

# A Rare Case of Thyrotoxic Periodic Paralysis 17-Year-old-Boy with Graves' Disease

Putu Dianisa Rosari Dewi<sup>1</sup>, I Made Arimbawa<sup>2</sup>

<sup>1-2</sup>Department of Child Health, Medical Faculty of Udayana University/Sanglah Hospital, Denpasar, Indonesia

**Abstract:** *Thyrotoxic periodic paralysis is an uncommon hyperthyroidism-related condition characterized by sudden-onset, recurrent and reversible episodes of muscle weakness. We reported one patient male, 17-year-old with sudden onset tetraparesis, inability to urinate without breathing difficulty. History of palpitation and increase of appetite since one month prior to admission. He also complained weight loss for the last two months. Physical examination revealed soft diffuse symmetric mass on anterior part of neck, 4x5 cm in size, fine border, fixed, moved when swallowing, no pain on palpation. The motor grade was II on upper limbs and I on lower limbs. Laboratory examinations showed severe hypokalemia, low TSH, low FT3, high FT4, and high TRab. Electrocardiography results were sinus tachycardia, right bundle branch block and inferior ischemic. Thyroid ultrasonography revealed enlargement of right and left thyroid and isthmus with hypervascularity, according to the Graves' disease. After the management with antithyroid drug, beta-adrenergic blocker and potassium supplementation for TPP, he has remained euthyroid state and symptom free on the follow-up.*

**Keywords:** thyrotoxic periodic paralysis, hypokalemia, Graves' disease

## 1. Introduction

Thyrotoxic periodic paralysis (TPP) is an uncommon hyperthyroidism-related condition characterized by abrupt onset muscle weakness and hypokalemia resulting from rapid intracellular shift of potassium [1]. It is primarily reported in adult males in Asian populations, yet incidence among non-Asian populations such as Caucasians, African Americans, and Hispanics is very low. Thyrotoxic periodic paralysis is very rarely seen in the pediatric population [2]. The disorder has been described most frequently in Asian males. A total of 2% of thyrotoxic patients in China and Japan were reported to have this complication, and of these, 23 of the 25 patients were males. In the United States, the incidence of TPP in a non-Asian ethnic population is approximately one-tenth that found in Asian countries, but it also predominates in males [3].

The clinical picture is the onset of generalized paralysis, more severe in the lower extremities and in the early morning, often occurring after strenuous exercise and/or a high-carbohydrate meal. Most attacks resolve spontaneously and leave no residual weakness, cardiac arrhythmias can be life-threatening [4]. Recovery can be hastened by the administration of potassium. Symptoms of hyperthyroidism may be minimal or nonexistent. Laboratory findings include low potassium and elevated creatine phosphokinase concentrations in serum; electrocardiographic changes characteristic of hypokalemia may be present, and abnormal thyroid function studies are found [1].

Hypokalemia in TPP is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment, mainly into the muscles. Sodium, chloride, calcium, and potassium channels on cell membranes are responsible for membrane excitability and muscle contractions. Disruption of any of these cellular transport mechanisms may cause abnormalities in muscle contractibility, and paralysis. Thyroid hormones can increase  $3Na^+/2K^+$  ATPase activity in skeletal muscle, liver, and

kidney to induce an influx of potassium into the intracellular space [4]. The management of TPP includes correction of hypokalemia and treatment of the underlying hyperthyroid state. During periodic paralysis and marked hypokalemia, immediate supplement with potassium chloride is needed to prevent major cardiopulmonary complications [1].

TPP usually presents in the third to fifth decade of life. We describe a rare case of an Asian adolescent male presenting with acute-onset paralysis and severe hypokalemia and highlight the importance of recognizing TPP.

## 2. Case Report

A 17-year-old Indonesian male was admitted to emergency room (ER) with symmetric paralysis of his lower extremities and weakness of his upper extremities. He felt weakness on both feet 15 hours prior to hospital admission. His mother found him on the floor of his bedroom and unable to move. He recalled that his legs "gave out" and had weakness on his upper extremities 10 hours before admitted. He also complained difficulty in urinating 6 hours before admitted. There were no history of fever, swallowing difficulty, shortness of breath nor cervical or pelvic pain. History of trauma was denied. Pain nor numbness in four extremities were denied.

One month prior, he began having episodes of palpitation but have not yet evaluated by cardiologist. Palpitation appeared all day long and became worse after heavy activity. History of having chest pain was denied. He also sweated heavily at the same time when palpitation appeared, which worsen at night.

Patient also felt increased appetite since the last two months. He had four to five meals per day but his weight decreases 2 kilograms for the last two months. History of frequent urination, increased thirst and fatigue were denied. There was no history of prolonged diarrhea. Defecation was said to be normal.

Patient complained neck lump since one year ago and getting bigger since two months before admitted. Lump was noticed since 1 year but it had increased in size since the past two months. The lump was located at front of the neck. There was no pain when patient swallowed or at any activity. Lump at any other site was denied. Voice changes, fever, and shortness of breath since lump enlarged were denied. There was no complaint of tremor and goggled eyes.

On arrival at the ER, his blood pressure was 90/60 mmHg, and the heart rate was 110 beats/min. He was alert with a respiratory rate of 20 breaths/min and a body temperature of 36.8°C. On physical examination, no exophthalmos nor skin change was present. Soft diffuse symmetric mass on front neck, 4x5 cm in size, fixated, fine border, follow down when swallowing, no pain in palpation, and no redness on the skin. No bruits were detected. The lower and upper limbs had flaccid paralysis with intact sensory function. The motor grade was grade II on the both arms and grade I on the both legs. The muscle tone was markedly decreased on the both legs. The deep tendon reflexes were markedly decreased on the both lower extremities. No respiratory difficulty was detected. He had no significant medical history and had received no medication. His family history was negative for familial hypokalemic periodic paralysis or thyroid disease. Laboratory tests revealed the following serum metabolite levels; on the day of arrival, sodium 141 [135-150] mmol/L,

potassium 1.53 [3.5-5.5] mmol/L, calcium 9.9 [8.6-10.3] mg/dL, blood urea nitrogen (BUN) 14.6 [7-20] mg/dL, and creatinin 0.47 [0.7-1.2] mg/dL. Thyroid function test showed thyroid-stimulating hormone (TSH) level of less than 0.01 [0.27-4.20]  $\mu$ U/mL, T3 level of 11.82 [0.8-2.0] ng/mL, and free T4 level of 7.66 [0.93-1.70] pmol/L. Electrocardiography obtained sinus tachycardia, heart rate 118 bpm, normal QRS complex, no prolonged PR interval, right bundle branch block, and inferior ischemic.

Twenty-four hours urinary collection was performed resulted in potassium urine was 46.49 mmol/24 hours [25.00-100.00], sodium 276.00 mmol/24 hours [30.00-300.00], chlorine 293.10 mmol/24 hours [85-170], calcium 8.25 mmol/24 hours [2.5-9.00]. Thyroid autoantibodies showed thyroid peroxidase antibody level of 2,230 [-34] IU/mL. Ultrasonography examination revealed enlargement of both thyroid glands with heterogeneous increased echogenicity and increase vascularization, in accordance with Graves' disease. Multiple atypical lymphadenopathy were also found in both cervical area and parotid area (Fig. 1). Bone age resulted appropriate with boys aged 18-year-old. Fine needle aspiration biopsy was performed cervical anterior lymphadenopathy resulted follicle cell proliferation with toxic sign in accordance to Graves' disease.

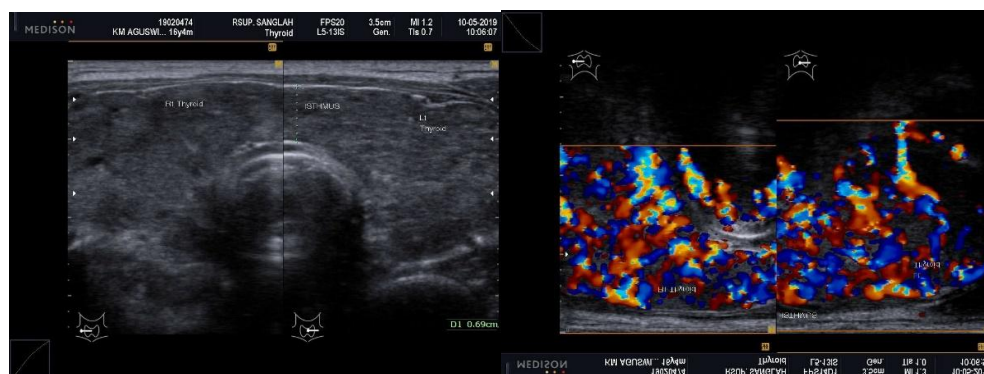


Figure 1 : Ultrasonography revealed enlargement thyroid glands and increased vascularization

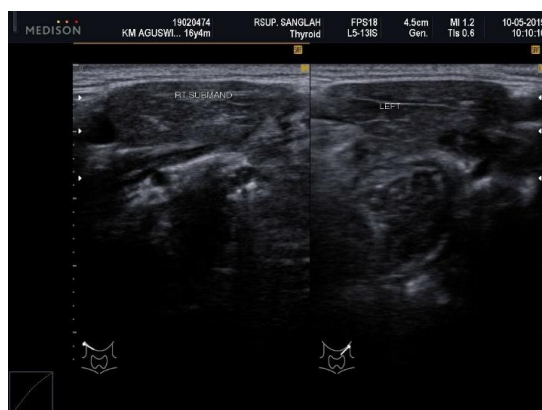


Figure 2: Multiple lymphadenopathy on cervical and parotid area as seen on ultrasonography

This patient was diagnosed this patient as thyrotoxic periodic paralysis associated with Graves' disease. He was given 0.75 mEq/kg of intravenous potassium chloride on a normal saline infusion in the emergency department. He was also prescribed with oral propranolol (10 mg BID) and methimazole (10 mg BID), which resulted in resolution of

his lower and upper extremities paralysis. On the first day of admission, his serum potassium level increased to 5.85 [3.5-5.5] mmol/L. Potassium correction was stopped and electrolyte was evaluated 3 days later with potassium level was 4.13 mmol/L. There was clinical improvement, concomitant with a progressive normalization of serum

electrolytes. Complete remission of symptoms was obtained in 24 hours. Upon discharge, the patient had completely recovered his neuromuscular functions and serial measurement of his serum potassium level in the hospital remained within normal limits without oral potassium supplements.

History of experiencing another paralysis episode was denied during 1 year follow-up.

### 3. Discussion

Thyrotoxic periodic paralysis is a sporadic muscle disorder characterized by episodes of muscle paralysis associated with hypokalemia in some, but not all, thyrotoxic individuals. [7]. Thyrotoxic periodic paralysis has been reported in various etiologies of hyperthyroidism including Graves' disease, subacute thyroiditis, toxic nodular goiter and TSH-secreting tumor [8]. A typical attack of thyrotoxic periodic paralysis lasts from a few hours to several days. Most attacks occur in the morning or evening [1]. The incidence of TPP in Chinese and Japanese thyrotoxic patients has been reported at 1.8% and 1.9%, respectively, whereas in North Americans at 0.1-0.2%. A male predominance has been widely described, with an overall male to female ratio ranging from 17:1 to 70:1 [4]. Some of 80% of TPP cases arise in the acute phase of hyperthyroidism. Muscle paralysis may be the only symptom at first manifestation of hyperthyroidism [6].

The pathogenesis of TPP is still unclear. A rapid and massive transfer of potassium from extracellular into intracellular compartments occurs in patients with TPP. In general, a transcellular K distribution is maintained by sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump activity. Thyroid hormone has been shown to increase Na/K-ATPase activity. Enhanced  $\beta$ -adrenergic activity in hyperthyroidism can also enhance Na/K-ATPase activity and administration of non-selective  $\beta$ -adrenergic blockers can abort or prevent TPP. Insulin also induces Na/K-ATPase activity; therefore, hyperthyroidism-induced hyperinsulinemia can also trigger TPP. Recently, a defect in potassium efflux may play an important role in the pathogenesis of TPP. Mutations in gene encoding Kir2.6, a skeletal muscle-specific Kir channel are also associated with TPP predisposing these patients with genetic variation to acute paralytic attack [9].

Graves' disease is the most common cause of hyperthyroidism in children, accounting for more than 95% of cases. The pathogenesis of Graves' disease is not completely understood but is believed to include a complex interaction of genetic, immune, and environmental factors. Hypokalaemic paralytic attacks only occur during hyperthyroidism. Prodromes include muscle aches, stiffness, weakness or cramps 1 hour to 3 days before paralysis. Before presentation, most patients have experienced less severe muscle weakness that resolved spontaneously [11]. Attacks usually begin with weakness of the proximal muscles of the lower extremities, and may progress to tetraplegia, with the degree of muscle weakness corresponding to serum potassium levels. No correlations with serum T3 or T4 levels

have been found. Bowel and bladder function, facial expression, swallowing, and respiration are usually unaffected [12]. Our patient presented with muscle aches and weakness before paralysis which began with weakness of the muscles from lower extremities and progress to tetraparesis and impaired bladder function.

High intracellular potassium is corrected by a corresponding increase in potassium efflux through the Kir channel. When the Kir channel is mutated or during conditions of elevated insulin or catecholamines, extracellular flow of potassium is inhibited. This diminished potassium efflux contributes significantly to the increase in intracellular potassium. It has been postulated that both over activation of Na/ K+ ATPase pump and a lack of compensated outward potassium. flow through the Kir channel must be present to cause TPP [13].

Patients with TPP often present with hypophosphatemia, hypomagnesemia, and low urine potassium excretion with a normal acid-base balance. Electrocardiographic changes can occur in TPP, including tachycardia, increased QRS voltage, and first-degree atrioventricular block [8]. A precipitating factor for an attack could be identified in 34% of patients. Precipitating factors include high carbohydrate ingestion, alcohol, infection (mainly respiratory or urinary tract infections have been described), excessive exercise, and use of  $\beta$ 2-adrenergic bronchodilators. Furthermore, an attack was inducible by glucose loading in a minority of patients. Patients usually experience attacks in the early mornings, and during warm seasons [14].

The clinical manifestations of Graves' disease are variably in many different age ranges. During childhood and adolescence, most patients with Graves' disease exhibit classic symptoms and signs. At the first, the specific symptoms and signs in the children are presence of diffuse goiter, tachycardia, anxiety, increased blood pressure, proptosis, increased appetite, tremor, easily sweating, and weight loss [15]. In our case, the patient complained of neck lump for one year without any symptoms. Since the last two months, the neck lump getting bigger with complained of palpitation, easily sweating, and increased of appetite.

Hyperthyroidism in children can have a wide variety of clinical manifestations, many of which are similar to those seen in adults. Children with Graves' disease are tall for age at presentation and their bone age tends to be advanced. A retrospective Italian study of 101 children with Graves' disease, although bone age was advanced at presentation, there were no adverse effects on subsequent growth, and adult height was consistent with genetic potential. In severe cases of hyperthyroidism, pubertal onset and progression may be delayed [16]. In our case, patient's height was consistent with his genetic potential and bone age examination was according to his age.

Medical providers should look specifically for signs and symptoms of hyperthyroidism including tachycardia, hypertension, exophthalmos, goiter, fine tremor, tongue fasciculation's, irregular menses, and weight loss [14]. Our patient's large goiter alerted the medical team to consider

TPP at presentation in the emergency department, which facilitated prompt diagnosis and treatment.

Generalized lymphoid hyperplasia occurs in Graves' disease and is associated with thymic hyperplasia. Thyroid ultrasonography generally reveals diffuse enlargement of the gland, a heterogenous background, and a general decrease in echogenicity. Other sonographic findings of hyperthyroidism often include hypervascularity and the presence of hypoechoic micronodules with an echogenic rim. Lymphadenopathy is often considered a finding concerning for malignancy. It is important to determine whether the lymphadenopathy is a result of the malignancy or the thyroiditis [17]. In our case, patient had multiple lymphadenopathies on cervical and parotid area. Biopsy was performed and resulted appropriate with Graves' disease.

A renal response to hypokalemia should be expected in patients with TPP. The urinary potassium excretion rate must be low in patients with TPP because hypokalemia is caused by an increased shift of potassium into cells [18]. Bone is extremely sensitive to thyroid hormone. Hypercalciuria and hyperphosphaturia have been reported in patients with documented hyperthyroidism [19]. In our case, urinary potassium level was normal while calcium urinary level was high.

The management of TPP includes correction of hypokalemia and treatment of the underlying hyperthyroid state. During periodic paralysis and marked hypokalemia, immediate supplement with potassium chloride is needed to prevent major cardiopulmonary complications [20]. In our case, this patient received 0.75 mEq/kg of intravenous potassium chloride. After potassium correction was given, potassium level was higher than normal but decreased gradually and symptoms of paralysis was resolved.

The danger of exogenous potassium administration is that potassium is released from cells rapidly when paralysis subsides, leading to the development of rebound hyperkalemia. Rebound hyperkalemia occurred in approximately 40% of patients of TPP, especially who received >90 mEq/dL of potassium chloride within the first 24 hr. In a retrospective study, Manoukian et al., reported that rebound hyperkalemia (potassium, >5.0 mEq/L) occurred in approximately 40% of patients with TPP, especially if more than 90 mEq of potassium chloride was given within 24 hours [11]. Lin, et al., recently conducted a case controlled study to evaluate whether potassium chloride supplementation speeded the recovery of TPP and the incidence of rebound hyperkalemia. They found that the average recovery time is 2 times shorter in patients with TPP treated with intravenous potassium chloride supplementation at a rate of 10 mEq/h than in controls [14]. In our case, this patient received total of 35 mEq of potassium. Rebound hyperkalemia occurred with insignificant sign and symptoms. Normal potassium level was achieved after 3 days.

The various options for treatment of Grave's disease in children include antithyroid drugs, radioactive iodine ablation, and thyroidectomy [12]. According to the American Thyroid Association guidelines, the suggested

starting dose of methimazole is 0.2–0.5 mg/kg/d, and methimazole should be used within a range of 0.1–1.0 mg/kg/d. Specifically, the suggested doses are 1.25 mg/d for infants, 2.5–5.0 mg/d for children aged 1–5 yr, 5–10 mg/d for children aged 5–10 yr, and 10–20 mg/d (i.e., the adult dose) for children and adolescents aged 10–18 yr. For severe cases, the dose can be increased to as high as twice the above-listed amounts.<sup>21</sup> In our case, this patient received 10 mg thyrozol BID then gradually decreased to 2.5 mg OD according to his TSH and fT4 level.

Graves' disease can lead to several complications such as cardiac arrhythmia and heart failure. Although dilated cardiomyopathy has been occasionally reported in adults with Graves' disease, it is rare in children [22]. In our case, we performed several examinations for her heart. The result from ECG monitoring was sinus tachycardia, from echocardiography there was mild tricuspid regurgitation and mild mitral regurgitation.

A patient is considered to be in remission if T3, T4, and TSH remain normal 1 year after discontinuation of antithyroid therapy [16]. The remission rates in various studies. The remission rates in adults with Graves' disease seem to be variable with studies from US reporting it at 20–30% remission after 12–18 months of dedication [23]. European study indicated a 50–60% remission rate after 5–6 years of treatment [24]. The remission rates in children seem to be lower than in adults. Remission rates in children with Graves' disease are around 20–30%, and seem to be worse for patients with large glands, high antibody levels or very high free T4 levels at diagnosis. Younger children have lower remission rates and higher relapse rates than older adolescents and adult patients [25]. In our case, the patient performs clinical improvement. His clinical manifestation at her first admission relieved, while waiting for the thyroid antibody result. This must be maintained by a good compliance from the patient to have continuous monitoring to doctor, or else thyrotoxicosis would appear again or worst, thyroid storm.

Because TPP does not recur once the patient is euthyroid, adequate control of hyperthyroidism is the mainstay of therapy. In conclusion, thyrotoxic periodic paralysis can occur in association with any of the cause of thyrotoxicosis. As we know, the most common cause of TPP in thyrotoxicosis is Graves' disease.

#### 4. Conclusion

A 17-year-old boy with sudden onset tetraparesis, inability to urinate without breathing difficulty. History of palpitation and increase of appetite since one month prior to admission. He also complained weight loss for the last two months. Physical examination revealed soft diffuse symmetric mass on anterior part of neck, 4x5 cm in size, fine border, fixed, moved when swallowing, no pain on palpation. The motor grade was II on upper limbs and I on lower limbs. Laboratory examinations showed severe hypokalemia, low TSH, low FT3, high FT4, and high TRab. Electrocardiography results were sinus tachycardia, right

bundle branch block and inferior ischemic. Thyroid ultrasonography was enlargement of right and left thyroid and isthmus with hypervascularity, according to the Graves' disease. Echocardiography revealed mild TR and mild MR. After the management with antithyroid drug, beta-adrenergic blocker and potassium supplementation for TPP, he has remained euthyroid state and symptom free on the follow-up.

## References

- [1] Lam L, Nair RJ, Tingle L. Thyrotoxic periodic paralysis. *Proc (Bayl Univ Med Cent)*. 2006;19(2):126-129.
- [2] Annie W. C. Kung, Thyrotoxic Periodic Paralysis: A Diagnostic Challenge, *The Journal of Clinical Endocrinology & Metabolism*, Volume 91, Issue 7, 1 July 2006, Pages 2490–2495.
- [3] Miller JD, Quillian W, Cleveland WW. Nonfamilial Hypokalemic Periodic Paralysis and Thyrotoxicosis in a 16-Year-Old Male. *Pediatrics*. 1997 Sep 1; 100(3):412.
- [4] Oh SB, Ahn J, Oh MY, et al. Thyrotoxic periodic paralysis associated with transient thyrotoxicosis due to painless thyroiditis. *J Korean Med Sci*. 2012; 27(7):822-826.
- [5] De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016; 388(10047):906-918.
- [6] Vijayakumar A, Ashwath G, Thimmappa D, Thyrotoxic Periodic Paralysis: Clinical Challenges, *Journal of Thyroid Research*, vol. 2014, Article ID 649502, 6 pages, 2014.
- [7] Hsieh CH, Kuo SW, Pei D, et al. Thyrotoxic periodic paralysis: an overview. *Ann Saudi Med*. 2004; 24(6):418-422.
- [8] Blick C, Nguyen M, Jialal I. Thyrotoxicosis. [Updated 2020 Dec 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482216/>
- [9] Kung AW, Lau KS, Cheung WM, Chan V. Thyrotoxic periodic paralysis and polymorphisms of sodium-potassium ATPase genes. *Clin Endocrinol (Oxf)*. 2006 Feb; 64(2):158-61. doi: 10.1111/j.1365-2265.2005.02442.x. PMID: 16430714.
- [10] Pirahanchi Y, Toro F, Jialal I. Physiology, Thyroid Stimulating Hormone. [Updated 2021 May 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499850/>
- [11] Manoukian MA, Foote JA, Crapo LM. Clinical and Metabolic Features of Thyrotoxic Periodic Paralysis in 24 Episodes. *Arch Intern Med*. 1999;159(6):601–606.
- [12] DeGroot LJ. Graves' Disease and the Manifestations of Thyrotoxicosis. [Updated 2015 Jul 11]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK285567/>
- [13] Cheng CJ, Kuo E, Huang CL. Extracellular potassium homeostasis: insights from hypokalemic periodic paralysis. *Semin Nephrol*. 2013;33(3):237-247.
- [14] Lin S-H, Huang C-L. Mechanism of Thyrotoxic Periodic Paralysis. *JASN*. 2012 Jun;23(6):985–8.
- [15] He L, Lawrence V, Moore WV, Yan Y. Thyrotoxic periodic paralysis in an adolescent male: A case report and literature review. *Clin Case Rep*. 2020 Nov 23; ccr3.3558.
- [16] Cassio A, Corrias A, Gualandi S, et al. Influence of gender and pubertal stage at diagnosis on growth outcome in childhood thyrotoxicosis: results of a collaborative study. *Clin Endocrinol (Oxf)*. 2006;64(1):53–57
- [17] Zhang K, Wu W, Wu Y, et al. Thymic lymphoid hyperplasia with Graves' disease in a 28-year-old female: a case report. *Gland Surg*. 2020;9(2):437-441.
- [18] Cheng CJ, Kuo E, Huang CL. Extracellular potassium homeostasis: insights from hypokalemic periodic paralysis. *Semin Nephrol*. 2013;33(3):237-247.
- [19] Dhanwal DK. Thyroid disorders and bone mineral metabolism. *Indian J Endocrinol Metab*. 2011;15 (Suppl 2):S107-S112.
- [20] Meseeha M, Parsamehr B, Kissell K, Attia M. Thyrotoxic periodic paralysis: a case study and review of the literature. *J Community Hosp Intern Med Perspect*. 2017;7(2):103-106. Published 2017 Jun 6.
- [21] Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association (Taskforce for the Revision of the Guidelines for the Treatment of Childhood-Onset Graves' Disease), Minamitani K, Sato H, Ohye H, Harada S, Arisaka O. Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016. *Clin Pediatr Endocrinol*. 2017; 26(2):29-62.
- [22] Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart*. 2007; 93:483–487.
- [23] Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: Management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011; 17:456–520.
- [24] Mazza E, Carlini M, Flecchia D, Blatto A, Zuccarini O, Gamba S, et al. Long-term follow-up of patients with hyperthyroidism due to Graves' disease treated with methimazole. Comparison of usual treatment schedule with drug discontinuation vs continuous treatment with low methimazole doses: A retrospective study. *J Endocrinol Invest*. 2008;31:866–72.
- [25] Hwang SM, Kim MS, Lee DY. Predictive factors for early response to methimazole in children and adolescents with graves disease: a single-institute study between 1993 and 2013. *Ann Pediatr Endocrinol Metab*. 2016;21:70-4