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Fever Unveils the Hidden Danger: A Case Report of Brugada Pattern Unmasked by Pyrexia

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Abstract

Brugada syndrome (BS) is rare and potentially lethal arrhythmogenic disorder characterized by specific electrocardiographic abnormalities, which are often seen as the Brugada pattern. In the case report presented, a patient who had no history of syncope or documented arrhythmias experienced a febrile episode that precipitated the sudden appearance of Brugada-like ECG changes. This occurrence underscores the need for clinicians to remain vigilant for BS in febrile patients, even in the absence of prior cardiac findings. The typical ECG features of Brugada syndrome are more prominent during febrile illnesses, likely due to the inflammatory response and electrolyte disturbances associated with fever, which can trigger or reveal Brugada syndrome ECG patterns in individuals at risk. Detecting an increased risk of dysrhythmia in these patients is crucial, as it appears to be linked to a higher likelihood of in-hospital mortality.

Keywords: Brugada pattern; Fever; Electrocardiogram

Introduction

BS is rare and potentially lethal arrhythmogenic disorder characterized by specific electrocardiographic abnormalities, which are often seen as the Brugada pattern. This condition is predominantly inherited and may result in sudden cardiac death because of ventricular arrhythmias. Even though classic Brugada pattern is seen in a baseline ECG, it is often unmasked by physiological stressors, such as fever. This case report aims to illustrate the incidence in which an unsuspected Brugada pattern develops under the context of a febrile illness: hence, an illustration of fever's important role in interconnecting with BS.

A 2021 publication in The American Journal of Cardiology stressed the fact that fever is a likely precipitant for revealing Brugada pattern abnormalities in patients who may not demonstrate symptoms at baseline [1]. Fever-induced unmasking of the Brugada pattern can be quite subtle, as it is not always recognized as an expression of underlying cardiac risk. This may delay diagnosis and intervention. Also, the baseline ECG may be normal in these patients adding to the diagnostic challenges.

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In the case report presented, a patient who had no history of syncope or documented arrhythmias experienced a febrile episode that precipitated the sudden appearance of Brugada-like ECG changes. This occurrence underscores the need for clinicians to remain vigilant for BS in febrile patients, even when initial evaluations do not reveal significant cardiac findings. Its finding is supported by the fact observed by Meregalli et al, wherein similar cases indicated that febrile states unmasked Brugada patterns. This changes both the approach to management as well as diagnosis for those patients [2].

Case Presentation

A 19-yr-old male pharmacy student from Alappuzha presented with 3-day history of fever accompanied by myalgia and cough. The patient reported no episodes of angina or dyspnea. On examination, he was febrile with a temperature of 100°F, but other physical findings were within normal limits. Laboratory investigations revealed a mild leukocytosis with a total count of 13,000/µL and positive C-reactive protein (CRP), indicating an inflammatory or infectious response. Serum electrolytes including sodium, potassium and magnesium were found to be within normal limits. Tests for malaria, dengue, typhoid, and leptospirosis were observed to be negative, and abdominal and pelvic ultrasound (USG) showed no abnormalities. Cardiac biomarkers, including Troponin I, were negative, suggesting no acute myocardial injury.

ECG conducted during patient's febrile state displayed Type1 Brugada pattern, distinguished by coved "ST-segment elevation in right pre-cordial leads V1 and V2 (Figure 1). This specific pattern, which is related to elevated risk of ventricular arrhythmias in addition to sudden cardiac death (SCD), had not previously been observed in patient's medical records. Several other conditions commonly linked with ST-segment elevation in right precordial leads, such as acute myocarditis, hypercalcemia, acute pericarditis", hyperkalemia, and arrhythmogenic right ventricular cardiomyopathy were also considered. 2D echocardiography was done which showed good biventricular function, intact valves and septum. However, based on echocardiography and lab tests, these differentials were found less likely. Given the patient's presentation and the unremarkable cardiac history, the initial management focused on addressing the febrile illness. The patient was treated with doxycycline and ceftriaxone for one week, targeting possible bacterial infections that could be causing the febrile state. Blood & urine cultures showed no growth. Further diagnostic study as to the etiology of fever was not done due to logistic reasons. Following the completion of antibiotic therapy, the patient's fever subsided, and a repeat ECG showed resolution of the Brugada pattern. (Figure 2) Upon follow-up patient is asymptomatic and has no brugada pattern in the ECG.

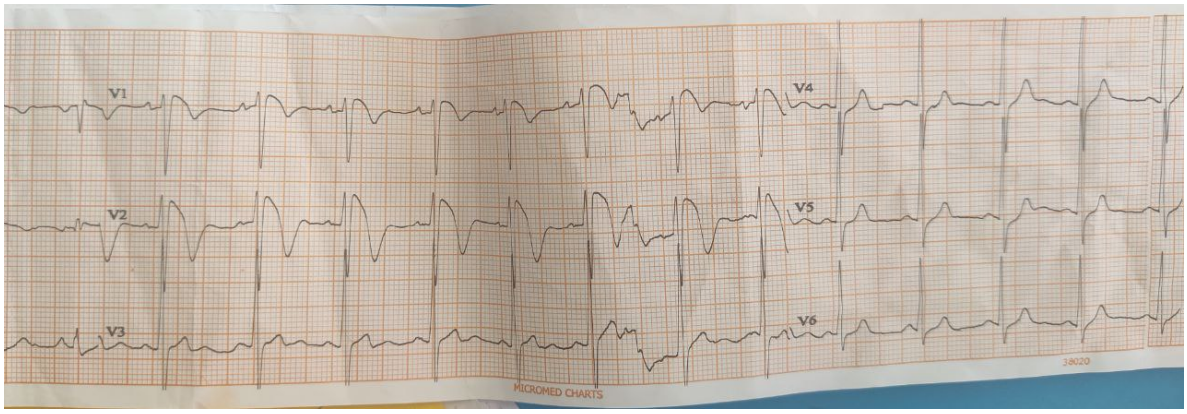

Figure 1: Electrocardiogram of the patient taken during fever episode showing coved ST segment elevation of 2mm followed by T wave inversion in V1-V2.

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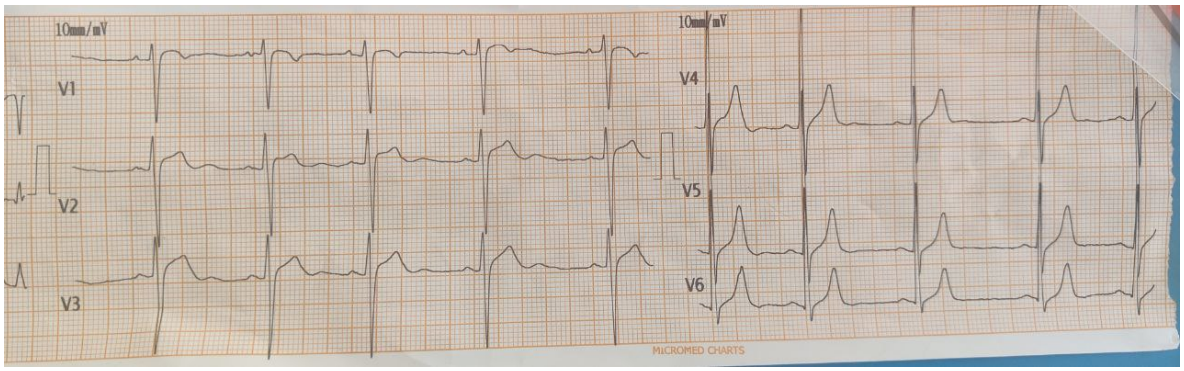

Figure 2: Electrocardiogram of the patient taken before discharge showing T wave inversion in V1 and saddleback ST elevation of <2mm in V2.

Discussion

BS initially introduced in 1992, is an important cause of SCD, syncope, as well as ventricular tachyarrhythmias in otherwise healthy young people without structural heart disease [3,4]. This is closely associated with "Sudden unexplained nocturnal death syndrome (SUNDS)" which has been reported globally and is concordant with Lai Tai in Thailand, bangungat in Philippines & Pokkuri in Japan [5]. Some 5% of cardiac arrest survivors have no detectable cardiac abnormalities, with half of these being attributed to BS.

Brugada pattern, linked to Brugada Syndrome (BS), is an ECG finding marked by distinct ST-segment elevation in right precordial leads (V1 and V2). This elevation typically appears as a coved or saddleback shape and is frequently followed by negative T-wave. It serves as key indicator of a genetic arrhythmogenic condition that heightens risk of ventricular arrhythmias and SCD, even in absence of structural heart abnormalities. BS is mainly an electrical condition, often inherited in autosomal dominant manner, and is typically caused by mutations in cardiac ion channel genes-most commonly SCN5A gene, which codes for cardiac sodium (Na^+) channel. This is also of variable penetrance and expressions, often making it quite unpredictable due to a risk of concealed by fever and electrolytes, medication imbalance.

A standard 12-lead ECG plays a vital role in identifying BS and informing appropriate treatment strategies. BS appears in 3 distinct ECG patterns: Type I is characterized by coved ST-segment elevation exceeding 2 mm along with an inverted T-wave; Type II is identified by saddleback-shaped ST elevation over 2 mm; and Type III also presents a saddleback configuration but with ST-segment elevation below 2 mm. Only Type I pattern is regarded as definitively diagnostic of BS, whereas Types II and III are suggestive but not confirmatory indicators of syndrome [6,7].

In cases where the ECG appears normal but high-risk factors are present; drug challenge examination may be required for unmasking characteristic ST-segment elevations in leads V1 to V3. High-risk factors that might warrant such provocative testing encompass family history of BS or SCD, and symptoms indicative of BS despite inconclusive ECG results [8].

BS is explained by 2 main physiological theories: "repolarization disorder model" and "depolarization disorder model." According to repolarization disorder model, a reduction in sodium (Na^+) current-stemming from loss-of-function mutations in Na^+ channels-leads to a more pronounced action potential in right ventricular epicardium compared with endocardium.

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This disparity in current can produce characteristic ECG abnormalities seen in BS and lead to potentially fatal arrhythmias. In contrast, depolarization disorder model posits that ECG findings are due to delayed depolarization resulting from slow conduction in right ventricular outflow tract. Heightened sympathetic activity as well as temperature-sensitive ion channel dysfunction may also contribute.

Arnon Adler et al studied incidence of Brugada pattern in 402 patients having fever and found that Type I Brugada pattern is significantly more frequent in patients with fever, indicating that asymptomatic Brugada syndrome may be more widespread than previously thought [9]. Also, most patients in the above study were asymptomatic in the 30-month follow-up. Hence most of the cases don't require Internal Cardioverter Defibrillator (ICD) therapy prophylactically. Our patient was asymptomatic in the 12-week follow-up. In cases where fever triggers BS, supportive care is advised, including the use of antipyretics and the antiarrhythmic drug quinidine [10].

It is worth to note the key points given by Professor Josep Brugada in managing patients with a Brugada ECG pattern:

1. Brugada pattern has a single definitive diagnostic form: only Type 1 confirms BS, while Types 2 and 3 may raise suspicion without providing a conclusive diagnosis.
2. Administering a drug challenge is advised when BS is suspected but resting ECG is either normal or shows non-diagnostic features (Types 2 or 3). Medications such as flecainide, procainamide, ajmaline, propafenone, disopyramide, as well as pilsicainide are employed for revealing syndrome. A test is deemed "positive" only if diagnostic Type 1 pattern emerges.
3. For improved detection of Brugada pattern-both at baseline and during pharmacological testing with Class I antiarrhythmic agents-placing right precordial leads as high as second intercostal space is recommended.
4. It is crucial to rule out alternative explanations for a Brugada-like ECG pattern, including conditions such as acute pericarditis, acute myocarditis, hemopericardium, right ventricular ischemia or infarction, Friedreich's ataxia, hyperkalemia, hypercalcemia, thiamine deficiency, "Long QT syndrome type 3, arrhythmogenic right ventricular cardiomyopathy, left ventricular hypertrophy, right or left bundle branch block, early repolarization syndrome, and hypothermia.
5. After confirming Type 1 ECG in multiple precordial leads and excluding other" possible causes, further clinical evidence should be gathered to support BS diagnosis.

   5.1. Medical history: SCD in a relative under 45yrs old or presence of Type 1 ECG among family members.

   5.2. Symptoms associated with arrhythmias: syncope, seizures, or gasping respirations during sleep.

   5.3. Documentation of ventricular fibrillation or ventricular tachycardia is also relevant. BS is definitively diagnosed if Type 1 ECG-either spontaneous or drug-induced—is accompanied by at least one of above clinical indicators. If Type 1 ECG is found without these supporting criteria, it is described as an 'idiopathic Brugada ECG pattern' rather than BS.
6. Risk stratification holds key role in identifying and managing patients at elevated risk of SCD (refer to Figure 3).

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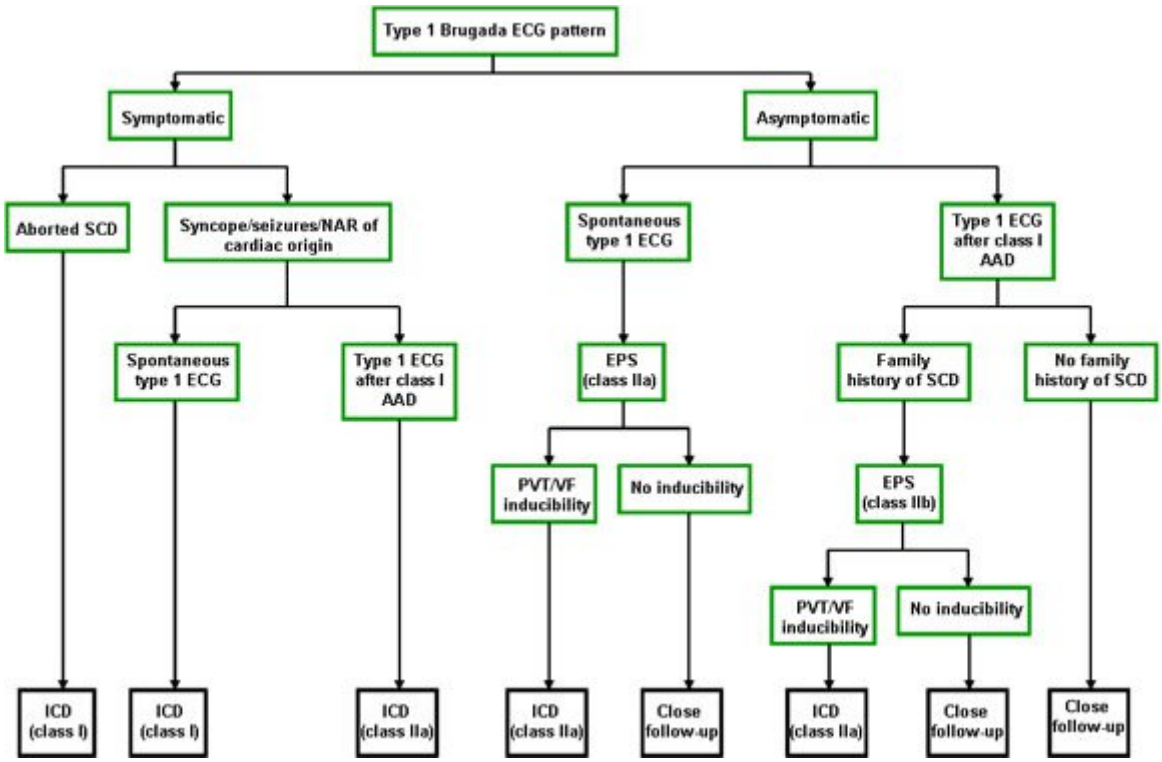

Figure 3: Current Risk Stratification Scheme and Recommendations of ICD in BS Patients. (AAD-anti-arrhythmic drugs; BS-Brugada syndrome; SCD-sudden cardiac death; ICD-implantable cardioverter-defibrillator; NAR-nocturnal agonal respiration; PVT–polymorphic ventricular tachycardia; VF-ventricular fibrillation) Ref: Prof. Josep Brugada, Management of patients with a Brugada ECG pattern -An article from the e-Journal of Cardiology Practice Vol. 7, N° 24 - 17 Mar 2009.

7. Treatment recommendations for BS patients:

7.1. ICD- Only established treatment shown to effectively prevent SCD is careful use of therapy. Accurate device programming is crucial to prevent unnecessary shocks triggered by conditions like sinus tachycardia or supraventricular tachycardia.

7.2. Most widely recognized explanation for ECG alterations and arrhythmogenic mechanisms in BS centers on reduction of inward positive currents (Na^+, $Ca2^+$), which influences transient outward potassium current (Ito). Quinidine is utilized clinically to prevent onset of ventricular fibrillation and to suppress spontaneous ventricular arrhythmias, especially among patients having ICDs experiencing multiple shocks, in cases where ICD implantation is not feasible, or for managing supraventricular arrhythmias.

7.3. Isoproterenol (which enhances ICaL current) in conjugation with quinidine has shown effectiveness in managing electrical storms associated with BS.

7.4. Additional drugs under investigation for BS include phosphodiesterase III inhibitors (cilostazol), tedisamile, along with dimethyl lithospermate B [11].

Conclusion

The typical ECG features of BS are more prominent during febrile illnesses, likely due to the inflammatory response and electrolyte disturbances associated with fever, which can trigger or reveal Brugada syndrome's ECG patterns in individuals at risk. This case is presented to highlight the potential link between fever and appearance of Brugada pattern on ECG. Detecting an increased risk of dysrhythmia in these patients is crucial, as it appears to be linked to a higher likelihood of in-hospital mortality.

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Such an impact from BS calls for this case, in which fever can be a major factor for diagnosis in BS, to emphasize the screening that needs to be performed more intensively in a patient presenting with fever and unexplained arrhythmias. Evaluation and management of BS is summarized in (Table 1) [12]. Such emphasis will again require the alertness of clinicians toward clinical conditions that may otherwise prove to be fatal with BS.

Table 1: Diagnosis and Management Summary of Brugada Syndrome.

At Risk	**Symptomatic:** 1. Cardiogenic syncope, 2. Ventricular arrhythmias, 3. Resuscitated cardiac arrest. **Asymptomatic:** 1. Type 1 ECG, 2. Type 2/3 ECG, 3. Family screening of first-degree relatives.
Evaluation and Testing	**Initial:** 1. Clinical: syncope, medications, medical history, family history, 2. ECG has high leads, 3. ECG: exclude structural abnormalities. **Discretionary:** 1. SCB provocation, 2. Holter monitor, 3. Further cardiac imaging as demonstrated, 4. EP study, 5. Cardiac MRI.
Diagnostic Criteria	**Definite:** Spontaneous Type 1 ECG variations in V1-V2 at ICS2-4. **Probable:** Type 1 ECG variations in V1-V2 at ICS2-4 having fever or SCB provocation.
Management	**Conservative:** 1. Avoid Brugada drugs, triggers, and promptly manage fever, 2. Advised for all patients having definite BrS, 3. Recommended for those with probable BrS, 4. Patients should undergo annual follow-up by cardiologist, 5. Any episodes of syncope or seizures should be immediately reported, 6. Family members should be informed and undergo appropriate screening. **Pharmacologic: Quinidine:** 1. Recurrent appropriate interventions by ICD devices, 2. Evaluate patients eligible for ICD but with reduced need, 3. Consider "medical management of atrial arrhythmias, 4. Use low-dose therapy (<600mg/d) to help minimize adverse effects, 5. Routine blood count monitoring is necessary. **Isoproterenol:** - During acute ventricular arrhythmias. **Interventional: ICD:** 1. Utilized for secondary prevention among individuals who have experienced resuscitated cardiac arrest, 2. Advised for primary prevention among patients presenting with spontaneous type 1 ECG and episodes of syncope, 3. Considered for primary prevention in those with provoked type 1 ECG alongside syncope, 4. Considered for primary prevention among asymptomatic patients with spontaneous type 1 ECG and other high-risk indicators. **Ablation:** 1. Quinidine intolerance, 2. Arrhythmic events despite quinidine.

Abbreviation: BrS: Brugada syndrome; **ECG:** Electrocardiogram; **EP:** Electrophysiology; **ICD:** Implantable cardioverter defibrillator; **ICS:** Intercostal space; **MRI:** Magnetic resonance imaging; **SCB:** Sodium channel blocker.

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