

CASE REPORT

PYREXIA-INDUCED BRUGADA PHENOCOPY

Nauman Khalid, Lovely Chhabra, Jeffrey Kluger

Department of Cardiovascular Medicine, Hartford Hospital, University of Connecticut School of Medicine, Hartford, CT-USA

Brugada syndrome (BS) is characterized by a typical electrocardiographic (ECG) pattern in the right precordial leads and a predisposition to develop ventricular arrhythmias. Mutations in α -subunit of cardiac sodium channel (SCN5A) have been linked to BS. Experimental studies in the literature suggest that this dysfunction of the mutated channel can be temperature sensitive. Several antiarrhythmics have been used in the management of BS but Implantable Cardioverter Defibrillators (ICD) remains the only effective treatment. We herewith present the case report of a 62-year-old man who developed a type-2 Brugada ECG phenotype in a febrile state with complete resolution once the fever subsided.

Keywords: Brugada syndrome; Electrocardiography; Brugada pattern

J Ayub Med Coll Abbottabad 2015;27(1):228–31

INTRODUCTION

Brugada syndrome is associated with a high risk of sudden death in young otherwise healthy individuals. Fever is known to unmask the Brugada electrocardiographic pattern and trigger life threatening ventricular tachyarrhythmias in patients with BS. However, fever can also produce a *de novo* Brugada electrocardiographic pattern in otherwise healthy individuals without any history of BS and management of such individuals often poses a clinical dilemma. Our case discusses the challenging and controversial aspects of management of Brugada ECG phenotypes in asymptomatic patients and who otherwise don't meet criteria for Brugada syndrome. We also provide a very comprehensive literature review on this subject.

CASE PRESENTATION

A 62-year-old man with medical history of dyslipidemia presented with complaints of productive cough, pleuritic chest pain, and subjective fever and chills of 4 days duration. He also reported weakness, fatigue and mild dyspnea. Family history was negative for coronary artery disease, arrhythmias, syncope or sudden cardiac death (SCD). His home medications included simvastatin and a daily multivitamin. He was a non-smoker, non-alcoholic and denied using any recreational drug use. His initial vital signs were remarkable for temperature of 102.6 °F but otherwise stable hemodynamics. Throat examination revealed no posterior pharyngeal erythema, exudates or tonsillar enlargement. Chest exam revealed mild rhonchorous breath sounds, however rest of the systemic examination was unremarkable.

An electrocardiogram at the time of admission revealed ST segment elevation of >2 mm in V1 with T-wave inversion and saddleback-shaped

ST-T segment in V2 consistent with a type-2 Brugada phenotype [Figure-1]. Chest radiograph revealed a dense consolidation consistent with left lower lobe pneumonia. Remainder of the laboratory work up including a complete blood count, basic metabolic panel, serial cardiac biomarkers, urinalysis and liver function tests were unremarkable. Echocardiogram revealed normal biventricular structure and function.

He was admitted to a telemetry floor for further monitoring where he was treated with antipyretics, intravenous fluids and antibiotics (ceftriaxone and azithromycin). He made remarkable clinical improvement on intravenous antibiotics. He remained afebrile and was discharged on Day 3 on oral levofloxacin.

A repeat ECG on Day 3 showed incomplete right bundle branch block and resolution of Brugada phenotype [Figure 2]. A drug challenge test, an electrophysiological study (EPS) or genetic testing were not performed because neither the patient nor any of his family members had history of arrhythmic symptoms, syncope or aborted/non-aborted SCD. Also, the first clinical manifestation of an underlying genetic mutation (Brugada syndrome) was considered quite unlikely at the age of 62 years. His both grandparents died in their late 80's from old age. His mother died from a stroke and renal failure at age 86 and his father died of a heart attack at 96 years of age. ECGs of the patient's first degree family members were reviewed from their primary care database. They were negative for Brugada phenotype. He was discharged with the recommendation of seeking urgent medical attention and prompt use of antipyretics in case of a febrile illness in future. He was also advised to seek prompt medical attention in the event of any syncope.

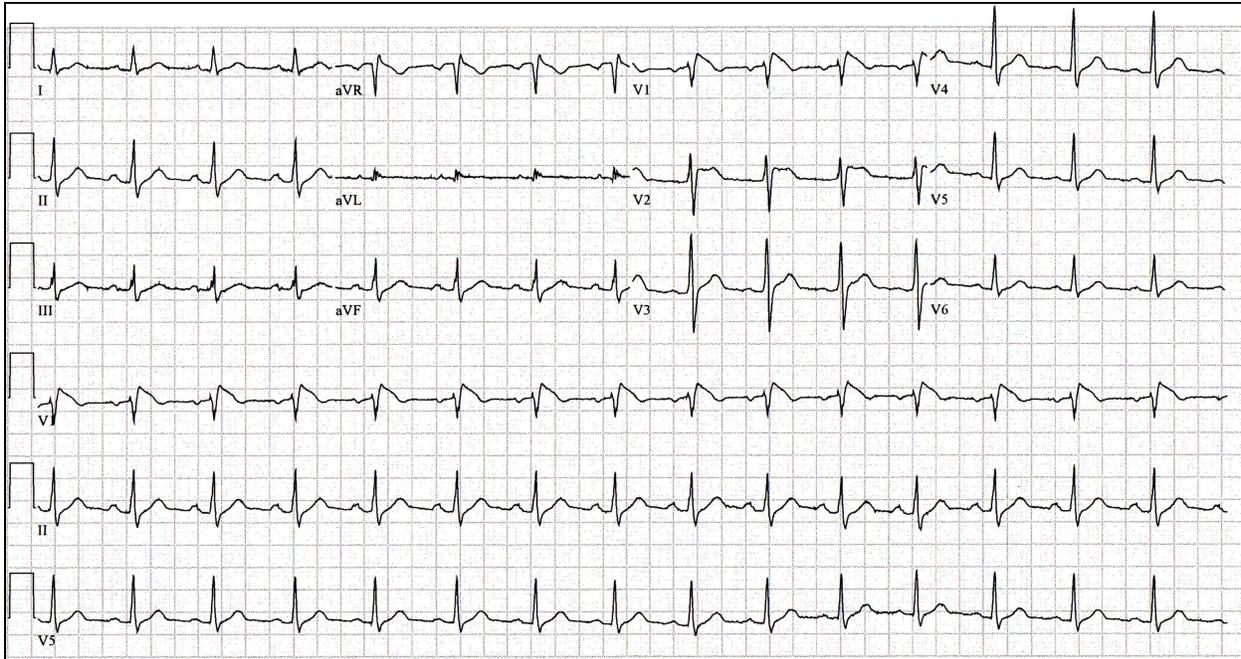


Figure-1: Electrocardiogram at the time of admission revealed ST segment elevation of >2mm in V1 with T-wave inversion and saddleback-shaped ST-T segment in V2 consistent with a type-2 Brugada phenotype. Patient was febrile at the time of this ECG (Temp: 102.6 F)

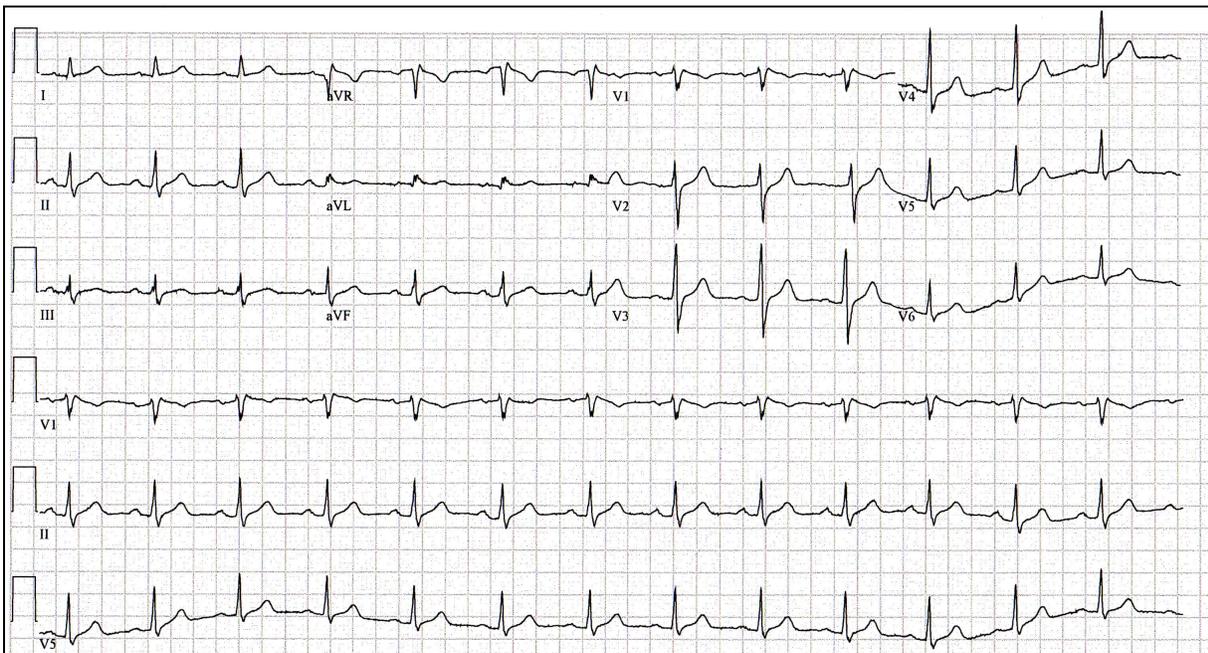


Figure-2: A repeat ECG on Day 3 showed incomplete RBBB but complete resolution of Brugada phenotype

DISCUSSION

Three types of ECG patterns for BS have been described in the literature.¹

Type-1 Brugada pattern (BP) is characterized by a coved ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave. BS is diagnosed with a type-1 pattern in >1 right pre-

cordial lead (V1–V3) in the presence or absence of a sodium channel blocking agent plus one of the following: a) presence of ventricular fibrillation or polymorphic ventricular tachycardia, b) family history of SCD, c) family history of type-1 ECG pattern, d) inducibility of VT with electrical stimulation, syncope or nocturnal agonal respirations.

ECG manifestations of BS are often concealed but can be unmasked by a sodium channel blocker or fever. Most commonly described agents are flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide.² Type-2 BP is characterized by a J-point elevation of >2 mm with a saddleback ST-T configuration, a trough/terminal ST-segment portion displaying >1 mm ST elevation, and then either a positive or biphasic T wave morphology. Type-3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. Both type-2 and type-3 patterns are non-diagnostic of BS. Diagnosis is also confirmed if a type-2 or type-3 BP converts to a type-1 pattern after a sodium channel blocker administration (ST-segment elevation should be ≥ 2 mm). One or more of the clinical criteria described above also should be present. Drug-induced conversion of type-3 to type-2 BP is inconclusive for the diagnosis.

Recently, a new criteria was proposed for diagnosis of BS³ suggesting only 2 ECG patterns: pattern-1 identical to classic type-1 of previous consensus (coved pattern); and pattern 2 joins types 2 and 3 of previous consensus (saddle-back pattern). Type-2 pattern is described in V1 and V2 in the presence of terminal positive wave called r'. Characteristically defined r' is a take-off of at least 0.2 mV followed by ST segment elevation of (≥ 0.5 mm) in a saddleback pattern and then followed by a T wave that is positive in V2 and of variable morphology in V1.³

Brugada syndrome is inherited in an autosomal dominant pattern. Brugada syndrome was linked to α -subunit of cardiac sodium channel (SCN5A) in 1998.⁴ Since then, more than 100 mutations in 7 genes have been associated with BS.⁵ These mutations result in either loss of function due to failure of expression of sodium channels, a shift in voltage and time dependence of sodium channel current activation, inactivation or reactivation, entry of sodium channel into an intermediate state of inactivation from which it recovers more slowly or accelerated inactivation of sodium channel.⁶

Many clinical situations have been reported to unmask or exacerbate the ECG pattern of BS. Examples are a febrile state, electrolyte abnormalities (hyperkalemia, hypokalemia, hypercalcemia etc), alcohol or cocaine intoxication and use of certain medications, including sodium channel blockers, vagotonic agents, alpha-adrenergic agonists, beta blockers, heterocyclic antidepressants, and a combination of glucose and insulin.⁷ Also, *de novo* drug induced Brugada patterns have been reported in otherwise healthy individuals.⁷ Several reports have suggested that a febrile state may unmask BS and trigger ventricular arrhythmias.⁸⁻¹² A large

prospective study analyzed 402 patients with fever and 909 patients without fever for ECG changes and concluded that type-1 BP was 20 times more common in febrile state.⁸ Similarly, Junttila *et al* analyzed 47 patients who presented during an acute medical event with a typical Brugada-type ECG¹¹ and noticed that 16 patients developed BP during a febrile state. Another study suggested that fever may increase the risk of cardiac arrest in patients with BS by 18%.⁹ Despite the clinical evidence, molecular mechanisms underlying fever-triggered ventricular arrhythmias in BS are not well understood. Different mechanisms have been proposed for unmasking of BS and arrhythmogenesis and are thought to involve the effect of fever to reduce sodium current. It is also suggested that accelerated inactivation of sodium channels may be temperature sensitive.¹⁰ Dumaine *et al* reported functional expression of a specific (T1620M) gene missense mutation in cardiac sodium channels in patients with BS.¹⁰ It was noted that loss of function of sodium channel current in such mutations was augmented at higher temperatures, suggesting that some patients may be at higher risk in febrile states. Conceptually, it is also possible that a febrile state could alter functional expression of other genetic mutations, however this needs further investigation. Some authors have suggested that BS should be considered in patients with unexplained syncope during febrile state. Genetic investigation may be considered in patients with an ECG suggestive of BP during fever, however this remains controversial as patients with BS may have negative genetic studies and also some patients without BS may have positive genetic mutations. Such patients should however be advised to take antipyretic drugs early in the course of any febrile illness.¹² Drug-challenge testing in asymptomatic type-2 or type-3 Brugada phenotype patients remains controversial and in fact is discouraged based on evidence from the recent studies. Most recent meta-analysis of the five largest available studies on BS recruited 2176 patients and compared prognostic value of classic risk factors in patients with and without Implantable Cardioverter Defibrillators (ICD)¹³ ICD-recorded fast ventricular arrhythmias were rare in patients without spontaneous type-1 ECG (e.g. drug induced type-1) pattern, asymptomatic patients, patients with no family history of SCD and negative EPS, due to high negative predictive value of these risk factors. Thus, in patients with none or one such clinical risk factors, an ICD should be avoided, whereas in patients with multiple risk factors, ICD implantation may be considered.¹³ Despite significant advances in diagnostic and genetic aspects of BS, little progress has been made in approach to its management. ICD remains the only effective treatment for BS.¹⁴ Class-

IA antiarrhythmic agents such as quinidine based on its ability to block Ito-mediated phase 1 epicardial action potential have been suggested to normalize ST-segment elevation in BS.¹⁵ Additionally, phosphodiesterase-3 inhibitors like cilostazol¹⁶ which augments the calcium current and reduces Ito by increasing the heart rate have been suggested. A large clinical trial, however, is needed to confirm the efficacy of these agents.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20(6):1391–6.
2. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;101(5):510–5.
3. Bayes de Luna A, Brugada J, Baranchuk A, Borggreffe M, Breithardt G, Goldwasser D, *et al.* Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. *J Electrocardiol* 2012;45(5):433–42.
4. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, *et al.* Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 1998;392(6673):293–6.
5. Hedley PL, Jorgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, *et al.* The genetic basis of Brugada syndrome: a mutation update. *Hum Mutat* 2009;30(9):1256–66.
6. Antzelevitch C. Genetic basis of Brugada syndrome. *Heart Rhythm* 2007;4(6):756–7.
7. Chhabra L, Spodick DH. Brugada pattern masquerading as ST-segment elevation myocardial infarction in flecainide toxicity. *Indian Heart J* 2012;64(4):404–7.
8. Adler A, Topaz G, Heller K, Zeltser D, Ohayon T, Rozovski U, *et al.* Fever-induced Brugada pattern: how common is it and what does it mean? *Heart Rhythm* 2013;10(9):1375–82.
9. Amin AS, Meregalli PG, Bardai A, Wilde AA, Tan HL. Fever increases the risk for cardiac arrest in the Brugada syndrome. *Ann Intern Med* 2008;149(3):216–8.
10. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, *et al.* Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circ Res* 1999;85(9):803–9.
11. Junttila MJ, Gonzalez M, Lizotte E, Benito B, Vernooy K, Sarkozy A, *et al.* Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. *Circulation* 2008;117(14):1890–3.
12. Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, *et al.* Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. *Cardiovasc Res* 2005;67(3):510–9.
13. Delise P, Allocca G, Sitta N, Distefano P. Event rates and risk factors in patients with Brugada syndrome and no prior cardiac arrest: a cumulative analysis of the largest available studies distinguishing ICD-recorded fast ventricular arrhythmias and sudden death. *Heart Rhythm* 2014;11(2):252–8.
14. Brugada J, Brugada R, Brugada P. Pharmacological and device approach to therapy of inherited cardiac diseases associated with cardiac arrhythmias and sudden death. *J Electrocardiol* 2000;33 Suppl:41–7.
15. Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *Pacing Clin Electrophysiol* 2001;24(9 Pt 1):1420–2.
16. Tsuchiya T, Ashikaga K, Honda T, Arita M. Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13(7):698–701.

Address for Correspondence:

Nauman Khalid, MD, 80 Seymour Street, Hartford, CT (06102)-USA

Email: khalid@uchc.edu

Tel: +1-860-977-2879