Ventricular fibrillation in Graves disease reveals a rare *SCN5A* mutation with W1191X variant associated with Brugada syndrome

Kristin Stawiarski, MD, John-Ross D. Clarke, MD, Ari Pollack, MD, Robert Winslow, MD, Sachin Majumdar, MD

From the Yale New Haven Health Heart and Vascular Center, Bridgeport Hospital, Bridgeport, Connecticut.

Introduction

Most thyrotoxicosis-related arrhythmias are supraventricular in origin. Ventricular arrhythmias, in the absence of underlying coronary disease or heart failure, are an unusual manifestation of thyrotoxicosis. We report a case of ventricular fibrillation (VF) in a patient with Graves' hyperthyroidism who was later revealed to have a rare *SCN5A* mutation associated with Brugada syndrome (BrS).

Case report

A 55-year-old woman presented with approximately 1 month of malaise, palpitations, exertional dyspnea, and muscle aches. She reported worsening anorexia, nausea, vomiting, and diarrhea for the few days prior to her presentation to the emergency department. Her medical history was significant for hypertension and a self-reported thyroid nodule. She was a lifelong nonsmoker and denied use of any stimulants, recreational drugs, or over-the-counter supplements. Her family history was significant for 3 family members on her father's side sustaining sudden cardiac death in their 50s–60s attributed to myocardial infarction.

Her initial physical examination revealed tachycardia, 125 beats per minute, a firm goiter without bruit, a fine resting hand tremor, and 3+ deep tendon reflexes. Her electrocardiogram (ECG) showed sinus tachycardia with a QTc of 436 ms (Figure 1). Laboratory analysis was significant for normal serum electrolytes, an undetectable TSH, free T4 >6.99 ng/dL (normal (n) = 0.7–2.19 ng/dL), total T3 >7.81 ng/mL (n = 0.97–1.7 ng/mL), thyroid-stimulating immunoglobulin level of 516% (n = <14%), and a thyroid binding inhibitory immunoglobulin level of 82.5% (n = <16%).

KEY TEACHING POINTS

- Thyrotoxicosis is rarely associated with ventricular fibrillation, and when present, underlying reversible causes should be excluded and in their absence the possibility of genetic predisposition to arrhythmias should be considered.
- The SCNA mutation can been seen in 20%–30% of patients with Brugada syndrome (BrS), with most variants exhibiting a loss-of-function property including the W1191X variant identified in our patient.
- BrS exists on a spectrum of heritable disorders with variable presentation. Not all cases of sudden cardiac arrest demonstrate the typical type 1 BrS pattern, as seen with our patient, who had the type 2 pattern.
- Thyrotoxicosis may lower the arrhythmia threshold in patients with a genetic predisposition for arrhythmias.
- Once a patient has a genetic mutation identified, family genetic screening is key for future risk factor modification even if the genotypic presence of BrS in the absence of symptoms is enough to invoke therapy including implantable cardioverter-defibrillator.

Technetium-99m pertechnetate thyroid scan showed homogeneous radiotracer uptake consistent with Graves disease. She was placed on telemetry given her elevated heart rate. Treatment was initiated with high-dose dexamethasone, methimazole, and propranolol for heart rate control as well as peripheral blockade of T4-to-T3 conversion.

During the early morning of her second hospital day, the patient developed VF (Figure 2A). She was found to be unresponsive and pulseless. Resuscitative efforts were

KEYWORDS Arrhythmias; Brugada syndrome; Genetic mutation; Hyperthyroidism; Implantable cardioverter-defibrillator; Ventricular fibrillation
(Heart Rhythm Case Reports 2021;7:95–99)

Conflict of Interest and Sources of Funding Statement: All authors have nothing to disclose with regard to commercial or financial support or conflicts of interest. **Address reprint requests and correspondence:** Dr Kristin Stawiarski, Yale New Haven Health Heart and Vascular Center, Bridgeport Hospital, 267 Grant St, Bridgeport, CT 06610. E-mail address: Kristin.stawiarski@bpthosp.org.

https://doi.org/10.1016/j.hrcr.2020.11.010

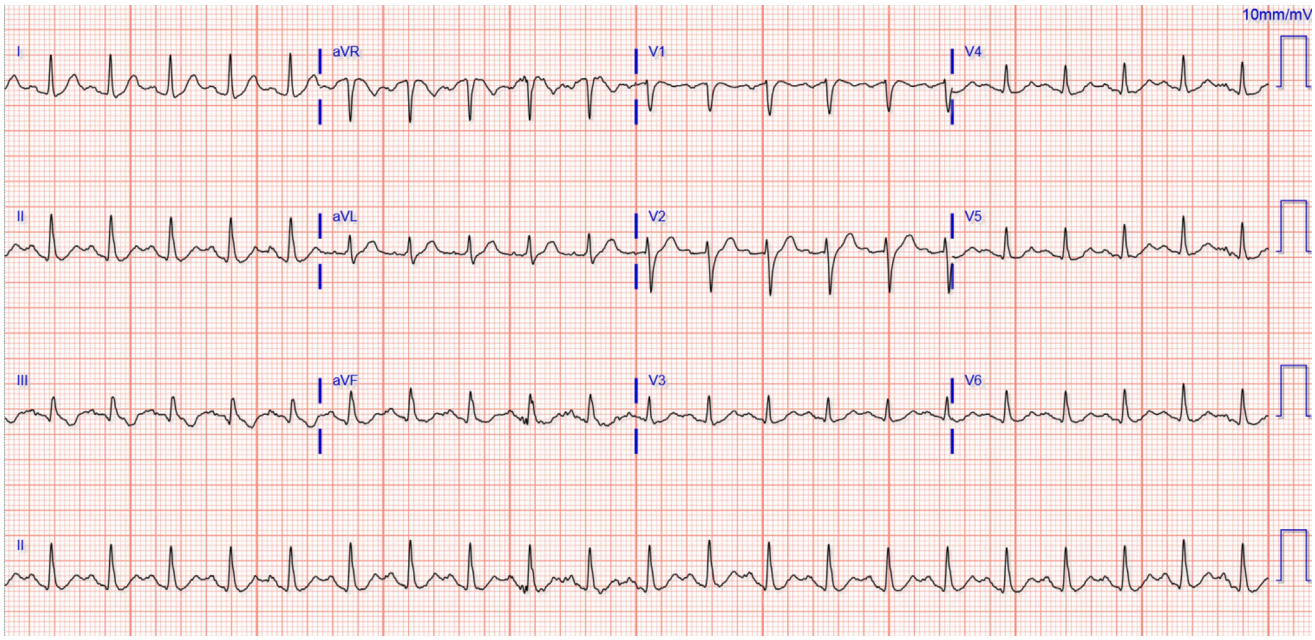

Figure 1 Initial electrocardiogram.

performed for 50 minutes prior to the return of spontaneous circulation. She required 5 defibrillator shocks, and boluses of amiodarone and lidocaine for refractory ventricular arrhythmia. Postarrest rhythm was an unstable bradyarrhythmia (Figure 2B) requiring transcutaneous pacing, plus norepinephrine and dopamine to maintain adequate perfusion. Given her bradycardia, glucagon infusion was started for the possibility of beta blocker toxicity. She had received a total of 320 mg of propranolol (80 mg every 6 hours) in the prior 24 hours owing to poorly controlled sinus tachycardia with rates up to the 160s and accompanying palpitations. Serum testing post arrest showed a potassium of 6.9 mmol/L (n = 3.5–5.1 mmol/L) (previously normal on admission), severe metabolic acidosis, and acute hepatocellular and kidney injury.

Admission troponin was negative and, post arrest, was only mild elevated and remained flat. Transthoracic echocardiogram post arrest revealed severely decreased biventricular function with a left ventricular ejection fraction of <30% and global hypokinesis. Repeat echocardiogram 24 hours later showed hyperdynamic left ventricular function accompanied by recovery of native sinus node function. Cardiac catheterization was deferred owing to declining renal function. Instead she underwent nuclear medicine stress testing, which revealed normal perfusion with breast attenuation. By her fourth hospital day she was biochemically euthyroid. No further arrhythmias were captured. After shared decision making, an implantable cardioverter-defibrillator (ICD) was placed prior to discharge for secondary prevention of ventricular arrhythmias.

Over the next 2 years in outpatient follow-up, further coronary artery disease was excluded with a coronary computed tomography angiogram. No further arrhythmias were detected on device interrogations. Follow-up ECGs did not reveal any QT prolongation. However, a single ECG post a subsequent admission for fever and pleural effusion revealed a convex "saddle-back" ST-segment elevation in V_1 concerning for possible type 2 Brugada pattern (Figure 3A).

Given her personal history of VF and significant paternal family history of sudden cardiac death (Figure 3B), genetic analysis was performed for QT and tachyarrhythmia disorders. This revealed a likely pathogenic variant in the *SCN5A* gene, W1191X, previously seen with BrS. Provocation testing for BrS was deferred, given that she already underwent ICD placement. She was counseled on the implications of this mutation, including the need to avoid QT-prolonging medications and aggressive control of fevers. Family genetic testing was recommended but to date has not yet been completed.

Discussion

Ventricular arrhythmias rarely occur in hyperthyroidism.[1–3] Although atrial fibrillation is the most common arrhythmia seen in 5%–15% of patients with hyperthyroidism, the varied regional distribution of β-1 and β-2 adrenergic receptors between the atria and ventricles may account for individual predisposition to either ventricular or atrial arrhythmias.[2] Thyroid hormones exert different effects on cardiac myocytes in both a genomic and nongenomic manner.[4] Cardiac gene transcription, including encoding for myosin heavy chain and ion channels, is regulated by triiodothyronine (T_3) binding to nuclear thyroid receptors and β adrenergic receptors.[4] T_3 also directly binds to various membrane ion channels, altering the depolarization and repolarization currents of cardiac pacemakers via nongenomic modulation.[4] Thyroid hormone levels have been positively correlated with QTc interval and a proposed mechanism for ventricular arrhythmias is through increased activation of

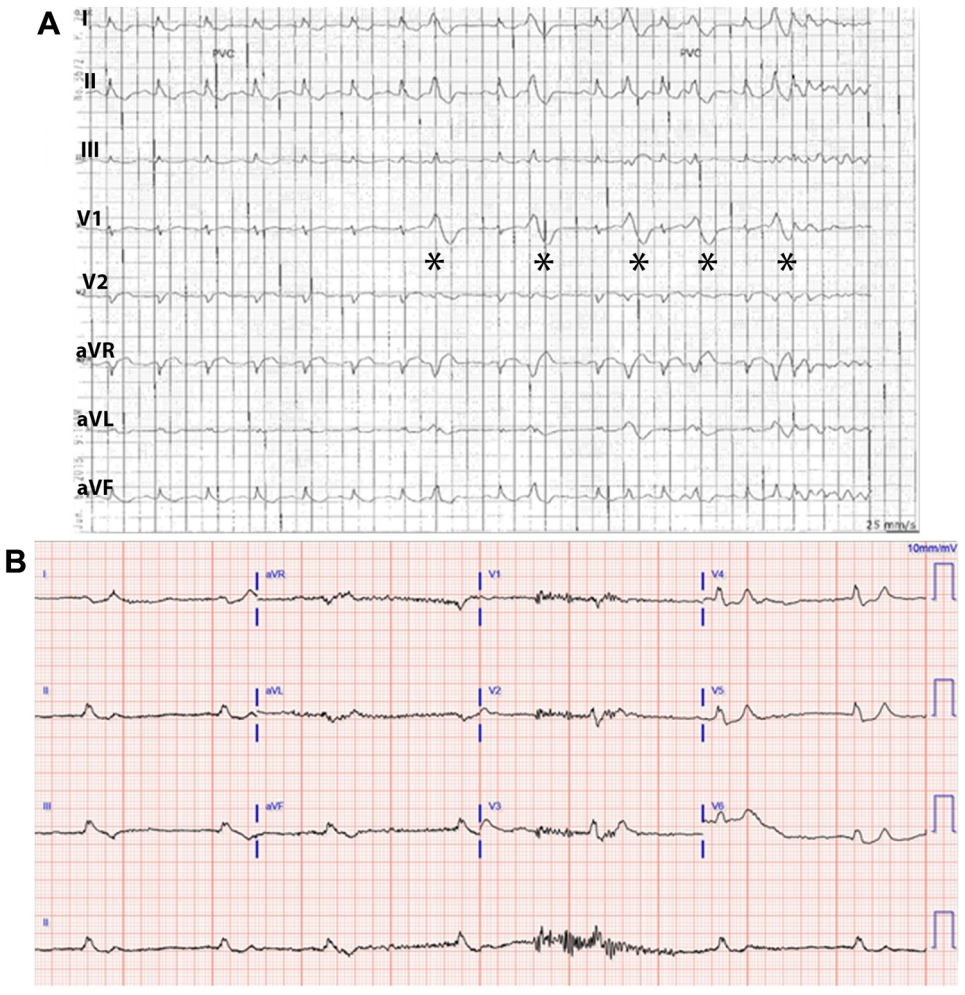

Figure 2 **A:** Telemetry events prior to ventricular fibrillation (VF) arrest. Normal sinus rhythm at an initial rate of 90–100 beats/min. There are frequent preceding premature ventricular contractions (*asterisk*), which are almost identical to the initiating premature ventricular complexes of VF. **B:** Electrocardiogram immediately post arrest showing irregular wide complex bradyarrhythmia.

the Na^+/K^+ adenosine triphosphatase, resulting in a prolonged QTc prolongation.[5] However, our patient had a normal QTc interval prior to the onset of VF, calling into question the direct toxicity of elevated thyroid hormones as the culprit of VF. A normal QTc also largely excludes major serum electrolyte disturbances. The postarrest hyperkalemia was likely a reflection of prolonged ischemia with severe metabolic acidosis rather than a trigger for the VF.

Beta-blocker overdose was also questioned as a possible cause of her cardiac arrest. Although propranolol typically leads to bradyarrhythmias, it has a higher membrane stabilizing activity compared to other beta blockers, which can inhibit myocardial fast sodium channels and result in wide QRS dysrhythmias.[6] However, our patient's last dose of propranolol was 4 hours before the VF, which coincides with the drug's half-life of 3–4 hours.[6] She had no liver abnormalities that would have altered drug metabolism. Circulatory collapse after propranolol administration during thyroid storm has been reported up to 6 hours after therapy initiation; however, these patients had low-output cardiac failure prior to arrest, unlike our patient.[6] Subclinical cardiomyopathy has further been proposed as a culprit in beta-blocker sensitivity.[6] Baseline cardiac function was not documented in our patient. However, she only had transient drop in ejection fraction that recovered 24 hours afterwards, pointing against overt cardiomyopathy. It is unlikely that beta-blocker therapy was the sole trigger for VF, but it may have played a role given the presence of her BrS variant.

In the majority of reported cases of ventricular arrhythmias in the setting of thyroid storm, risk factors for coronary artery disease were often identified.[1,3] Our patient did not carry any of these traditional risk factors. Likewise, her flat troponin trend makes ischemic myocardial injury or coronary vasospasm unlikely precipitants of VF. In support of this, she saw rapid ventricular recovery and a subsequent low-risk stress test, further swaying the hypothesis away from coronary ischemia.

With reversible causes of VF narrowed, there was growing suspicion that our patient carried a genetic predisposition for sudden cardiac death. It was not until 6 months post arrest that a follow-up ECG revealed a suspicious type 2 Brugada pattern (Figure 3A). ECG was not repeated at different intercostal space levels to possibly reveal a Brugada pattern.

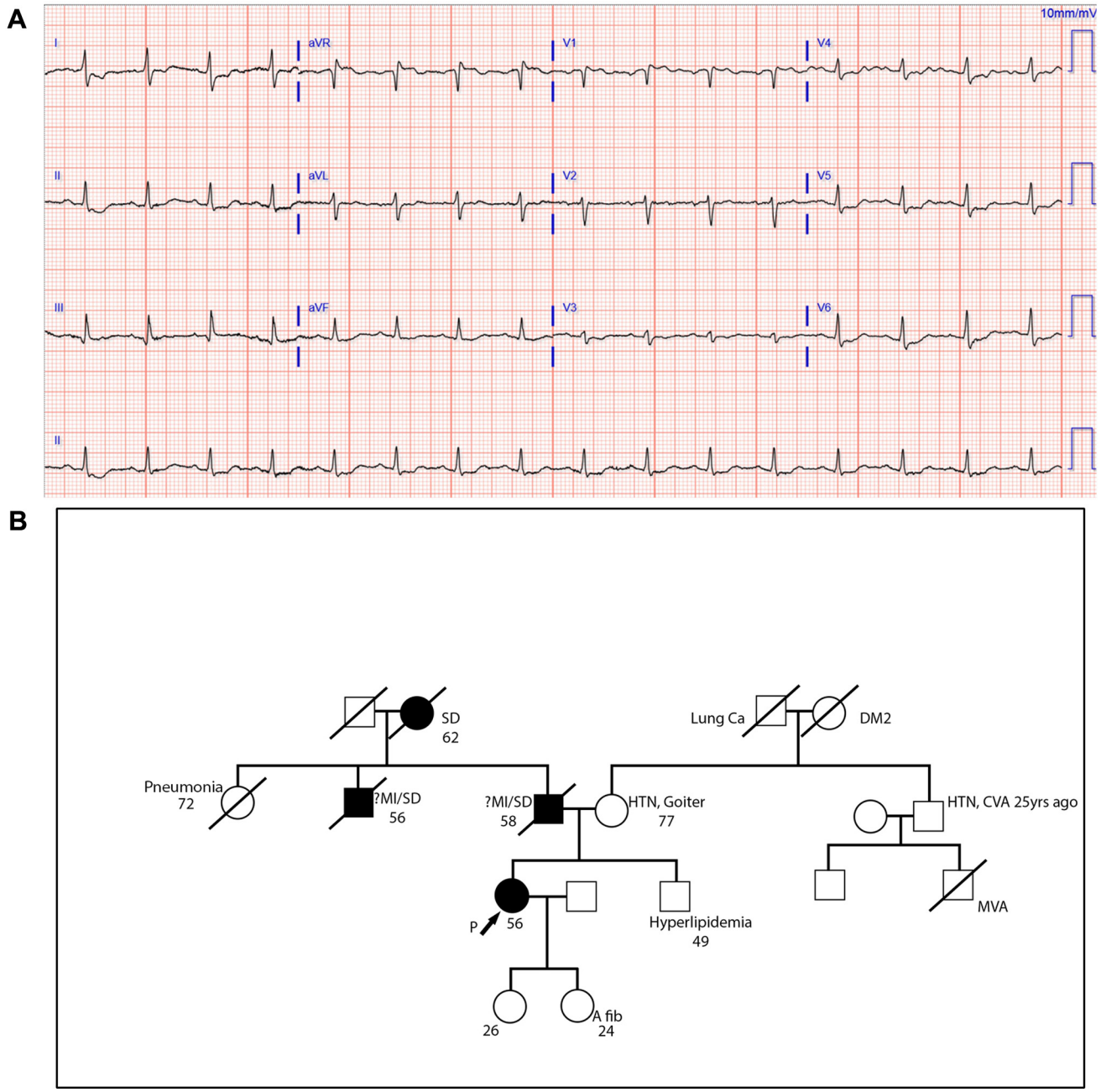

Figure 3 **A:** Follow-up electrocardiogram showing a ≥0.5 mm convex ST-segment elevation in lead V_1 concerning for the nondiagnostic type 2 "saddle-back" Brugada pattern. **B:** Pedigree structure of patient's family. Circles indicate females; squares indicate males. Numbers beside each symbol represent the individual's age in years. Text adjacent to each symbol indicates the significant medical history for each individual. Filled symbols indicate individuals with sudden cardiac death presumed to be related to W1191X mutation. Symbols with a crossed line indicate deceased individuals, with the cause of death listed in the adjacent text. The proband (our patient) is marked by an arrow and the letter "P." CVA = cerebrovascular accident; DM2 = diabetes mellitus type II; HTN = hypertension; Lung Ca = lung cancer; MI = myocardial infarction; MVA = motor vehicle accident; SD = sudden death.

The typical diagnostic type 1 BrS pattern was never documented.[7] On review of her VF, the QRS morphology resembled a left bundle branch pattern that was similar to the frequent premature ventricular contractions (PVCs) that preceded the arrhythmia. Such a phenomenon has been previously described in patients with BrS.[8] As the PVC coupling intervals shortened, it is likely that her VF was triggered by a focal reentrant circuit generated as the PVC fired near the peak of the T wave.[9]

Review of family history via pedigree suggested the presence of a heritable cardiac arrhythmia syndrome in an autosomal dominant pattern (Figure 3B). Aside from the patient's daughter, who had a normal ECG, additional ECG data were not available for other family members to screen for possible Brugada pattern or prolonged QT. The patient's genetic analysis revealed a pathogenic variant of the *SCN5A* gene, W1191X. Other relatives aside from the proband have not yet been tested.

The *SCN5A* gene itself encodes for the $Na_v1.5$, voltage gated Na^+ channel, the predominant isoform in the heart.[10] Mutations in the *SCN5A* gene are associated with a number of hereditary arrhythmias. Up to 20%–30% of patients with BrS have a mutation in SCN5A, most of which are expressed as a reduction in cardiac sodium current.[10] The W1191X mutation is one of these loss-of-function mutations.[11] This nonsense mutation results in a glycine-to-alanine substitution, leading to a premature stop codon at amino acid position 1191.[11] W1191X has been implicated in BrS, long QT syndrome subtype 3, and cardiac conduction disturbance.[10] Individuals with such syndromes may exhibit incomplete penetrance with variable distinct phenotypic manifestations.[12] This may be evident in successive generations of our patient, given that her daughter has atrial fibrillation at a young age. Demographic and exogenous modifiers can affect the rates of ECG phenotype expression and the risk of sudden cardiac death.[12] Thyrotoxicosis is likely one of those modifiers. Thyroid storm has been previously implicated in unmasking the type 1 BrS ECG pattern in a young 18-year-old patient with VF arrest.[13] However, on genetic analysis the SCN5A mutation was not present. We add our current presentation as further support of the hypothesis that a thyrotoxic state may lower the arrhythmia threshold in a patient already at higher risk for arrhythmias.

Evidence in support of ICD implantation in BrS has been limited to symptomatic patients with either syncope, cardiac arrest, or ventricular arrhythmias and a spontaneous type 1 pattern only.[14] This classic pattern was not totally excluded in our patient, as she did not undergo formal provocation testing or repeat ECG in other intercostal spaces. Medication challenge was deferred, as this would not offer further diagnostic or prognostic value to a patient that already suffered a cardiac arrest, and had an ICD implanted with no recurrent arrhythmias recorded. Our case highlights that BrS exists on a spectrum of disease and that sudden cardiac death remains a risk even for those patients without a type 1 pattern, and recommendations for ICD placement may need to be expanded.

Previously, a positive family history for BrS was not considered to be a predictor of adverse events. Genotype is not necessarily correlated with adverse outcomes, but rather the clinical findings and symptoms of each individual are the basis for risk stratification. However, this leaves patients and physicians in a "watch-and-wait" holding pattern that could be catastrophic.

Patients with identified gene mutations should have their family members undergo cascade screening of relatives. This will help identify those patients with a carrier status, allowing for education around avoidance of potential triggers such as QT-prolonging medications, as well as aggressive fever control in times of systemic illness. There is currently no role for prophylactic ICD placement in asymptomatic family members.

Conclusion

VF in hyperthyroidism is rare in the absence of reversible causes, underlying coronary disease, or heart failure. However, our case illustrates that hyperthyroidism may modify arrhythmia threshold in the individuals harboring genetic variants predisposing to VF. Our patient had a rare pathogenic variant of the *SCN5A* gene, W1191X, and was later noted to have a type 2 BrS ECG pattern. Therefore, in patients with a family history suggestive of sudden cardiac death, the presence of VF in the setting of hyperthyroidism should raise suspicion for a possible underlying genetic abnormality. Genetic testing may be necessary, as ECG manifestations may not be obvious and family history may be incomplete.

Acknowledgments

The authors would like to thank Allen E. Bale, MD (Department of Pathology) and James M. McGrath, MD, PhD (Department of Genetics) at Yale University School of Medicine for their assistance with the genetic analysis.

References

1. Ando T, Henmi T, Haruta D, et al. Graves' disease complicated by ventricular fibrillation in three men who were smokers. Thyroid 2011;21:1021–1025.
2. Nadkarni PJ, Sharma M, Zinsmeister B, Wartofsky L, Burman KD. Thyrotoxicosis-induced ventricular arrhythmias. Thyroid 2008;18:1111–1114.
3. Kobayashi H, Haketa A, Abe M, et al. Unusual manifestation of Graves' disease: ventricular fibrillation. Eur Thyroid J 2015;4:207–212.
4. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007;116:1725–1735.
5. Colzani RM, Emdin M, Conforti F, Passino C, Scarlattini M, Iervasi G. Hyperthyroidism is associated with lengthening of ventricular repolarization. Clin Endocrinol (Oxf) 2001;55:27–32.
6. Abubakar H, Singh V, Arora A, Alsunaid S. Propranolol-induced circulatory collapse in a patient with thyroid crisis and underlying thyrocardiac disease: a word of caution. J Investig Med High Impact Case Rep 2017;5. 2324709617747903.
7. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1046–1059.
8. Kakishita M, Kurita T, Matsuo K, et al. Mode of onset of ventricular fibrillation in patients with Brugada syndrome detected by implantable cardioverter defibrillator therapy. J Am Coll Cardiol 2000;36:1646–1653.
9. Viskin S, Lesh MD, Eldar M, et al. Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. J Cardiovasc Electrophysiol 1997;8:1115–1120.
10. Makita N. Phenotypic overlap of cardiac sodium channelopathies: individual-specific or mutation-specific? Circ J 2009;73:810–817.
11. Shin DJ, Kim E, Park SB, et al. A novel mutation in the SCN5A gene is associated with Brugada syndrome. Life Sci 2007;80:716–724.
12. Giudicessi JR, Ackerman MJ. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. Transl Res 2013;161:1–14.
13. Korte AK, Derde L, van Wijk J, Tjan DH. Sudden cardiac arrest as a presentation of Brugada syndrome unmasked by thyroid storm. BMJ Case Rep 2015; 2015:bcr2015212351.
14. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018; 72:e91–e220.