocrinology, Affiliated Dongguan Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, China

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, acute thyrotoxic myopathy, 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; the distal muscle group and bilateral symmetry are subsequently involved in the sequence [5]. According to the proximal muscle group, 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

Xiuwei Zhang, Dongguan People's Hospital, No. 3, South Wandao Road, Xingu Chong, Wanjiang District, Dongguan City, Guangdong Province, Tel: +86-13580915733; e-mail: dgzxw@163.com

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 Caucasions [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 male) [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 meolism 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

aggravated. Furthermore, urinary calcium-phosphorus ratio > 1.7 in TPP patients acts as a sensitive and specific indicator to diagnose TPP [21, 22]. Next, TPP may be characterized by high renal potassium excretion at the early stage, and patients should pay attention to the risk of reflex hyperkalaemia when receiving potassium replacement therapy [23].

First, the symptoms of hyperthyroidism should be mitigated in treatments. Subsequently, oral or intravenous potassium supplementation and oral triamterene can be exploited during TPP attacks. Potassium supplementation 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 acetylocholine 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 endplate, 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

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	Slow progress of disease Muscle weakness and atrophy	Obscure onset, and the symptoms are atypical Rapidly developing severe muscle weakness Bulbar paralysis No obvious muscle atrophy Sometimes it can be combined with hyperthyroidism crisis	Common in men aged 20–40 years Periodic proximal lower limb muscle weakness or paralysis No family history of the same disease The symptoms of hyperthyroidism are mild High carbohydrate diet (overeating), exercise, and stress can induce TPP attack
Laboratory examination	Serum potassium, CK, and myoglobin levels were normal	Only nonspecific changes were found in muscle biopsy	During the attack, blood potassium and phosphorus decreased, accompanied by mild hypomagnesaemia 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	Nonspecific myopathy changes	Compound muscle action potential decrease Muscle action potential has no response to adrenaline

TSH — thyroid-stimulating hormone; CK — creatine kinase; T3 — triiodothyronine; T4 — thyroxine; EMG — electromyography; TTKG — transtubular potassium concentration gradient (TTK = urinary potassium concentration ÷ serum potassium concentration) ÷ (urinary osmotic pressure ÷ blood osmotic pressure) [30, 31]

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

crisis. To treat hyperthyroidism combined with myasthenia gravis, the treatment of MG largely involves anticholinesterase, immunosuppressant, thymectomy, etc. The effect of the hyperthyroidism 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

1. Kammer G, Hamilton C. Acute bulbar muscle dysfunction and hyperthyroidism. Am J Med. 1974; 56(4): 464–470, doi: 10.1016/0002-9343(74)90477-x, indexed in Pubmed: 4818413.
2. Lin SH. Thyrotoxic Periodic Paralysis. Mayo Clinic Proceedings. 2005; 80(1): 99–105, doi: 10.1016/s0025-6196(11)62965-0, indexed in Pubmed: 15667036.
3. Kung AWC. Clinical review: Thyrotoxic periodic paralysis: a diagnostic challenge. J Clin Endocrinol Metab. 2006; 91(7): 2490–2495, doi: 10.1210/jc.2006-0356, indexed in Pubmed: 16608889.
4. Hara K, Miyata H, Motegi T, et al. Thyrotoxicosis Presenting as Unilateral Drop Foot. Intern Med. 2017; 56(15): 2053–2056, doi: 10.2169/internalmedicine.56.8374, indexed in Pubmed: 28768980.
5. Ruff RL, Weissmann J. Endocrine myopathies. Neurol Clin. 1988; 6(3): 575–592, indexed in Pubmed: 3065602.
6. Aguer C, Harper ME. Skeletal muscle mitochondrial energetics in obesity and type 2 diabetes mellitus: endocrine aspects. Best Pract Res Clin Endocrinol Metab. 2012; 26(6): 805–819, doi: 10.1016/j.beem.2012.06.001, indexed in Pubmed: 23168281.
7. HOCH FL. Biochemical actions of thyroid hormones. Physiol Rev. 1962; 42: 605–673, doi: 10.1152/physrev.1962.42.4.605, indexed in Pubmed: 13954890.
8. Lawrie RA. The relation of energy-rich phosphate in muscle to myoglobin and to cytochrome-oxidase activity. Biochem J. 1953; 55(2): 305–309, doi: 10.1042/bj0550305, indexed in Pubmed: 13093682.
9. Harper ME, Seifert EL. Thyroid hormone effects on mitochondrial energetics. Thyroid. 2008; 18(2): 145–156, doi: 10.1089/thy.2007.0250, indexed in Pubmed: 18279015.
10. Korényi-Both A, Korényi-Both I, Kayes BC. Thyrotoxic myopathy. Pathomorphological observations of human material and experimentally induced thyrotoxicosis in rats. Acta Neuropathol. 1981; 53(3): 237–248, doi: 10.1007/BF00688027, indexed in Pubmed: 7223366.
11. Kang MH. ‚Kir'-ing thyrotoxic periodic paralysis. Clin Genet. 2010; 78(2): 136–138, doi: 10.1111/j.1399-0004.2010.01452_3.x, indexed in Pubmed: 20662856.
12. Maciel RMB, Lindsey SC, Dias da Silva MR. Novel etiopathophysiological aspects of thyrotoxic periodic paralysis. Nat Rev Endocrinol. 2011; 7(11): 657–667, doi: 10.1038/nrendo.2011.58, indexed in Pubmed: 21556020.
13. Kelley DE, Gharib H, Kennedy FP, et al. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. Arch Intern Med. 1989; 149(11): 2597–2600, doi: 10.1001/archinte.149.11.2597, indexed in Pubmed: 2818118.
14. Zhao SX, Liu W, Liang J, et al. China Consortium for the Genetics of Autoimmune Thyroid Disease. Assessment of Molecular Subtypes in Thyrotoxic Periodic Paralysis and Graves Disease Among Chinese Han Adults: A Population-Based Genome-Wide Association Study. JAMA Netw Open. 2019; 2(5): e193348, doi: 10.1001/jamanetworkopen.2019.3348, indexed in Pubmed: 31050781.
15. Falhammar H, Thorén M, Calissendorff J. Thyrotoxic periodic paralysis: clinical and molecular aspects. Endocrine. 2013; 43(2): 274–284, doi: 10.1007/s12020-012-9777-x, indexed in Pubmed: 22918841.
16. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012; 23(6): 985–988, doi: 10.1681/ASN.2012010046, indexed in Pubmed: 22460532.
17. Paninka RM, Carlos-Lima E, Lindsey SC, et al. Down-regulation of Kir2.6 channel by c-termini mutation D252N and its association with the susceptibility to Thyrotoxic Periodic Paralysis. Neuroscience. 2017; 346: 197–202, doi: 10.1016/j.neuroscience.2017.01.019, indexed in Pubmed: 28131627.
18. Chu PY, Cheng CJ, Tseng MH, et al. Genetic variant rs623011 (17q24.3) associates with non-familial thyrotoxic and sporadic hypokalemic paralysis. Clin Chim Acta. 2012; 414: 105–108, doi: 10.1016/j.cca.2012.08.004, indexed in Pubmed: 22910584.
19. Paninka RM, Mazzotti DR, Kizys MML, et al. Whole genome and exome sequencing realignment supports the assignment of KCNJ12, KCNJ17, and KCNJ18 paralogous genes in thyrotoxic periodic paralysis locus: functional characterization of two polymorphic Kir2.6 isoforms. Mol Genet Genomics. 2016; 291(4): 1535–1544, doi: 10.1007/s00438-016-1185-0, indexed in Pubmed: 27008341.
20. Ryan DP, da Silva MR, Soong TW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. Cell. 2010; 140(1): 88–98, doi: 10.1016/j.cell.2009.12.024, indexed in Pubmed: 20074522.
21. Venance SL, Cannon SC, Fialho D, et al. CINCH investigators. The primary periodic paralyses: diagnosis, pathogenesis and treatment. Brain. 2006; 129(Pt 1): 8–17, doi: 10.1093/brain/awh639, indexed in Pubmed: 16195244.
22. Lin SH, Chu P, Cheng CJ, et al. Early diagnosis of thyrotoxic periodic paralysis: spot urine calcium to phosphate ratio. Crit Care Med. 2006; 34(12): 2984–2989, doi: 10.1097/01.CCM.0000242249.10856.49, indexed in Pubmed: 16971853.
23. Tu ML, Fang YW, Leu JG, et al. An atypical presentation of high potassium renal secretion rate in a patient with thyrotoxic periodic paralysis: a case report. BMC Nephrol. 2018; 19(1): 160, doi: 10.1186/s12882-018-0971-9, indexed in Pubmed: 29973184.
24. Tella SH, Kommalapati A. Thyrotoxic Periodic Paralysis: An Underdiagnosed and Under-recognized Condition. Cureus. 2015; 7(10): e342, doi: 10.7759/cureus.342, indexed in Pubmed: 26623197.
25. Yu TS, Tseng CF, Chuang YY, et al. Potassium chloride supplementation alone may not improve hypokalemia in thyrotoxic hypokalemic periodic paralysis. J Emerg Med. 2007; 32(3): 263–265, doi: 10.1016/j.jemermed.2006.06.009, indexed in Pubmed: 17394988.
26. Rhee EP, Scott JA, Dighe AS. Case records of the Massachusetts General Hospital. Case 4-2012. A 37-year-old man with muscle pain, weakness, and weight loss. N Engl J Med. 2012; 366(6): 553–560, doi: 10.1056/NEJMcpc1110051, indexed in Pubmed: 22316449.
27. Boddu NJ, Badireddi S, Straub KD, et al. Acute thyrotoxic bulbar myopathy with encephalopathic behaviour: an uncommon complication of hyperthyroidism. Case Rep Endocrinol. 2013; 2013: 369807, doi: 10.1155/2013/369807, indexed in Pubmed: 23840978.
28. Chapman EM, Maloof F. Bizarre clinical manifestations of hyperthyroidism. N Engl J Med. 1956; 254(1): 1–5, doi: 10.1056/NEJM195601052540101, indexed in Pubmed: 13272862.
29. Haiyang Z, Xinhuan L, Shaozhen Q, et al. Clinicial analysis of 69 patients with acute hyperthyroid myopathy and its treatment. Chinjendmet. 2012.
30. Musso C, Liakopoulos V, De Miguel R, et al. Transtubular potassium concentration gradient: comparison between healthy old people and chronic renal failure patients. Int Urol Nephrol. 2006; 38(2): 387–390, doi: 10.1007/s11255-006-0059-5, indexed in Pubmed: 16868716.
31. Ethier JH, Kamel KS, Magner PO, et al. Urine electrolytes and osmolality: when and how to use them. Am J Nephrol. 1990; 10(2): 89–102, doi: 10.1159/000168062, indexed in Pubmed: 2190469.
32. Song RH, Yao QM, Wang B, et al. Thyroid disorders in patients with myasthenia gravis: A systematic review and meta-analysis. Autoimmun Rev. 2019; 18(10): 102368, doi: 10.1016/j.autrev.2019.102368, indexed in Pubmed: 31404702.
33. Sekiguchi Y, Hara Y, Takahashi M, et al. Reverse ‚see-saw' relationship between Graves' disease and myasthenia gravis; clinical and immunological studies. J Med Dent Sci. 2005; 52(1): 43–50, indexed in Pubmed: 15868740.
34. Fan L, Ma S, Yang Y, et al. Clinical differences of early and late-onset myasthenia gravis in 985 patients. Neurol Res. 2019; 41(1): 45–51, doi: 10.1080/01616412.2018.1525121, indexed in Pubmed: 30311866.
35. Jiang R, Hoehn KB, Lee CS, et al. Thymus-derived B cell clones persist in the circulation after thymectomy in myasthenia gravis. Proc Natl Acad Sci U S A. 2020; 117(48): 30649–30660, doi: 10.1073/pnas.2007206117, indexed in Pubmed: 33199596.
36. Nakamura T, Murakami M, Horiguchi H, et al. A case of thymic enlargement in hyperthyroidism in a young woman. Thyroid. 2004; 14(4): 307–310, doi: 10.1089/105072504323030979, indexed in Pubmed: 15142365.
37. Wortsman J, McConnachie P, Baker JR, et al. Immunoglobulins that cause thymocyte proliferation from a patient with Graves' disease and

an enlarged thymus. Am J Med. 1988; 85(1): 117–121, doi: 10.1016/0002-9343(88)90516-5, indexed in Pubmed: 3260449.
38. Datt V, Tempe DK, Singh B, et al. Anesthetic management of patient with myasthenia gravis and uncontrolled hyperthyroidism for thymectomy. Ann Card Anaesth. 2010; 13(1): 49–52, doi: 10.4103/0971-9784.58835, indexed in Pubmed: 20075536.
39. Trabelsi L, Charfi N, Triki Ch, et al. [Myasthenia gravis and hyperthyroidism: two cases]. Ann Endocrinol (Paris). 2006; 67(3): 265–269, doi: 10.1016/s0003-4266(06)72597-5, indexed in Pubmed: 16840920.
40. ENGEL AG. Thyroid function and myasthenia gravis. Arch Neurol. 1961; 4: 663–674, doi: 10.1001/archneur.1961.00450120077009, indexed in Pubmed: 13696794.
41. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. Clin Endocrinol (Oxf). 1995; 42(1): 45–50, doi: 10.1111/j.1365-2265.1995.tb02597.x, indexed in Pubmed: 7889631.
42. Claytor B, Li Y. Challenges in diagnosing coexisting ocular myasthenia gravis and thyroid eye disease. Muscle Nerve. 2021; 63(5): 631–639, doi: 10.1002/mus.27118, indexed in Pubmed: 33247453.