CLINICAL VIGNETTE

Subtle Signs of Thyrotoxicosis in Thyrotoxic Periodic Paralysis

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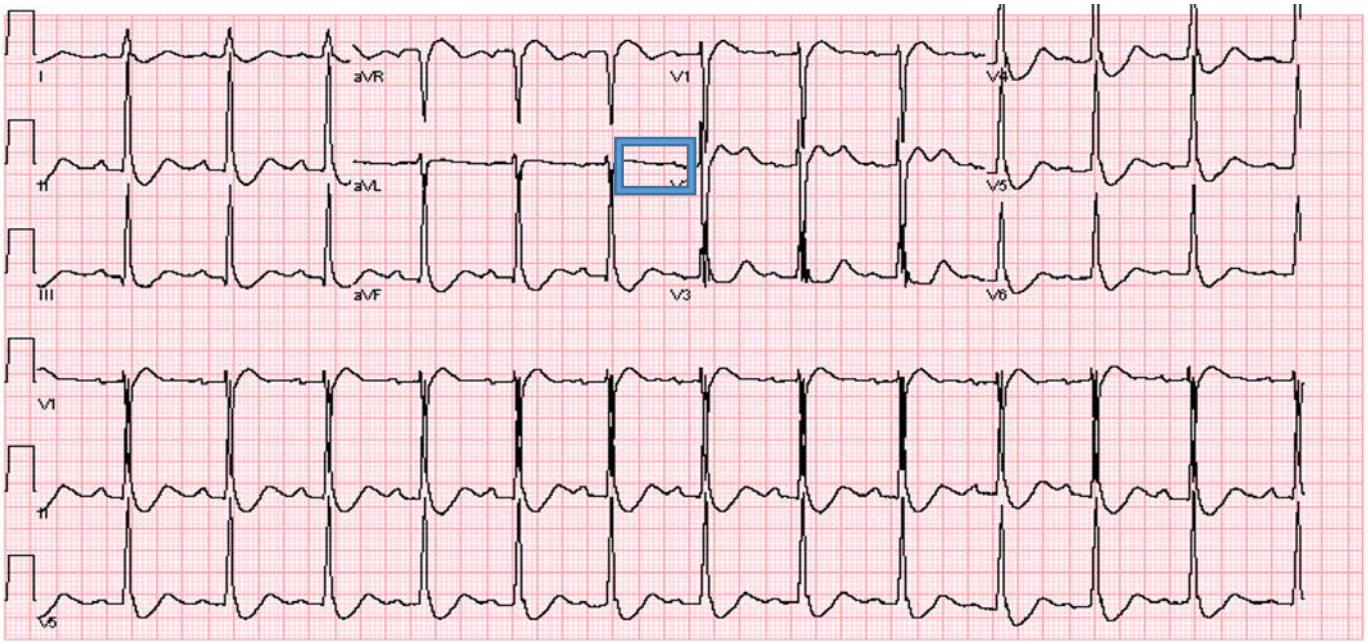
Case Report

A 26-year-old Asian male with a past medical history of Graves' disease presented to the emergency department after he awakened with bilateral lower and upper extremity weakness that morning. The patient was unable to stand unassisted and was brought to the ER by a friend. He had a similar episode more than five years prior that was less severe and lasted for a week before evaluation at an outside hospital. A potassium level of 2.5 was noted and he was discharged after electrolyte repletion. Enroute to the ED, the patient vomited and briefly lost consciousness. He denied recent URI, fever, chills, palpitations, weight loss, blurry vision, diarrhea, excessive sweating, or changes in hair or nails. He also denied recent steroid use, diuretic use or recent vigorous exercise. He was in his usual state of health prior to that moment.

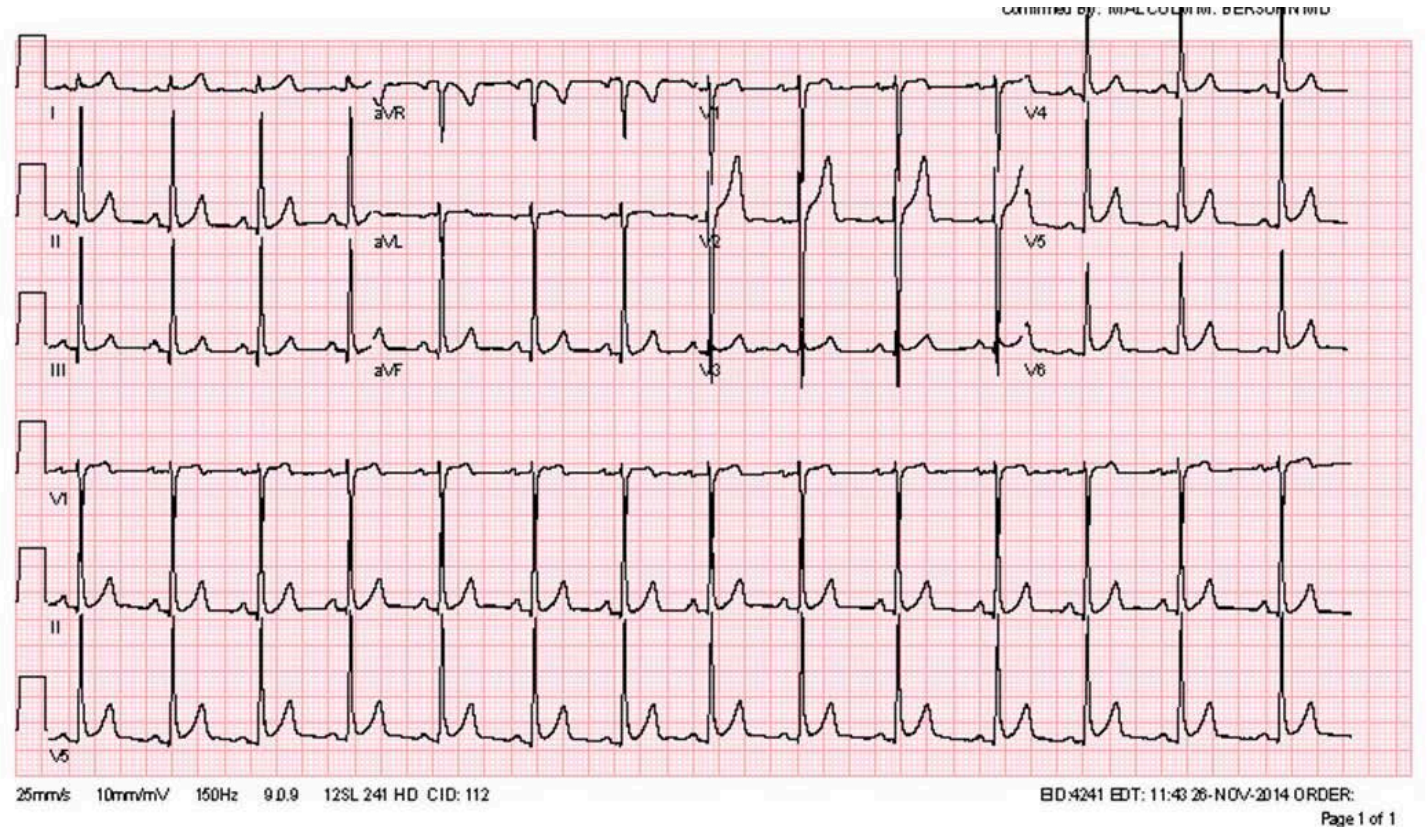
On physical exam he was afebrile with tachycardia and normal blood pressure. He had decreased strength in upper and lower extremities with diminished deep tender reflexes. He had no other neurologic deficits. A slight fine tremor was present.

Laboratory studies revealed a potassium of 1.5 mEq/L (3.6-5 mEq/L), magnesium 1.5 mg/dl (1.7-2.6mg/dl), phosphorus 1.2 mg/dl (2.7-4.5 mg/d;), TSH .007, elevated T4 and T3. EKG showed inverted t waves. The patient was given 1L of NS with 40 mEq KCL as well as 40 mEq of oral KCL. He was admitted to telemetry with pacemaker pads placed.

After the initial electrolyte repletion, potassium increased to 2.7 and he received additional 80 mEq of potassium chloride orally. Thyroid ultrasound the following day revealed a mildly enlarged thyroid with heterogeneous appearance with several nodules, moderate vascularity, and no microcalcifications. Thyroid scan revealed increased radioiodine uptake of 83% at 21 hours (normal- 10-36%) which was consistent with Graves Disease. Urine K/Cr ratio of 7.4 ruled out renal tubular acidosis, Gitelmans, and Barters. Despite subtle clinical signs of thyrotoxicosis, the patient's overall clinical picture of hyperthyroidism with electrolyte abnormalities was consistent with thyrotoxic periodic paralysis. He was started on oral propranolol 20 mg TID and methimazole 10mg BID. After aggressive electrolyte supplementation, the patient returned to clinical baseline with full strength, normal EKG and discharged with close follow up, including scheduled radioactive iodine ablation.



(Fig. 1. U-wave boxed in V2)



(Fig 2. EKG post potassium repletion)

Discussion

Thyrotoxic periodic paralysis (TPP) may be difficult to diagnose as it is often mistaken for more common causes of hypokalemia and lower extremity weakness; and subacute presentation of thyrotoxicosis and lack of awareness of the disorder.[1] Asian males are disproportionately affected. Thyrotoxic Asian males have TPP incidence of roughly 2% versus 0.2% in other groups in North America.[1-4] Over 95% of TPP occurs in males even though hyperthyroidism occurs more frequently in females.[4,5] The vast majority of patients present with their first episode between ages 20-40.[2]

It is important to distinguish TPP from other acute conditions that may require immediate intervention. These include myasthenia gravis, Guillain- Barre syndrome, transverse myelitis, acute thyrotoxic myopathy, tick paralysis, botulism, and spinal cord compression.[6] Once periodic paralysis has been identified as a possible cause, it is important to distinguish between the different subtypes: hypokalemic periodic paralysis, thyrotoxic periodic paralysis, hyperkalemic periodic paralysis and Andersen syndrome. While TPP is understood to be secondary to a hyperthyroid state, hypokalemic/hyperkalemic periodic paralysis is believed to be due to an autosomal dominant genetic defect in calcium or sodium ion channels on the muscle membrane. Andersen syndrome is caused by an autosomal dominant defect of the inward rectifying potassium channel.

Patients with TPP typically present with weakness or periodic flaccid paralysis of the proximal muscles which can be triggered by fasting, high carbohydrate meals or vigorous exercise. These episodes vary in frequency and duration but may occur several times a week with a duration from several hours up to days. Attacks may occur at any time, but they are frequently at night or early morning.

The pathogenesis of TPP is not fully understood with several current theories. First, thyroid hormone increases skeletal muscle tissue, liver and kidney sensitivity to beta-adrenergic activation which increases sodium-potassium ATPase activity.[2] This is responsible for driving potassium into the cell which may lead to hypokalemia. Second, insulin resistance may play a key role as downstream effects lead to hyperinsulinism which further drives potassium into the cell. Both increased sensitivity of the sodium-potassium ATPase and hyperinsulinism are thought to act synergistically in decreasing potassium levels. The hyperinsulinism theory may explain why high carbohydrate meals are associated with exacerbations. Third, other studies identified patients with ion channel defects. A gene encoding Kir2.6, an inward rectifying potassium channel expressed on skeletal muscle was present in 10 of 30 subjects with thyrotoxic periodic paralysis.[7] This channel is particularly sensitive to thyroid hormone and may also be implicated in the pathogenesis of Graves disease. There is also speculation that testosterone may contribute to the pathogenesis by increasing

the sodium-potassium ATPase, which may explain the higher incidence in males. Ultimately, the hypokalemic state leads to weakness and paralysis as potassium plays a critical role in muscle contraction. Other etiologies include thyrotoxicosis from TSH secreting pituitary adenomas, exogenous thyroid hormone, excess iodine and medications including amiodarone.

Patients often present with hypokalemia, hypophosphatemia, hypomagnesemia, and a normal acid base status. Patients also demonstrate a low potassium excretion rate on spot urine potassium- creatinine ratio. This test is helpful to distinguish this from other forms of potassium wasting such as Barters, Gitelman's, and renal tubular acidosis. Thyroid function tests show low TSH with elevated T4, T3 and increased T3 uptake. EKG may show sinus tachycardia with signs of hypokalemia such as prominent U waves, prolonged PR intervals, increased P-wave amplitude and widened QRS complexes. First degree AV block, atrial and ventricular arrhythmias are often present, depending on severity of hypokalemia.

Treatment is determined by the severity of presentation. Patients with acute paralysis need admission and monitoring for cardiac arrhythmias and dysphagia. Potassium supplementation is critical with oral repletion protocols of 30 mEq of potassium every two hours,with maximum of 90 mEq in 24 hours or improvement of symptoms.[8] Intravenous potassium supplementation may be needed if the patient is too weak to swallow. Close monitoring of serum potassium is needed throughout treatment. Beta blockers have been shown to decrease symptoms and can be given until euthyroid. Propranolol 40 to 120 mg/day, with potassium supplementation has improved symptoms by controlling excessive adrenergic activity and preventing episodes.[9] Patients refractory to potassium supplementation may be treated with IV propranolol. One mg of IV propranolol every 10 minutes with a maximum dose of 3 mg has been propossed.[9] Beta blockade is felt to reverses the hypersensitivity of the sodium potassium channel.[9] Another goal of therapy is to prevent further attacks by reestablishing a euthyroid state. Whether the cause of hyperthyroidism is Graves disease, a toxic adenoma, exogenous thyroid intake, TSH mediated hyperthyroidism, it is critical to treat the underlying condition. This patient was given methimazole and scheduled for radioactive iodine ablation to treat his underlying Grave's Disease.

Conclusion

TPP is a rare diagnosis and should be considered in patients presenting with weakness or flaccid paralysis of the proximal muscles. It is important to keep TPP in the differential even if overt signs of thyrotoxicosis are not present.

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