CASE REPORT

Electrocardiographic pattern of Brugada syndrome disclosed by a febrile illness: clinical and therapeutic implications

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Background Recent studies have identified a direct link between the ionic mechanisms responsible for the electrocardiographic (ECG) pattern of the Brugada syndrome (BS) and the in vitro experimental temperature, pointing to the possibility that some BS patients may display the ECG phenotype only during a febrile state, being in this setting at risk of lethal arrhythmias.

Case report A 53-year-old man referred to the emergency room for abdominal pain and fever. The ECG showed dome-shaped ST-segment elevation in V1–V3, as in the typical BS. The personal and family history were unremarkable for syncope and sudden death and physical, laboratory and ultrasound examinations were negative. On day 3, at normal body temperature, the patient’s ECG returned to normal and the ECG abnormalities were later reproduced with intravenous flecainide. The patient refused the implantation of a loop recorder and was discharged after 6 days. He has remained asymptomatic during 2 years of follow-up.

Conclusions The typical ECG phenotype of BS disclosed by a febrile illness confirms the in vitro experimental data that previously established a correlation between ECG pattern of BS and temperature variations. The clinical and therapeutic implications of these findings are discussed.

Key Words: Asymptomatic Brugada syndrome, fever, sudden death.

Introduction

The Brugada syndrome (BS) is a major cause of sudden death in young men with no evidence of structural heart disease. According to the original description[1], the disease is electrocardiographically characterized by ST-segment elevation in V1 through V3 coved, saddle-back or dome-shaped, an apparent right bundle branch block (RBBB), and rapid polymorphic ventricular tachycardia capable of degenerating into ventricular fibrillation. Moreover, there is the evidence that in patients with BS, early repolarization abnormalities (prominent J wave) and not RBBB represent the hallmark of the electrocardiographic (ECG) pattern[2]. In most patients, the typical widened S wave in lateral leads, commonly observed in RBBB, is absent and the QRS duration is usually normal.

Recently, the BS was linked to different mutations in SCN5A, the gene encoding for the alpha subunit of the cardiac sodium channel[3]. In addition, it has been demonstrated that the ionic mechanisms responsible for the ECG phenotype of the disease are temperature dependent[4], pointing to the possibility that some BS patients may be at risk only during a febrile state.

In this paper we describe a patient with the typical ECG pattern of BS disclosed by fever, and discuss the
clinical and electrophysiological implications of these findings.

Case report

A 53-year-old man referred to the emergency room with the chief complaint of abdominal pain and fever. The 12-lead ECG showed dome-shaped ST-segment elevation with a prominent J wave in V1 – V3, as in the typical BS (Fig. 1). The family and personal history were unremarkable for syncope or sudden death.

During hospitalization, serial cardiac enzymes measurements and echocardiographic examination were performed, with normal results.

On day 3, after recovery from the influenza-like febrile illness, the ECG returned to normal, except for non-specific ST-T abnormalities in V1 and V2, together with minor right intra-ventricular conduction delay (Fig. 2). Holter monitoring and signal-averaged ECG were unremarkable, and a maximal treadmill test showed no additional ST changes or ventricular arrhythmias.

On day 4, a test with flecainide, a sodium channel blocking drug that has been used to unmask the ECG pattern in concealed forms of BS[5], was performed. The ECG after 2 mg kg⁻¹ of flecainide i.v. infusion showed the typical and prominent J wave in V1 – V3, as observed on admission (Fig. 3).

In order to identify potentially lethal arrhythmias, a loop-recorder implantation was suggested, but the patient

![Figure 1](https://example.com/image1)

**Figure 1** 12-Lead ECG on admission. Typical ECG features of BS during febrile state are evident.
refused consent. Therefore, all close relatives were trained to perform basic life support manoeuvres and to deliver shocks with an automatic external defibrillator. On day 6, the patient was discharged uneventfully, and no arrhythmic event has occurred during 2 years of follow-up.

**Discussion**

BS is a genetically determined arrhythmogenic disease with sporadic or familial expression, caused by different mutations affecting the cardiac sodium channel gene, $\text{SCN5A}^{[3]}$. In the case of T1620M missense mutation, inactivation of the inward sodium current is faster, so that repolarizing $\text{K}^{+}$ current (transient outward current, $\text{I}^{\text{to}}$) is left unopposed during phase 1 of the action potential, resulting in loss of the dome (phase 2) of right ventricular epicardial cells in which $\text{I}^{\text{to}}$ is prominent, but not in the endocardial tissue, exhibiting a small $\text{I}^{\text{to}}$. The resulting transmural voltage gradient is believed to constitute the basis for ST-segment elevation, as clinically observed, as well as for aberration in the

*Figure 2* 12-Lead ECG after remission of the febrile illness. Minor ST-T changes are present, the tracing being otherwise normal.
J wave. On the other hand, the transepidermal and transmural dispersion of repolarization and refractoriness might also give rise to phase 2 re-entrant extrasystoles, capable of precipitating lethal arrhythmias [6].

The change in the function of the mutant channel is observed at physiological human body temperature, but not at room temperature, at which in vitro experiments are usually performed. At temperatures above the physiological range, the sodium channel decay is much faster with slower recovery from inactivation [4]. These observations suggest that some asymptomatic BS patients may display the typical ECG pattern during a febrile state, being in this setting at risk of ventricular arrhythmias.

A case of BS and fever-induced ventricular fibrillation has been described by Rebollo et al. [7]. These authors argued that the occurrence of ventricular arrhythmia in their patient could have been related to faster activation/inactivation kinetics of sodium channels, and reduced calcium inward current during the febrile state, as well as to dysionia caused by excessive sweating.

In our case, a febrile illness disclosed the typical ECG pattern of BS in an asymptomatic man in whom structural heart disease had been ruled out; the ECG abnormalities were reproduced with intravenous flecainide. This observation is in agreement with previous laboratory findings, that have demonstrated
a definite link between high temperatures and the alteration of sodium channel kinetics due to SCN5A gene mutations[6].

Even though the gene analysis has not been performed in our patient, the occurrence of fever-related typical ECG modifications in the absence of structural heart disease might provide indirect evidence of sodium channel mutation. Such a finding, together with reproduction of the ECG features after a class IC drug challenge, suggests that the patient may represent a sporadic and asymptomatic case of BS, according to the diagnostic criteria described in a recent review[3].

To date, there is no general agreement to perform an electrophysiological study (EPS) in asymptomatic patients with a typical BS ECG (either at rest or after challenge with class IC drugs)[6]. Indeed, the prognosis of these patients is ill-defined and data on the predictive value of EPS are discordant.

Brugada et al[1], in their series of 22 asymptomatic patients observed six serious events (27%) after 34 months of follow-up, with no significant differences with respect to symptomatic patients. In a subsequent series of 136 asymptomatic patients undergoing EPS, the same authors report seven arrhythmic events (5%) after 25 months of follow-up. The negative predictive value of EPS was 99%, the positive predictive value 13%, the diagnostic accuracy 70.5%[10]. According to these data, every asymptomatic patient with a typical ECG phenotype should undergo EPS and should be reassured in the presence of a negative test.

Atarashi et al[11], in a series of 67 asymptomatic Japanese patients (no patient underwent EPS), report two serious events (2.9%) after a 3-year follow-up: one death due to unknown causes and one ventricular fibrillation treated with an implantable cardioverter defibrillator (ICD).

Priori et al[12], in a series of 30 asymptomatic patients observed no events after a follow-up of 33 months. The same authors underscored the low specificity (34%) of EPS in predicting the occurrence of cardiac arrest in the general BS population, without any statistically significant difference between inducible and non-inducible patients with respect to serious arrhythmic events[13]. In addition, they demonstrated that association of history of syncope with baseline BS ECG correlates with high risk of death[13]. According to these data, the clinical decision should not be guided by EPS results, which might only reflect temporary electrical instability, lacking in predictive value of future events. Therefore, Priori et al[12] in asymptomatic patients, have proposed a diagnostic algorithm that recommends loop-recorder implantation, in order to identify potentially lethal arrhythmias and proceed towards a more aggressive therapeutic strategy with an ICD.

In accordance with the current literature, we did not perform EPS in our patient, due to the negative personal and family history, as well as the absence of a baseline typical ECG, the ST-T abnormalities being evident only during a febrile illness and on flecainide testing. On a theoretical basis, this patient should be considered at risk for life-threatening arrhythmias during fever episodes, and data from a loop recorder, which was declined by the patient, could have been helpful toward an informed therapeutic decision.

References