Fever following Covid-19 vaccination in subjects with Brugada syndrome: Incidence and management

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Abstract

Background: Fever is a potential side effect of the Covid-19 vaccination. Patients with Brugada syndrome (BrS) have an increased risk of life-threatening arrhythmias when experiencing fever. Prompt treatment with antipyretic drugs is suggested in these patients.

Aim of the study: To evaluate the incidence and management of fever within 48 h from Covid-19 vaccination among BrS patients.

Methods: One hundred sixty-three consecutive patients were enrolled in a prospective registry involving five European hospitals with a dedicated inherited disease ambulatory.

Results: The mean age was 50 ± 14 years and 121 (75%) patients were male. Prevalence of Brugada electrocardiogram (ECG) pattern type-1, -2, and -3 was 32%, 44%, and 24%, respectively. Twenty-eight (17%) patients had an implantable cardioverter-defibrillator (ICD). Fever occurred in 32 (19%) BrS patients after 16 ± 10 h from vaccination, with a peak of body temperature of 37.9° ± 0.5°. Patients with fever were younger (39 ± 13 vs. 48 ± 13 years, \( p = .04 \)). No additional differences in terms of sex and cardiovascular risk factors were found between patients with fever and not. Twenty-seven (84%) out of 32 patients experienced mild fever and five (16%) moderate fever. Pharmacological treatment with antipyretic drugs was required in 18 (56%) out of 32 patients and was associated with the resolution of symptoms. No patient required hospital admission and no arrhythmic episode was recorded in patients with ICD within 48 h after vaccination. No induced type 1 BrS ECG pattern and new ECG features were found among patients with moderate fever.
1 | INTRODUCTION

Brugada syndrome (BrS) is an inherited disease characterized by an increased risk of sudden cardiac death (SCD) in patients with structurally normal hearts.\(^1\) Near a quarter of BrS patients have also a family member suffering from this condition.\(^2\) Several genetic mutations BrS related have been found\(^3\)\(^-\)\(^5\); the most common mutation involves the SCN5A gene, encoding the sodium channel of cardiac cells.\(^6\) Electrocardiogram (ECG) is the most useful tool to diagnose BrS; however, electrocardiographic abnormalities are not always and constantly present, therefore in cases without spontaneous BrS type 1 ECG, pharmacological testing with sodium channel blocking drugs is required to unmask the diagnosis.\(^7\)

Fever has been reported not only unmasking the type-1 Brugada ECG but also occasionally triggering ventricular arrhythmias. In an international registry on BS, 6% of the arrhythmic events (AEs) occurred during a febrile illness, mostly involving the pediatric population (age <16 years). Patients with fever-induced arrhythmias had a family history of sudden death, a history of syncope, and spontaneous type-1 Brugada-ECG in 17%, 40%, and 66% of cases, respectively.\(^8\) Of note, ventricular tachyarrhythmias could be triggered in a resting situation with a different genotype-phenotype response.\(^9\)

One of the causes of fever in the recent Covid-19 pandemic context may be represented by vaccination. Vaccination is crucial in reducing the occurrence of severe acute respiratory syndrome coronavirus 2 infections and represents one of the most effective strategies in controlling the pandemic worldwide. Fever has been reported as a side effect of Covid-19 vaccination with an incidence ranging from 7% to 16%.\(^10\) Aim of the study was, therefore, to evaluate the incidence of fever and potential management among Covid-19 vaccinated patients with BrS.

2 | METHODS

2.1 | Study population

One hundred sixty-three patients with BrS were collected in a prospective European registry including five referral centers with a dedicated inherited disease ambulatory (University Hospital “Policlinico Riuniti,” Foggia, Italy; University Hospital “Policlinico G. Martino,” Messina, Italy; Bonomo Hospital, Andria, Italy; University Hospital Mannheim, Germany; and Bergmannsheil University Hospital, University of Bochum, Germany).

Clinical characteristics such as age, sex, SCN5A mutation, family history of SCD, body temperature during fever, and pharmacological and electrical therapy were also assessed. Structural heart disease was exclud ed with conventional diagnostic methods including treadmill test, echocardiogram, and/or cardiac magnetic resonance imaging.

Brugada type-1 ECG was defined as ST-segment elevation with coved type morphology of ≥2 mm in one or more right precordial leads in the fourth, third, and/or second intercostal space. Type-2 was defined as ≥2-mm J-point elevation, ≥1-mm ST-segment elevation, and a saddleback appearance, followed by a positive or biphasic T-wave in one or more right precordial leads. Type-3 was defined as having either a saddleback or coved appearance, but with an ST-segment elevation <1 mm in one or more right precordial leads. All of the patients with Brugada ECG pattern type-2 and -3 underwent pharmacological testing with flecainide or ajmaline intravenous with conversion to pattern 1.\(^7\)

2.2 | Fever and management

Fever was classified with temperature as none (≤37.5°C), mild (37.6–38.4°C), moderate (38.5–38.9°C), severe (39.0–40.0°C), or life-threatening (≥40.1°C).\(^11\) During routine cardiological visits, patients were instructed to assume antipyretics when they had a fever and to avoid a list of drugs potentially harmful.\(^12\)

The protocol for fever management after covid-19 vaccination consisted of temperature measurement when symptoms occurred and every 6 h for the first 48 h after vaccination.

Body temperature was measured either temporal, axillary, or tympanic. For body temperature higher than 37.5°C, patients were allowed to take antipyretics each 6 h until the temperature reached 37.5°C. Antipyretics suggested were nonsteroidal anti-inflammatory drugs like ibuprofen (10 mg/kg) or paracetamol (1 g) every 6 h.

Patients included in the present study received complete vaccination, including one or two doses as pharmacological protocol approved in the European Union. Patients were followed in the outpatient clinic (once every 12–24 months) or whenever clinical circumstances required unscheduled visits. At each visit, follow-up data (including ECGs) were collected. Each patient after 3 ± 1 month of Covid-19 vaccination underwent a cardiological examination. The
subgroup of patients with an implantable cardioverter-defibrillator (ICD) (n = 28, 17%) was monitored for arrhythmias. Adverse events were defined as cardiovascular hospitalization, ICD shock recorded during ICD monitoring, and all-cause death. All patients provided written informed consent to research, which was approved by the Human Research Ethics Committee in each center.

2.3 | Statistical analysis

Continuous variables are presented as mean ± standard deviation and compared with the t-Student test, categorical variables as a percentage and compared with χ². Two-sided p < .05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical features of the study population

One hundred sixty-three patients were enrolled in the study. The mean age was 50 ± 14 years, 121 (75%) patients were male (Table 1). Prevalence of spontaneous Brugada ECG pattern type-1, -2, and -3 was 32%, 44%, and 24%, respectively. Twenty-eight (17%) patients had an ICD. Thirty-two out of 163 patients underwent genetic testing and five (15%) patients had an SNC5A mutation.

Thirty-four out of 163 (21%) patients had history of syncope, among these patients 41% (n = 14) had a spontaneous BrS type 1 pattern, 4 out of 15 had polymorphic ventricular tachycardia/ventricular fibrillation (PVT/VF) induced during electrophysiological study (EPS) and 41% (n = 14) underwent ICD implantation. Twenty-three out of 163 (14%) patients had family history of SCD (n = 23), 52% (n = 12) had a spontaneous BrS type 1 pattern, 5 out of 11 had PVT/VF induced during EPS, and 52% (n = 12) underwent ICD implantation.

3.2 | Covid-19 vaccination

Patients underwent Covid-19 vaccination between March and September 2021. One hundred forty-seven (90%) patients received messenger RNA (mRNA) vaccine (131 [80%] patients received BNT162b2 mRNA vaccine and 16 [10%] patients mRNA-1273 vaccine) and 15 patients (10%) received adenoviral-based vaccine (10 [6%] patients received ChAdOx vaccine and 5 [4%] patients Ad26.COV2.S vaccine).

3.3 | Fever after covid-19 vaccination

Fever occurred in 32 (19%) BrS patients after 16 ± 10 h from vaccination, with a peak body temperature of 37.9° ± 0.5° and mean duration was 2.7 ± 1.7 h. A higher incidence of fever was found among patients receiving adenoviral-based versus mRNA vaccine (40 vs. 18% p = .03). Patients that experienced fever were younger (39 ± 13 vs. 48 ± 13 years, p = .04). No additional differences in terms of sex and cardiovascular risk factors were found between patients with fever and not (Table 1).

Twenty-seven (84%) out of 32 patients experienced mild and five (16%) moderate fever. Pharmacological treatment with antipyretic drugs was required in 18 (56%) out of 32 patients and was associated with the resolution of symptoms. Thirteen (48%) out of 27 patients

| TABLE 1 Baseline features of Brugada syndrome patients undergoing covid-19 vaccination and evaluation of patients that experienced fever and not |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | General population | Fever           | No fever        | p               |
| Number of patients | 163             | 32              | 131             |                 |
| Ethnicity (n.)    |                 |                 |                 |                 |
| Caucasian         | 163             | 32              | 131             |                 |
| Age (years)       | 50 ± 14         | 39 ± 13         | 48 ± 13         | .04             |
| Male sex          | 74%             | 78%             | 73%             | .65             |
| Cardiovascular risk factors |
| Smoker            | 23%             | 5%              | 24%             | .64             |
| Hypertension      | 20%             | 10%             | 23%             | .13             |
| Diabetes          | 6%              | 3%              | 7%              | .68             |
| Family history of IHD (%) | 4%     | 6%              | 4%              | .62             |
| Paroxysmal atrial fibrillation | 6%   | 0%              | 6%              | .21             |
| ECG pattern       |                 |                 |                 |                 |
| BrS pattern type 1 | 32%            | 29%             | 32%             | .83             |
| BrS pattern type 2 | 44%            | 45%             | 46%             | .41             |
| BrS pattern type 3 | 24%            | 26%             | 22%             | .45             |
| SCN5A mutation carriers, n. (32 patients evaluated) | 5/32 | 0/8 | 5/24 | .56 |
| Family history of SCD, n (%) | 14% | 4% | 14% | .06 |
| History of syncope (%) | 20% | 25% | 20% | .62 |
| Positive EPS (n) (29 patients evaluated) | 9/29 | 3/7 | 6/22 | .64 |
| ICD implant (%)    | 17%             | 13%             | 18%             | .61             |
| Drug therapy      |                 |                 |                 |                 |
| Beta blockers (%)  | 5%              | 3%              | 5%              | .78             |
| Quinidine (%)      | 2%              | 3%              | 1%              | .87             |

Note: Bold value statically significant (p < 0.05).

Abbreviations: BrS, Brugada syndrome; ECG, electrocardiogram; EPS, electrophysiological study, ICD, implantable cardiac defibrillator; IHD, ischemic heart disease; SCD, sudden cardiac death.
with mild fever required a single paracetamol 1000 mg tablet to achieve fever resolution; all patients (N = 5) with moderate fever required two tablets of paracetamol for fever resolution, one tablet given at fever onset and one other after 6 h (Figure 1).

Patients with body temperature between 37.4° and 37.9° had a shorter duration of fever when compared with patients with body temperature ≥38° (1.7 ± 0.5 vs. 3.5 ± 1.8 h, p < .01).

Patients with moderate fever underwent ECG examination and no induced type 1 BrS pattern and new ECG features were found. No patient required hospital admission and had syncope or fatigue episodes. No arrhythmic episodes were recorded in patients with ICDs within 48 h after vaccination.

Additional side effects after vaccination were recorded among 74 (45%) BrS patients: 38 (23%) patients experienced joint pain, 32 (19%) injection site pain, and 4 (3%) chest pain (Table 2).

At 3 ± 1 months, follow-up no adverse events and arrhythmias among patients with ICD were recorded.

4 | DISCUSSION

We report the incidence and management of fever following Covid-19 vaccination among BrS patients in a multicenter European registry. The main findings of the study are as follows:

1) Nineteen percent of BrS patients had a fever within 16 ± 10 h after vaccination with a peak body temperature of 37.9° ± 0.5°.
2) Pharmacological treatment with antipyretic drugs was needed in 56% of patients with fever.

3) No arrhythmic episode was recorded during 3 months follow-up after vaccination among ICD recipients.

Fever is a well-known factor able to unmask the electrocardiographic pattern of BrS, occasionally triggering ventricular arrhythmias. Experimental studies showed that increased temperature may cause a dysfunction of sodium channel current kinetics and/or sodium channel blocking drugs. Among febrile patients, there is a higher prevalence of Brugada type-1 ECG pattern. Adler et al. evaluated ECGs of 1311 consecutive patients with fever or not admitted to the emergency department; the authors found that the type-I Brugada ECG pattern had a prevalence of 2% in the febrile group versus 0.1% in the afebrile group. All patients with fever-induced type I Brugada pattern were asymptomatic with no adverse events during 30-month follow-up.

In a worldwide registry of arrhythmic events in BrS including 687 patients, 6% of the arrhythmic events occurred during a febrile illness. History of syncope and spontaneous type 1 Brugada-ECG were found in 40% and 66% of patients, respectively. Interestingly, most of the fever-related arrhythmias were observed in the pediatric population (age <16), especially during early childhood (age 0–5, 65%), followed by a marked decline during late childhood (age 6–15, 16.7%) and adulthood (age 16–70, 3.6%) with a subsequent marked rise to 25% in the elderly.

In a cohort of 88 patients with Brugada type 1 fever-induced, Mizusawa et al. found that during a follow-up period of 44 months, three male patients (3.4%) developed arrhythmic events (ICD shock [n = 1] and cardiac arrest [n = 2]). One of these arrhythmic events occurred during fever. The risk of VF in asymptomatic patients with fever-induced type 1 was 0.9%/year overall (3/88, 43.6 ± 37.4 months), and 1.1%/year in men (3/67, 48.8 ± 41.1 months).

When comparing fever versus drug-induced Brugada type-1 pattern, Mizusawa et al. found that fever pattern had similar ST-elevation but did not prolong PR interval and QRS as drug-challenge does. A potential explanation is that fever has less sodium channel blocking effect than drugs. Moreover, the right ventricular outflow tract has developmentally lower protein Nav1.5 and
connexin43 levels compared to the right or left ventricle, causing lower conduction reserve.17

At the state of the art, no data have been published on the role of antiarrhythmic agents to prevent fever-induced type 1 Brugada ECG, however prompt antipyretics administration seems to reduce the risk of fever-triggered cardiac arrest.18

On the basis of potential risk of arrhythmias during fever, the 2013 consensus statement on the management of inherited arrhythmias suggests, among lifestyle recommendations for patients with BrS, immediate treatment of fever with antipyretic drugs (class I indication).19

Incidence of fever after Covid-19 vaccination in the general population has been already published,6 but no data on fever incidence in BrS patients are available so far.

After the BNT162b2 mRNA vaccine, fever (temperature, ≥38°C) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older. Only 0.8% and 0.2% of vaccine recipients reported fever with temperatures higher than 38.9°C after the first and second dose.20 Similar data were found with the mRNA-1273 vaccine.21 On the other side, temperature higher than 37.8°C was reported by 7.0% of ChAdOx vaccinated22 and 12% of Ad26.COV2.S.23

Data from the present study are in line with those reported in the general population of Covid-19 vaccinated and show that also in BrS patients there is a higher incidence of fever among younger patients. Moreover, among patients with moderate fever that underwent ECG examination, no type 1 induced BrS pattern was observed.

Present data suggest that out-of-hospital Covid-19 vaccination is safe also for BrS patients. Body temperature measurements in case of symptoms and every 6 h within the first 48 h after vaccination are however recommended. Prompt antipyretic administration is safe, and effective and can be performed independently by patients (Figure 2). In case of fever unresponsive to drugs, hospital monitorization is required especially in high-risk patients with spontaneous type-1 Brugada ECG pattern, family history of sudden cardiac death, and/or history of syncope.

**FIGURE 2** Proposed algorithm for fever management after Covid-19 vaccination in Brugada syndrome (BS) patients. High-risk patients include those with a history of syncope and/or spontaneous type-1 Brugada ECG and/or family history of sudden cardiac death. Low-risk patients include those with type-2 and -3 Brugada ECG without a history of syncope and without a family history of sudden death. ECG, electrocardiogram; ICD, implantable cardiac defibrillator.

Fever is a common side effect in BrS patients after the Covid-19 vaccination, affecting one out of five BrS patients. Careful evaluation of body temperature and prompt treatment with antipyretic drugs may be needed.
6 | LIMITATIONS

First, there is no standard approach for pharmacological treatment of fever in the case of Covid-19 vaccination and BrS. Second, only Caucasian patients were enrolled in the present study and there were no Asiatic on Black patients. Third, only patients older than 18 years old were enrolled in the study. Fourth, patients without ICD were not monitored with Holter-ECG during the first 48 h after vaccination. A fifth, larger population would provide additional information on life-threatening arrhythmias after covid-19 vaccination in a high-risk population as patients with BrS.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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