Graves' disease–induced complete heart block and asystole

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Introduction

Complete heart block or third-degree atrioventricular (AV) block is a disease of the cardiac conduction system that results in lack of electrical conduction from atria to the ventricles. It is more common in the older patient and it is most often owing to age-related degeneration and fibrosis of the conduction system.[1] Hypothyroidism is a known, but rather uncommon, cause of AV block, particularly in young and middle-aged adults.[1] Hyperthyroidism is an extremely rare cause and has been described in only a few case reports, most commonly in association with acute inflammatory states, infections, or medications such as digoxin.[2–4] We present a case of a young male patient with symptomatic complete heart block and asystole in the setting of newly diagnosed Graves' disease.

Case report

A 41-year-old man with no significant past medical history presented with syncope. The patient described loss of consciousness without preceding chest pain, dyspnea, or palpitations. Prior to this episode, the patient noted a several-day history of subjective fevers and a nonproductive cough, but denied a history of tick bites, rashes, or arthralgia.

Upon arrival to the hospital, he was hypertensive but vital signs and physical examination were otherwise unremarkable. Electrocardiogram showed sinus tachycardia with a complete heart block and an accelerated junctional rhythm (Figure 1). Initial laboratory evaluation revealed a normal complete blood count and electrolytes (potassium 4.5 mmol/L, total calcium 9.3 mg/dL [normal range 8.9–10.1 mg/dL], phosphorus 2.6 mg/dL [normal range 2.5–4.5 mg/dL], and magnesium 1.9 mg/dL [normal range 1.7–2.3 mg/dL]). Inflammatory markers were mildly elevated, with a C-reactive protein of 48.9 mg/L and erythrocyte sedimentation rate of 33 mm/h. Lyme serology was negative. Of note, he had a severely depressed thyroid-stimulating hormone (TSH) (<0.01 mIU/L) and an elevated free thyroxine level (T4) of 4 ng/dL (reference range 0.9–1.7 ng/dL), which was confirmed on repeat testing.

Echocardiography revealed a structurally normal heart with left ventricular ejection fraction of 59%. Computed tomography angiography of the chest was negative for pulmonary embolism and dissection. Cardiac magnetic resonance imaging (MRI) demonstrated no evidence of myocarditis or infiltrative disease.

While hospitalized, he sustained recurrent syncope in the context of 10- and 13-second periods of complete heart block without an escape rhythm.

Further evaluation revealed a positive thyroid receptor antibody with a level of 2.41 IU/L (normal <1.75 IU/L), highly suggestive of Graves' disease in the setting of elevated T4 and suppressed TSH. He was treated with methimazole. Given his long periods of recurrent asystole with syncope, temporary pacing wires were placed on initial presentation. The patient required minimal V pacing, with rhythms mostly consistent with sinus tachycardia and an accelerated junctional rhythm. However, given his initial presentation with syncope and prolonged pauses, a permanent dual-chamber pacemaker was ultimately placed.

At 5 months' follow-up, thyroid hormone levels normalized and he was clinically euthyroid on methimazole (Figure 2). He had no recurrent syncope or pre-syncope. Holter monitoring and device interrogations showed normal sinus rhythm with atrial pacing and 1 brief period of AV sequential pacing.

Discussion

Thyroid hormones, mainly mediated through the actions of tri-iodothyronine (T_3), have adrenergic, chronotropic, and inotropic effects on the heart.[5] Indeed, many of the known clinical effects of hyperthyroidism, such as tachycardia, sweating, and palpitations, mimic a state of catecholamine excess. However, measured plasma levels of catecholamines

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KEY TEACHING POINTS

- Though the most common cardiovascular effects of hyperthyroidism are sinus tachycardia, atrial fibrillation, and atrial or ventricular premature complexes, complete atrioventricular (AV) block can occur, but it remains a rare occurrence.
- Identifying underlying thyroid dysfunction in patients presenting with AV block is critical, as treating the underlying thyroid dysfunction can help remove the stimulus triggering the arrhythmias. In addition, medications used to treat hyperthyroidism include beta blockers, which can be detrimental in patients with AV block.
- There is no consensus on the management of patients with thyrotoxicosis and AV block, and further studies need to be performed to understand the natural progression and optimal timing and duration of device-based therapy.

tend to be normal to low in hyperthyroidism,[6] suggesting that a state of heightened adrenergic sensitivity exists.[7] However, evidence for this has been conflicting, and β-adrenergic receptor knockout mouse studies have shown similar cardiovascular effects from exposure to thyroid hormone compared to those with intact receptors.[8]

T_3 results in transcriptional modulation of several components central to enhancing contractile function, including alpha-myosin heavy chains, sarcoplasmic reticulum proteins, calcium-activated ATPase (Ca^{2+}-ATPase), phospholamban (a protein that regulates calcium ion uptake into the sarcoplasmic reticulum), the Na^{+}-K^{+}-ATPase pump, and voltage-gated potassium channels. Furthermore, thyroid hormones, themselves, decrease systemic vascular resistance.[9] These effects combined result in an overall increased heart rate and cardiac output and widened pulse pressure (Figure 3).[5]

It is not surprising, therefore, that the most common cardiovascular effects of hyperthyroidism are sinus tachycardia and atrial fibrillation.[5] Though the mechanisms of tachyarrhythmias in hyperthyroidism are therefore quite clear (increasing the rate of systolic depolarization and diastolic repolarization, decreasing the action potential duration and the refractory period of the atrial myocardium and AV node[10]), the mechanism of hyperthyroidism-related bradyarrhythmias and AV block is less well understood. Furthermore, previous cases of thyrotoxicosis causing complete heart block that were reported in the literature were associated with other coexisting factors, such as acute infection[3] or coadministration of cardiac medications.[2] Nevertheless, our case highlights that this presentation, which is different from the classic atrial fibrillation arrhythmia associated with hyperthyroidism, in the absence of other acute precipitating factors supports the postulation that thyroid hormone can act directly on the AV node. Although the patient's cardiac MRI did not demonstrate any obvious signs of inflammation at any point within the myocardium, one case report describing a similar presentation—which is the only published case report to include an autopsy, to our knowledge—demonstrated interstitial inflammation of the AV node, the His bundle, and its branches.[11]

Throughout the course of his hospitalization, various rhythms were noted, which included sinus tachycardia, an accelerated junctional rhythm, and complete heart block. The presence of these rhythms in the setting of thyrotoxicosis and in the absence of structural heart disease is peculiar. An accelerated junctional rhythm arises when the rate of an AV junctional pacemaker exceeds that of the sinus node. Although no studies have been done to specifically evaluate the underlying pathophysiology of this arrhythmia in states of thyrotoxicosis, it is well known that the AV node is under autonomic regulation. Furthermore, calcium dynamics have been shown to play a key role in AV node automaticity.[12] As previously mentioned, T_3 plays a key role in regulation of molecules involved in calcium flux, including sarcoplasmic reticulum proteins and calcium ATPase. Additional mechanistic studies are required to further elucidate the intricacies of this arrhythmia in this clinical setting.

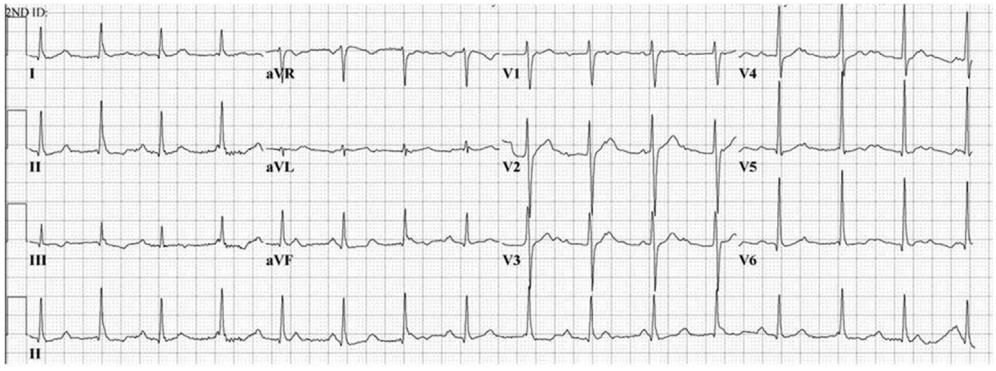

Figure 1 Electrocardiogram acquired from the patient on presentation, which shows complete dissociation of atrial and ventricular activity consistent with third-degree atrioventricular block.

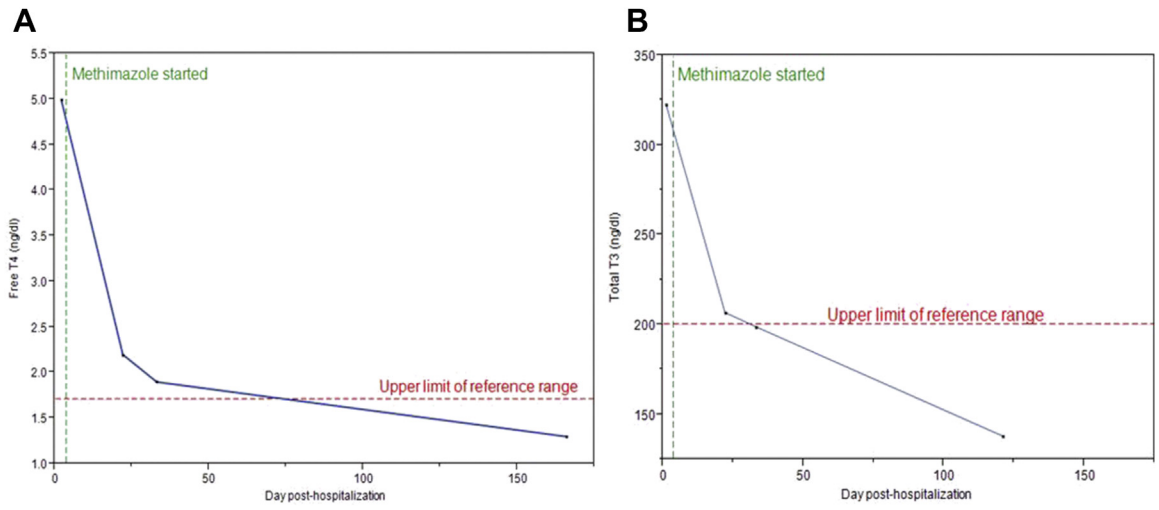

Figure 2 Change in thyroid hormone levels with therapy. **A:** Change in free T_4 (in ng/dL), and **B:** change in total T_3 (in ng/dL), following initiation of methimazole (day 4 of hospitalization). Both indices were elevated on presentation and normalized with methimazole therapy.

However, an important clinical entity to consider is thyrotoxic periodic paralysis, which is a condition that can occur in patients with hyperthyroidism, characterized by abrupt onset of paralysis and hypokalemia, and can result in AV block, ventricular fibrillation, and asystole. This condition can occur in any patient but is most commonly seen in men of Asian descent. Common precipitants of this condition include exercise and a carbohydrate-rich meal. Although the condition classically results in hypokalemia, normokalemic patients have been described.[13]

Though the data regarding the degree of reversibility in patients with AV block who have their hyperthyroidism treated are lacking, perhaps owing to the rarity of this presentation, it has been shown that in patients with thyrotoxicosis and atrial fibrillation with no underlying valvular heart disease, 62% of patients spontaneously reverted to sinus rhythm within 1 year after commencing treatment of their thyrotoxicosis, and typically within 8–10 weeks after achieving a euthyroid state.[14] The other important point to consider is that medications that are often used to treat hyperthyroidism

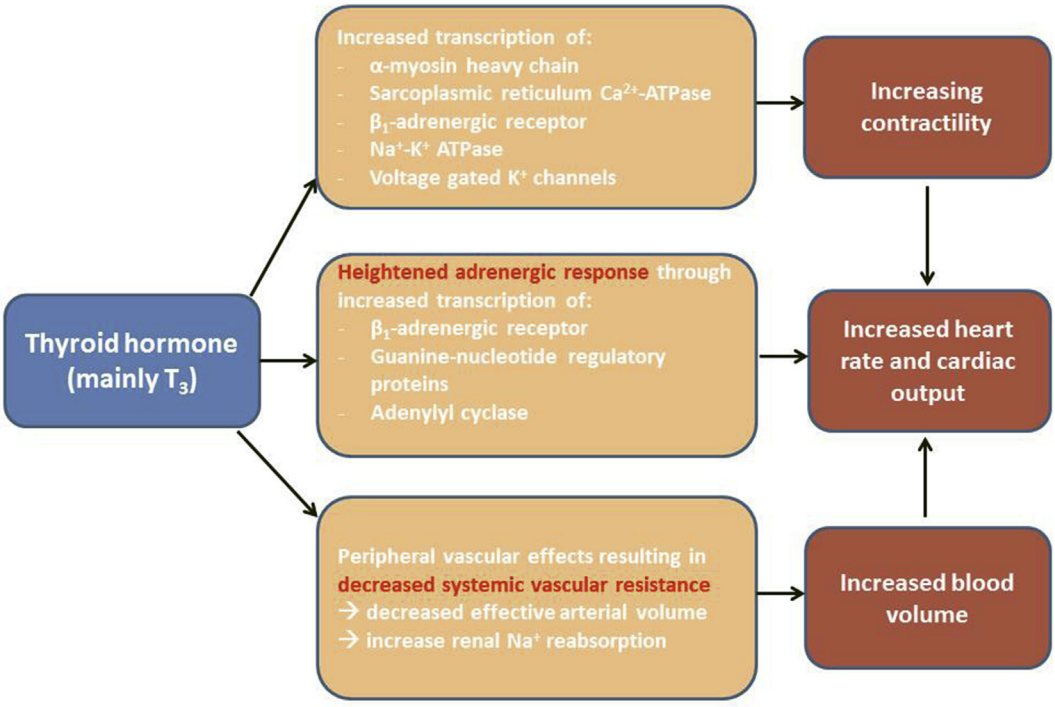

Figure 3 Schematic outlining the cardiovascular effects of thyroid hormone (mainly mediated through T_3). Thyroid hormone results in an increase in the transcription of molecules central to contractile function, such as α-myosin heavy chain and sarcoplasmic reticulum Ca^{2+}-ATPase, which results in a positive inotropic effect. It also results in an increase in adrenergic response through increased transcription of β_1-adrenergic receptors and guanine-nucleotide regulatory proteins, resulting in a positive chronotropic effect. The hormones also have peripheral vascular effects resulting in decreased systemic vascular resistance, which results in increased blood volume as a response through increased renal sodium reabsorption. All these effects combined result in an increase in cardiac output.[5]

include beta blockers, which can be detrimental in patients with AV block.

There are scant data and no guidelines to guide the management of patients with thyrotoxicosis who present with high-grade AV block. Our patient presented with third-degree AV block along with symptomatic periods of asystole. Current guidelines recommend permanent pacing for patients with third-degree heart block.[15] The guidelines also, however, stress that potentially reversible causes such as medications, ischemia/infarction, electrolyte abnormalities, and Lyme disease should ideally not be treated with permanent pacing.[15] There is no specific mention of advanced AV block in the specific setting of thyroid dysfunction.[15]

There is no clear indication as to how long pacing is required or at what point explanting the pacemaker could be safely considered. One study, by Ozcan and colleagues,[4] followed 21 patients with AV block associated with hyperthyroidism, of whom 20 patients (95.2%) underwent pacemaker implantation. Nine patients had normalization of their TSH with therapy, but 8 of those patients had persistent or recurrent AV block. Meanwhile, 12 patients had persistently low TSH levels despite therapy and all of those patients had persistent AV block during the initial hospital follow-up period (21 days), and 10 of the 12 patients had persistent AV block and were therefore pacemaker dependent on extended follow-up. It is important to note that the time to resolution of the AV block after starting medical therapy was more than 21 days, and therefore, prolonged temporary pacing is often not a reasonable option, which makes implantation of a permanent pacemaker a plausible option despite this being a "transient risk factor." Although this study was limited by a small sample size and a short duration of follow-up, it highlights that AV dysfunction does persist in a substantial proportion of patients despite treatment of their underlying thyroid dysfunction, in contrast to the high degree of reversibility of atrial fibrillation once the underlying hyperthyroidism is treated.

Conclusion

We present a case of symptomatic complete heart block and asystole in the setting of newly diagnosed Graves' disease. Although hyperthyroidism is a known but rare cause of advanced AV block, there are insufficient data on optimal management of these patients, especially regarding device implantation. Further studies are required to better understand the degree of reversibility of AV block in this setting and the optimal timing and duration of cardiac pacing.

References

1. Barra SNC, Providência R, Paiva L, Nascimento J, Marques AL. A Review on Advanced Atrioventricular Block in Young or Middle-Aged Adults. Pacing Clin Electrophysiol 2012;35:1395–1405.
2. Kramer M, Shilo S, Hershko C. Atrioventricular and sinoatrial block in thyrotoxic crisis. Br Heart J 1985;54:600–602.
3. Stern MP, Jacobs RL, Duncan GW. Complete heart block complicating hyperthyroidism. JAMA 1970;212:2117–2119.
4. Ozcan KS, Osmonov D, Erdinler I, Altay S, Yildirim E, Turkkan C, Hasdemir H, Cakmak N, Alper AT, Satilmis S, Gurkan K. Atrioventricular block in patients with thyroid dysfunction: prognosis after treatment with hormone supplementation or antithyroid medication. J Cardiol 2012;60:327–332.
5. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501–509.
6. Bayliss R, Edwards O. Urinary excretion of free catecholamines in Graves' disease. J Endocrinol 1971;49:167–173.
7. Carvalho-Bianco SD, Kim BW, Zhang JX, Harney JW, Ribeiro RS, Gereben B, Bianco AC, Mende U, Larsen PR. Chronic cardiac-specific thyrotoxicosis increases myocardial β-adrenergic responsiveness. Mol Endocrinol 2004; 18:1840–1849.
8. Bachman ES, Hampton TG, Dhillon H, Amende I, Wang J, Morgan JP, Hollenberg AN. The metabolic and cardiovascular effects of hyperthyroidism are largely independent of β-adrenergic stimulation. Endocrinology 2004; 145:2767–2774.
9. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol 2017;14:39–55.
10. Freedberg A, Papp JG, Williams E. The effect of altered thyroid state on atrial intracellular potentials. J Physiol 1970;207:357–369.
11. Ortmann C, Pfeiffer H, Du Chesne A, Brinkmann B. Inflammation of the cardiac conduction system in a case of hyperthyroidism. Int J Legal Med 1999; 112:271–274.
12. Kim D, Shinohara T, Joung B, Maruyama M, Choi EK, On YK, Han S, Fishbein MC, Lin SF, Chen PS. Calcium dynamics and the mechanisms of atrioventricular junctional rhythm. J Am Coll Cardiol 2010;56:805–812.
13. Kannan L, Kim YN. Thyrotoxic periodic paralysis in long standing Graves' disease: an unusual presentation with normokalemia. N Am J Med Sci 2015;7:119.
14. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of atrial fibrillation in the post-thyrotoxic state. Am J Med 1982;72:903–906.
15. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1–e62.