Fever-induced Brugada pattern: How common is it and what does it mean?

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BACKGROUND Fever is known to unmask the Brugada pattern on the electrocardiogram (ECG) and trigger ventricular arrhythmias in patients with Brugada syndrome. Genetic studies in selected cases with fever-induced Brugada pattern have identified disease-causing mutations. Thus, "fever-induced Brugada" is a recognized clinical entity. However, its prevalence has not been systematically evaluated.

OBJECTIVE The purpose of this study was to assess the prevalence of Brugada pattern in consecutive patients with fever.

METHODS ECGs of patients with fever admitted to the emergency department were evaluated for the presence of Brugada pattern and compared with ECGs of consecutive nonfebrile patients.

RESULTS ECGs of 402 patients with fever and 909 without were evaluated. Type I Brugada pattern was 20 times more common in the febrile group than in the afebrile group (2% vs 0.1%, respectively, $P = .0001$). All patients with fever-induced type I Brugada pattern were asymptomatic and remained so during 30 months of follow-up.

CONCLUSION Type I Brugada pattern is definitively more common among patients with fever, suggesting that asymptomatic Brugada syndrome is more prevalent than previously estimated.

KEYWORDS Brugada syndrome; Ventricular fibrillation; Fever

ABBREVIATIONS **AIDS** = acquired immunodeficiency syndrome; **ECG** = electrocardiogram

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Brugada syndrome is a genetic disease presenting with a characteristic electrocardiogram (ECG) and a tendency to develop malignant polymorphic ventricular arrhythmias that may lead to syncope or cardiac arrest. The characteristic ECG, which includes a coved-type ST-segment elevation ≥2mm in the right precordial leads, is termed "type I" Brugada ECG pattern and is required to make the diagnosis of Brugada syndrome.[1] Too often, however, the ECGs of patients with Brugada syndrome have lesser degrees or different contours of ST-segment elevation ("saddleback" rather than "coved"), which are termed type II or type III Brugada pattern. These ECG patterns are suggestive, but not diagnostic, of this disease. Moreover, in a given patient with Brugada syndrome there are marked day-to-day changes in ECG morphology. For example, in a large series of patients with documented Brugada syndrome who underwent repeated ECG recording over the years,[2] only every third ECG was diagnostic (ie, showed the type I pattern) and every third ECG was completely normal, making the diagnosis of Brugada syndrome challenging.

In 1999, Dumaine et al[3] reported the results of functional expression studies of a genetic mutation (T1620M) identified in patients with Brugada syndrome, showing that the loss of function of sodium channel current was accentuated at higher temperatures. The authors suggested the possibility that a febrile state may unmask the Brugada syndrome. Subsequent years witnessed a large number of reports documenting the ability of fever to unmask Brugada syndrome by promoting a type I Brugada ECG in susceptible individuals.[4–11] Fever has been reported not only to accentuate the Brugada ECG pattern but also to actually trigger ventricular arrhythmias.[4,10,12] Indeed, fever was the precipitating factor of arrhythmias in 18% of patients presenting with cardiac arrest in a large series of patients with symptomatic Brugada syndrome.[13] Thus, the concept of "fever-induced Brugada syndrome" is well accepted. However, we do not really know how common (or rare) this phenomenon is because no large studies have systematically evaluated this issue. Therefore, in the present study, we prospectively analyzed ECG recordings of consecutive febrile patients (using afebrile

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patients as controls) and further investigated those who were positive for type I Brugada pattern.

Methods

Febrile and afebrile groups

Between January 2010 and August 2012, we prospectively collected ECG recordings of all febrile patients (defined as oral temperature >38°C [>100.4°F]) who were evaluated in our emergency medicine department. Because our hospital has a separate pediatric emergency room, only adults were studied. Also, to ensure that all patients presenting with fever in a given day were included in the study, we studied only those who presented to the emergency room during the morning shift of weekdays when specific physicians (KH, TO) were present. A control group of afebrile patients was used for comparison. This control group was randomly selected from a much larger patient population that was evaluated in the same emergency room during the same time period as the study (fever) group but were found to be afebrile (oral temperature <37.0°C [<98.6°F]). We did *not* specifically request ECGs with the precordial electrodes placed at higher intercostal spaces for patients with fever. All the ECGs from the fever and the control groups were evaluated separately by 2 experienced cardiologists (AA, RR) for the presence of Brugada pattern types I, II, and III. Any inconsistencies were settled by a third expert (SV). Type I, II, and III Brugada patterns were defined according to standard criteria and as endorsed by the Consensus Document,[1] including recent important updates on the ECG diagnosis of Brugada syndrome[14] with the only exception that an ECG with a right bundle branch block pattern and classic coved-type ST-segment elevation was considered type I *even* in the absence of negative T waves in leads V_1–V_3. This is because *when a coved ST segment-elevation is obvious,* (1) the presence of inverted T waves is no longer considered a requisite for defining Brugada syndrome by most experts; (2) ECGs in a patient with typical coved type I pattern may or may not have a negative T wave on different days[15]; and (3) the prognosis of coved-type ST-segment elevation without T-wave inversion is similar to that of the "classic" type I pattern.[15]

Clinical data were collected *only* for patients with type I Brugada pattern. These patients also underwent a standard evaluation for possible Brugada syndrome *upon complete resolution of their fever* and after providing informed consent. The evaluation included the following tests: (1) repeated ECG, (2) exercise test, (3) ajmaline challenge test, (4) 12-lead Holter test, and (5) echocardiogram. All of these ECG tests were performed with leads located in the standard location and once more with all 6 precordial leads located in the second and third intercostal spaces. The ajmaline test was performed according to recommended protocol (1 mg/kg over 5 minutes).[1]

Follow-up

All patients diagnosed with fever-induced Brugada were followed in our institution's arrhythmia clinic. All patients were evaluated for the occurrence of atrial fibrillation, syncope, or sudden death. The occurrence of these events in family members was also evaluated.

Statistical analysis

Using the observed proportion of Brugada ECG pattern, we estimated the 95% confidence interval based on the binomial distribution iterated through all possible outcomes.[16] The χ^2 test was used to compare the prevalence of Brugada between the febrile and afebrile groups. To compare age differences between patients with and without fever-induced Brugada ECG, we used the T-test with Welch approximation (variance not assumed equal). To compare the frequency of patients with fever-induced type I Brugada, age >60 and <60 years, we used the Fisher exact test.

Results

ECG recordings from 402 febrile and 909 afebrile patients were compared. Febrile and afebrile patients were of similar age (62 ± 22 years vs 61 ± 19 years, P = NS), but males were overrepresented in the febrile group (60% vs 49%, P <.001).

Eight of 402 patients with fever, but only 1 of 909 afebrile patients, had a type I Brugada pattern (Figure 1). Thus, a type I Brugada pattern was 20 times more prevalent among febrile patients (2% vs 0.1%, P = .0001). The estimated 95% confidence intervals for the presence of type I ECG were 1%–3.9% for patients with fever vs 0.016%–0.6% for afebrile patients. Limiting the analysis of the frequency of type I Brugada to male patients revealed similar results: 7 (3%) of males with fever but only 1 (0.2%) of afebrile males had a type I Brugada (P = .0015).

All of the 8 patients with fever-induced type I Brugada pattern presented to the emergency room because of symptoms related to fever or the underlying infection (Table 1). Specifically, none of them reported syncope- or arrhythmia-related symptoms at the time of presentation. Thus, *in all cases, the fever-induced type I Brugada pattern was an incidental finding*. Mean age at the time of diagnosis of fever-induced type I Brugada was 46 years (range 31–57 years), and 7 (87%) of them were male. Interestingly, patients with fever-induced type I Brugada ECG were younger than patients with fever but no Brugada (46 ± 10 years vs 62 ± 22 years, P = .002). Mean temperature at the time of type I Brugada recording was 39°C (range 38.4°–40°C [101.1°–104°F]). A scatter plot of the heart rate and temperature of patients with fever, as recorded when the ECG was performed, failed to reveal any differences between patients with and those without type I ECG during fever (data not shown).

The *only* patient with a type I Brugada ECG discovered in the nonfebrile group was admitted due to smoke inhalation as a result of fire in a sauna. The finding of the Brugada pattern was incidental in this case as well.

Type II or III Brugada patterns were also found more frequently among febrile patients: 7 (1.7%) of febrile patients but only 4 (0.4%) of afebrile patients had a type II or III