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.

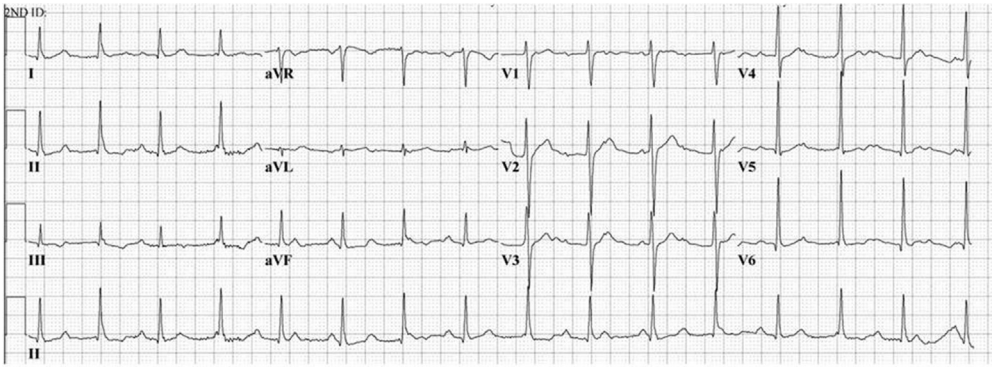

Figure 1 Electrocardiogram acquired from the patient on presentation, which shows complete dissociation of atrial and ventricular activity consistent with third-degree atrioventricular block.