Accepted Manuscript

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Yoav Michowitz, MD, Anat Milman, MD PhD, Georgia Sarquella-Brugada, MD PhD, Antoine Andorin, MD, Jean Champagne, MD, Pieter G. Postema, MD PhD, Ruben Casado-Arroyo, MD PhD, Eran Leshem, MD, Jimmy JM. Juang, MD PhD, Carla Giustetto, MD, Jacob Tfelt-Hansen, MD DMSc, Yanushi D. Wijeyeratne, MD, Christian Veltmann, MD, Domenico Corrado, MD PhD, Sung-Hwan Kim, MD, Pietro Delise, MD, Shingo Maeda, MD PhD, Jean-Baptiste Gourraud, MD PhD, Frederic Sacher, MD, Philippe Mabo, MD, Yoshihide Takahashi, MD PhD, Tsukasa Kamakura, MD PhD, Takeshi Aiba, MD PhD, Giulio Conte, MD PhD, Aviram Hochstadt, MD, Yuka Mizusawa, MD, Michael Rahkovich, MD, Elena Arbelo, MD PhD, Zhengrong Huang, MD PhD, Isabelle Denjoy, MD, Carlo Napolitano, MD PhD, Ramon Brugada, MD PhD, Leonardo Calo, MD, Silvia G. Priori, MD PhD, Masahiko Takagi, MD PhD, Elijah R. Behr, MD, Fiorenzo Gaita, MD, Gan-Xin Yan, MD PhD, Josep Brugada, MD PhD, Antoine Leenhardt, MD, Arthur A.M. Wilde, MD PhD, Pedro Brugada, MD PhD, Kengo F. Kusano, MD PhD, Kenzo Hirao, MD PhD, Gi-Byoung Nam, MD PhD, Vincent Probst, MD PhD, Bernard Belhassen, MD

PII: S1547-5271(18)30346-1

DOI: 10.1016/j.hrthm.2018.04.007

Reference: HRTHM 7551

To appear in: *Heart Rhythm*

Received Date: 20 January 2018

Please cite this article as: Michowitz Y, Milman A, Sarquella-Brugada G, Andorin A, Champagne J, Postema PG, Casado-Arroyo R, Leshem E, Juang JJ, Giustetto C, Tfelt-Hansen J, Wijeyeratne YD, Veltmann C, Corrado D, Kim S-H, Delise P, Maeda S, Gourraud J-B, Sacher F, Mabo P, Takahashi Y, Kamakura T, Aiba T, Conte G, Hochstadt A, Mizusawa Y, Rahkovich M, Arbelo E, Huang Z, Denjoy I, Napolitano C, Brugada R, Calo L, Priori SG, Takagi M, Behr ER, Gaita F, Yan G-X, Brugada J, Leenhardt A, Wilde AAM, Brugada P, Kusano KF, Hirao K, Nam G-B, Probst V, Belhassen B, Fever-Related Arrhythmic Events in the Multicenter Survey on Arrhythmic Events in Brugada Syndrome (SABRUS), *Heart Rhythm* (2018), doi: 10.1016/j.hrthm.2018.04.007.

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Fever-Related Arrhythmic Events in the Multicenter Survey on Arrhythmic Events in Brugada Syndrome (SABRUS)

Brief title: Brugada Syndrome and Fever-related Arrhythmias

Yoav Michowitz MD[1], Anat Milman MD PhD[1], Georgia Sarquella-Brugada MD PhD[2,3], Antoine Andorin MD[2,4], Jean Champagne MD[5], Pieter G. Postema MD PhD[2,6], Ruben Casado-Arroyo MD PhD[7], Eran Leshem MD[1,8], Jimmy JM Juang MD PhD[9], Carla Giustetto MD[10], Jacob Tfelt-Hansen MD DMSc[2,11], Yanushi D. Wijeyeratne MD[12], Christian Veltmann MD[13], Domenico Corrado MD PhD[2,14], Sung-Hwan Kim MD[15], Pietro Delise MD[16], Shingo Maeda MD PhD[17], Jean-Baptiste Gourraud MD PhD[2,4], Frederic Sacher MD[18], Philippe Mabo MD[19], Yoshihide Takahashi MD PhD[17], Tsukasa Kamakura MD PhD[20], Takeshi Aiba MD PhD[20], Giulio Conte MD PhD[21], Aviram Hochstadt MD[22], Yuka Mizusawa MD[2,6], Michael Rahkovich MD[1,23], Elena Arbelo MD PhD[24], Zhengrong Huang MD PhD[25], Isabelle Denjoy MD[2,26], Carlo Napolitano MD PhD[2,27], Ramon Brugada MD PhD[28], Leonardo Calo MD[29], Silvia G. Priori MD PhD[2,27], Masahiko Takagi MD PhD[30], Elijah R. Behr MD[2,12], Fiorenzo Gaita MD[10], Gan-Xin Yan MD PhD[31], Josep Brugada MD PhD[24], Antoine Leenhardt MD[2,26], Arthur A.M. Wilde MD PhD[2,6], Pedro Brugada MD PhD[2,21] Kengo F. Kusano MD PhD[20], Kenzo Hirao MD PhD[17], Gi-Byoung Nam MD PhD[32], Vincent Probst MD PhD[2,4], Bernard Belhassen MD[1]

Word count: 5583

1) Department of Cardiology, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
(2) European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-HEART).
(3) Pediatric Arrhythmias, Electrophysiology and Sudden Death Unit, Cardiology Department, Hospital Sant Joan de Déu, Barcelona - Universitat de Barcelona, Spain.
(4) L'institut du Thorax, Service de Cardiologie, CHU de Nantes, Nantes, France.
(5) Quebec Heart and Lung Institute, Quebec City, Canada.
(6) Heart Centre AMC, Department of Clinical and Experimental Cardiology, AMC, University of Amsterdam, Amsterdam Netherlands.
(7) Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium.
(8) Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.
(9) Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.
(10) Division of Cardiology, University of Torino, Department of Medical Sciences, Città della Salute e della Scienza Hospital, Torino, Italy.

(11) Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Denmark.
(12) Cardiovascular Sciences, St. George's University of London and Cardiology Clinical Academic Group St. George's University Hospitals NHS Foundation Trust, London, UK.
(13) Rhythmology and Electrophysiology, Department of Cardiology, Hannover Medical School, Hannover, Germany.
(14) Department of Cardiac, Thoracic and Vascular Sciences University of Padova, Padova, Italy.
(15) Division of Cardiology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea.
(16) Division of Cardiology, Hospital of Peschiera del Garda, Veneto, Italy.
(17) Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan.
(18) Hôpital Cardiologique du Haut-Lévêque & Université Bordeaux, LIRYC Institute.), Bordeaux, France.
(19) Cardiology and Vascular Disease Division, Rennes University Health Centre, Rennes, France.
(20) Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan.
(21) Heart Rhythm Management Centre, UZ-VUB, Brussels, Belgium.
(22) Department of Internal Medicine J, Tel-Aviv Medical Center, Tel Aviv, Israel.
(23) Arrhythmia Services, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.
(24) Cardiology Department, Cardiovascular Institute, Hospital Clinic and IDIBAPS, Barcelona, Catalonia, Spain.
(25) Department of Cardiology, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China.
(26) Service de Cardiologie et CNMR Maladies Cardiaques Héréditaires Rares, Hôpital Bichat, Paris, and Université Paris Diderot, Sorbonne, Paris, France.
(27) Molecular Cardiology, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.
(28) Cardiovascular Genetics Center, University of Girona-IDIBGI, Girona, Spain; Medical Science Department, School of Medicine, University of Girona, Girona, Spain; Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain.
(29) Division of Cardiology, Policlinico Casilino, Roma, Italy.
(30) Division of Cardiac Arrhythmia, Kansai Medical University Medical Center, Moriguchi, Japan.
(31) Lankenau Medical Center, Wynnewood, Pennsylvania, USA.
(32) Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

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Funding: None.
Disclosures: None.

Address for correspondence:
Bernard Belhassen, MD
Department of Cardiology
Tel-Aviv Sourasky Medical Center
Weizman St 6, Tel-Aviv, 64239, Israel
E-mail: bblhass@gmail.com
Phone: 972.52.4.266.856
Fax: 972.153.52.4.266.856

Abstract

Background: The literature on fever related arrhythmic events (AE) in Brugada syndrome (BrS) is currently limited to few case reports and small series.

Objective: The current study aims to describe the characteristics of fever-related AE in a large cohort of BrS patients.

Methods: SABRUS is a multicenter study on 678 BrS patients with first AE documented at time of aborted cardiac arrest (ACA) (n=426) or after prophylactic ICD implantation (n=252).

Results: In 35(6%) of the 588 patients with available information, the AE occurred during a febrile illness. Most of the 35 patients were male (80%), Caucasian (83%) and proband (70%). Age at time of AE was 29±24 (range 0.3-76) years. Most patients (80%) presented with ACA and 6 (17%) with arrhythmic storm. Family history of sudden death, history of syncope and spontaneous type 1 Brugada-ECG were noted in 17%, 40% and 66% of patients, respectively. VF was induced at EPS in 9/19(47%) patients. An *SCN5A* mutation was found in 14/28(50%) patients. The highest proportion of fever-related AE was observed in the pediatric population (age <16), with disproportionally higher event rate in the very young (0-5 years old) (65%). Males were involved in all age groups and females only in the pediatric and elderly groups. Fever-related AE affected 17 Caucasians aged<24 years, but no Asians aged <24 years.

Conclusions: The risk of fever-related AE in BrS markedly varies according to age group, gender and ethnicity. Taking these factors into account could help the clinical management of BrS patients with fever.

Key words: Fever, Brugada syndrome, children, elderly, gender, ethnicity

Introduction

Brugada syndrome (BrS) is an inherited disease that predisposes to sudden cardiac death (SCD), mainly affecting males aged 27-59 years old[1]. Several factors are known to precipitate an arrhythmic event (AE) in BrS patients such as specific drugs[2], increase in vagal tone[3] and fever[4].

The *SCN5A*-encoded α-subunit of the NaV1.5 cardiac sodium channel has been linked to BrS and mutations in *SCN5A* are identified in 14–26% of BrS cases[5]. Dumaine et al.[6] were the first to link temperature with the function of a mutant *SCN5A* sodium channel. Later it was demonstrated that fever may induce type 1 ECG in BrS patients[7]. Two large studies demonstrated that in unselected populations with fever, type 1 Brugada-ECG may be seen in 2-4% of patients[8,9] and Mizusawa and colleagues[10] recently demonstrated that patients who have fever-induced type 1 ECG (F-type 1) have an increased risk for syncope and VF. However, there are only few case reports and small series describing patients with BrS and proven fever-related AE. The Survey on Arrhythmic events in BRUgada Syndrome (SABRUS) is a multicenter study that collected data on the first AE in 678 patients with BrS[1]. The objective of the present study was to describe the characteristics of patients with fever-related AE in this large SABRUS patient cohort.

Methods

The study was approved by the Tel Aviv Medical Center Institutional Review Board committee. The SABRUS patients originated from 23 centers in 10 Western and 4 Asian countries[1]. Sixteen (69.5%) centers provided data from their institution only, whereas the remaining 7 (31.5%) provided data from multiple institutions from their countries.

Data acquisition. Study inclusion criteria consisted of 1) a typical type 1 Brugada-ECG either spontaneously (i.e. unrelated to drugs or fever) or following the intravenous administration of a cardiac sodium channel blocking drug; 2) a first documented AE (sustained ventricular tachyarrhythmia). The detailed information collected on each patient included whether or not the AE was associated with fever (oral temperature $\geq 38^0$c or an axillary temperature $\geq 37^0$c). Other collected variables were previously described[1]

Definitions.

- Group A: Patients with documented aborted CA in whom the BrS-diagnosis was made during work-up performed after CA; Group B: Patients with a BrS-diagnosis in whom prophylactic ICD implantation was performed for any reason and in whom an AE requiring appropriate ICD shock therapy was documented during follow-up by ICD interrogation.

Proband status: Proband was defined as the first patient of a family who has been diagnosed with the type-1 Brugada-ECG (spontaneous or drug-induced). A non-proband was defined as a family member of a known BrS-patient.

Genetic analysis: When a *SCN5A* mutation was identified it was classified by its known pathogenicity.

Age groups: For analyzing the effect of age on fever-related AE, patients were divided into 8 age categories: 1) early childhood: 0-5 years; 2) late childhood: 6-15 years; 3) adult life: 16-70 years, divided in 5 equal bins of 11 years; 4) elderly: age>70 years old.

Model for predicting the risk of AE per day of fever. In order to predict the risk of AE per day of fever (day at risk) in each age group a model which took in account the data provided by all 23 main centers participating in SABRUS was built. These centers were invited to participate in a registry by providing the age and gender distribution of the entire BrS population followed at their own center (with or without prior AE). The centers from Western and Asian countries were assumed to include Caucasian and Asian patients, respectively, based on SABRUS results.[1]

The Delphi method [11] was used in order to estimate the average number of fever days per year in the 8-different age groups (described in the supplemental data).

Statistical analysis.

Assumptions of normality of the different ages were assessed by Kolmogorov–Smirnov test and Q-Q plots. Differences between non-normally distributed ages were assessed using a Mann–Whitney U test. Ratio differences were examined by a Chi-square test or a Fisher's exact test as appropriate. Statistical significance was defined as $P<0.05$. Scale variables are presented as Median [IQR] for when not normally distributed. All calculations were performed using SPSS version 24 (IBM, Armonk, NY, USA).

Results

Study patient cohort.

In 588 (86.7%) of the 678 SABRUS patients, there was information available on a possible relationship between AE and fever. In 35 (5.95%) of these 588 patients, the AE occurred during a febrile illness. These 35 patients comprised the study group.

Characteristics of patients with fever-related AE (Supplemental Table 1).

The vast majority (n=32) of study patients were provided from the main SABRUS centers while only 3 were from subsidiary medical centers.

Most patients were male (28 of 35, 80%) and Caucasian (29 of 35, 83%) with a mean age of 29±24 (range 0.3-76) years at the time of AE. The vast majority (28 of 35, 80%) presented with aborted CA (group A). Six (17%) patients presented with VF storm. Most patients were probands (70%). A family history of SCD and a history of syncope were noted in 17% and 40% of patients, respectively. A spontaneous type 1 Brugada-ECG was observed in 24 (66%) of patients. VF was induced at EPS in 9 (47%) of the 19 patients who underwent the procedure. An *SCN5A* mutation was found in 14 (50%) of the 28 patients who underwent genetic testing. In 12 of them the *SCN5A* mutations were identified as pathogenic (n=6, 50%) and likely pathogenic (n=4, 33.3%) while 2 (16.7%) were classified as a "variant of unknown significance". In the remaining 2 patients information regarding mutation pathogenicity was not available.

Comparison between patients with or without fever-related AE.

Age distribution was markedly different in the 2 patient groups (Fig. 1A). In the study group, 13 (37.1%) of the 35 AE occurred in the pediatric population (age $\leq$16 years) particularly in the very young ($\leq$5 years) (11 of 13, 84.6%); the AE occurred between ages 16-70 in 20 (57.1%) patients and after age 70 in 2 (5.7%) patients (Fig. 1A). In contrast, in the patients with AE not related to fever, the AE mainly occurred (96%) between 16-70 years and rarely in the pediatric and elderly age groups (2.9% and 1.1%), respectively, ($P< 0.001$) (Fig. 1A). The highest AE rate was observed 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 (Fig. 1A).

Comparisons between patients with and without fever-related AE are presented in Table 1. Patients with fever-related AE had a lower proportion of males (80% vs. 92%, P=0.03) and probands (70% vs. 87%, P=0.02). In contrast, they were more likely to be younger at time of AE [median age (IQR) of 25 (3-46) vs. 43 (34-52), P<0.001)], to belong to Group A (80% vs. 59%, P=0.02), to be Caucasian (83% vs. 56%, P=0.007) and to be *SCN5A* mutation carriers (50% vs. 31%, P=0.04).

Other variables including family history of SCD, history of syncope, positive EPS, spontaneous type 1 Brugada-ECG and presentation with an arrhythmic storm were not significantly different among the 2 groups.

Comparison between males and females with fever-related AE (Supplemental Table 2A).

Females with fever-related AE were younger [(median age (IQR) of 3 (0.4-16) vs. 35.5 (7.25-46.75), P=0.04]. The age distribution of males and females and the percentage of fever-related AE at different age groups are presented in Figure 1B. As shown, all fever-related AE in females were censored from early childhood until age of 16 with no other cases during adulthood except for a single 70-year old female. In contrast fever-related AE in males occurred in all age groups. The rate of fever-related AE tended to be higher in female patients aged<26 years as compared to males in the same age group (43% vs. 16.7%, P=0.065). Another difference between males and females concerned the EPS response. An inducible arrhythmia was observed in 64% of tested males but in none of the females (P=0.03). Other analyzed variables were not gender specific.

Comparison between children (age<16) and adults (age≥16) with fever-related AE (Supplemental Table 2B).

There was a non-significant trend toward a higher percentage of females (38% vs. 9%, P=0.08) and Caucasians (100% vs. 73%, P=0.06) among children with fever-related AE as compared to

adults. An *SCN5A* mutation was significantly more frequently observed in children (77% vs. 27% in adults, P=0.008). Other variables including mode of AE presentation, proband status, family history of SCD, history of syncope, spontaneous type 1 Brugada-ECG, inducible arrhythmia at EPS and VF storm were not different between children and adults.

Comparison between Caucasians and Asians with fever-related AE (Supplemental Table 2C).

Caucasians tented to be younger than Asians [median age (IQR) of 22 (3-45) vs. 42 (31-61), P=0.05]. Among the patients with fever-related AE, there were 17 Caucasians aged≤24 years old including 11 patients aged≤5 years whereas the younger Asian patient was 25 years old. Caucasians tended to exhibit a spontaneous type 1 Brugada-ECG (P=0.06). The other variables tested were not significantly different in respect to patient ethnicity.

Percentage of patients with AE per age group and estimation of arrhythmic risk for 1000 fever days.

Twenty-two of the 23 main SABRUS centers provided the age and gender distribution of the entire BrS population followed at their own center (with or without prior AE). The registry comprised 6441 patients (73.4% males, 88% Caucasians) including 500 patients with and 5941 without AE. Of note, the other 178 SABRUS patients who were not followed by the main participating centers and in whom the denominator from which these patients were collected was unknown, were not included in the present sub-analysis. In 77 of the 500 SABRUS patients, there was no information available about the possible association of fever with AE and therefore these 77 patients were also excluded from further analysis. A flowchart describing patient selection is presented in Figure 2. As shown, overall 32 patients had fever-related AE and 6332

patients did not have fever-related AE (including 5941 patients without AE and 391 patients with AE not related to fever).

The age-group distribution of the patients with and without fever-related AE is presented in supplemental table 3, demonstrating that 70.9% of the BrS population were 27-59 years old. This table also denotes the estimated yearly fever days from the Delphi method.

The supplemental figure demonstrates the percentages of patients with fever related AE in each age group out of the total BrS population (i.e. including also patients without and arrhythmic event) that were followed by the main participating centers. As shown a disproportionally high percentage of events is seen in age group 0-5 compared to all other age groups.

Figure 3 demonstrates the estimated AE rate per 1000 fever days according to the specific age group. It shows an estimated rate of 14.8 AE (95% CI 7.4, 26.3) per 1000 fever days in BrS patients aged 0-5 years old with similar rates between females and males. In contrast, the estimated AE rate dropped to 0.33-2.5 events per 1000 fever days in all other age groups.

Discussion

Main findings.

The present study describes the largest series ever reported of BrS patients with fever-related AE. It shows that ≈6% of AE in BrS were associated with fever. These AE mainly occurred in Caucasians males, in all age groups and often with a presentation of aborted CA. The highest proportion of fever-related AE was observed in the pediatric population (age<16), with disproportionally higher event rate in the very young (0-5 years old). Marked gender differences were noted with involvement of males in all age groups contrasting with exclusive female involvement in the pediatric and elderly groups. Fever-related AE did not involve any Asian patient aged<25 years old.

Prior reports on fever-related AE.

Supplemental Table 4 summarizes all previous publications of fever-related AE in BrS comprising 40 patients in 22 reports. Only 4 (18%) of the 22 reports included patients (n=9) who originated from Asian countries. Careful analysis of these publications, as well as contact with the respective authors, enabled us to confirm that up to 15 cases included in SABRUS had been already published, however with very limited data that did not include age and gender in most of them[4, 12, 13]. The largest report includes 7 patients[12] while 16 (72%) of these 22 publications dealt with case reports. Age and gender were provided for 18 (45%) and 23 (57%) patients, respectively. Male involvement was observed in all age groups; however, there were 8 females with fever induced AE at very young age (≤2 years, n=6) or after menopause (≥50 years, n=2). ECG data was provided on 18 patients (45%) showing spontaneous type 1 Brugada-ECG in 8 (44%). Thirteen out of 19 tested patients (68%) had *SCN5A* mutations. EPS was performed in 4 patients and was positive in all of them.

Fever induced Brugada ECG pattern.

A prevalence of 2-4% of fever induced Brugada pattern (F-type 1) among febrile patients referred to the emergency department was reported in 2 studies [8]-[9]. . This estimate, which is 20 times higher than the known prevalence of BrS in the general population[14,15], suggests that fever induced Brugada-ECG changes are benign asnone of the patients in these 2 studies developed an AE during follow up. However, Mizusawa et al.[10] found that among 88 asymptomatic patients at baseline who developed F-type 1 Brugada-ECG, 3 (3.4%) developed an AE including 1 which was fever-related. The AE event rate in these 88 asymptomatic patients was 0.9%/year i.e. similar to the event rate in patients with spontaneous type 1 (0.5-0.8% /year) [10]. Thus, Mizusawa

et al.[10] suggested that the occurrence of F-type 1 is probably a sign of poorer prognosis, yet it by no means implies that the risk for AE is present only or mainly during fever.

Gender and fever-related AE.

In the total SABRUS population of 678 patients with AE, females accounted for 8.7% of the cohort[1]. In the present study, however, females involved 20% of the population which exhibited fever-related AE.

One possible explanation for this apparent higher propensity of females to develop fever-related AE deals with the higher SCN5A mutation rate observed in patients with fever-related AE (50% vs. 31% in those without fever-related) (Table 1), especially in females (80% vs. 43% in males) (Supplemental Table 2A). In this scenario, one could hypothesize on a more proarrhythmic effect of fever in mutation carriers.

Another interesting finding of our study was the exclusive occurrence of AE in females at childhood or the elderly while this occurred at all age groups in males. This was also observed by others (see Supplemental Table 4) and suggests an "antiarrhythmic protection" in females during their reproductive period. Several theories were raised regarding the protective role of female gender on disease manifestation including: gender differences in ionic currents[16] and the effect of sex hormones[17]. Thus, one may speculate that estrogen and not the absence of testosterone is the main protector against fever-related AE in females during their reproductive period.

Children and fever-related AE.

Children (age<16 years) represented a considerable proportion of patients with fever-related AE (37.1%) despite they comprised only 4.3% the total SABRUS population[1]. We found that children of both genders exhibited a considerable risk of fever-related AE as compared with patients in all other age groups. AE were related with fever in 65% and 16.7% of patients aged 0-

5 and 6-15, respectively, while this was the case in only 3.9% of those patients aged ≥16 years. Previous studies [18,19] suggested a higher risk of fever-related symptoms in children; however most described episodes of syncope and not a proven AE.[19,20] As children have more febrile illnesses compared to adults it was speculated that a greater risk exposure may lead to this high rate of fever-related symptoms[19]. However, when taking into account both total BrS population and the average yearly fever days in each age group we found that the risk of AE in a comparable risk exposure (i.e. 1000 fever days) is much higher only among *children aged 0-5 years* compared to any other group. On the other hand, the higher event rate in children aged 6-15 may be related to more fever days with similar event rate per 1000 fever days as adults. The exact mechanism of this cluster of events in ages 0-5 is unknown and should be further investigated. Nevertheless, it has clinical implications as discussed below.

Another interesting finding of the present study was the higher rate of *SCN5A* mutation in children with fever-induced AE (77%) as compared to adults (27%) (P=0.02). The significance of this very high mutation rate should be interpreted with caution since our study was not powered to determine whether BrS children *without SCN5A* mutation have lower risk of AE during fever. Nevertheless, significantly lower mutation rates (59 of 201, 29.4%, P=0.001) were found in children without previous documented AE aged <16 years (Andorin and Probst, Sarquella-Brugada, Giustetto and Conte, personal communication, 2017). Therefore, it is possible that the presence of *SCN5A* mutation in children may indicate a higher arrhythmic risk during fever.

Ethnicity and fever-related AE.

There were 2 main differences between Caucasians and Asians with regard to fever-related AE. First, Caucasians predominated much more in the fever-related AE group than in the afebrile-

related AE group. Secondly, Asians with fever-related AE were much older and the youngest in our cohort was 25 years old. A review of the literature (Supplemental Table 4) confirms the extreme rarity of the involvement of Asians in fever-related AE, especially in children, with a single report of rapid monomorphic VT in a 2.2 year-old Korean child[21]. The lower risk for fever-related AE in Asian children may suggest that their mutation is sensitive to testosterone, which absence during childhood may also protect from the effect of fever. Further research is needed to explore this possibility.

Clinical implications.

Our results demonstrate that fever-related AE is the first manifestation of the disease in the majority of patients and may occur in a substantial number of previously asymptomatic patients without spontaneous type 1 Brugada-ECG. Therefore, in accordance with the current guidelines[22], aggressive antipyretic therapy should be administered to any BrS patient with fever. In addition, special attention should be given to those children (especially those aged 0-5 years) with syncope and/or febrile seizures who should undergo ECG to exclude the possibility of transient BrS-related AE[23]. A survey conducted among pediatric electrophysiologists found that only 3% of them recommend admission for observation of BrS children with fever.[24] Our findings suggest that a policy of lower threshold for in-hospital observation should be adopted in children, especially in Caucasians aged $\leq$ 5 years. However, based on our present study and prior reports, the risk of AE of any type (fever-related or not) in Asian children seems to be extremely low allowing to recommend a more liberal hospitalization policy. Moreover, our data suggest that the presence of *SCN5A* mutation in children may indicate a higher arrhythmic risk during fever. Finally, BrS females at their reproductive age also have a very low AE risk and can be

managed conservatively with antipyretics at outpatient settings, unless any alarming symptoms occur.

Limitations.

In 13.3% subjects from SABRUS there was no information available regarding the occurrence of fever during the AE, therefore we cannot exclude the possibility of selection bias. Not all SABRUS patients were followed by the participating centers and the denominator from which these patients were collected was unknown. Yet, even if these 178 patients had been excluded the results demonstrated in Table 1 and Supplemental Tables 2 would not change meaningfully (Supplemental tables 5-6), thus minimizing the possibility of a bias. The study is retrospective and details regarding whether the patients had type 1 Brugada-ECG changes during fever (F-type 1) were not available, precluding the analysis of F-type ECG changes as a risk factor for AE. In addition our survey did not collect data on QT interval measurements and the possibility of overlap syndrome of long QT and BrS in part of our cohort cannot be excluded. Nevertheless, we relied on reports from leading centers in the field. Also, information regarding ablative or 1A antiarrhythmic therapy which might have influenced the tendency for fever related AE was not collected. Our model of AE event risk per 1000 fever days may not be accurate since it is based on a calculated estimation of 10 experts since we do not know the exact risk exposure (fever days). Nevertheless, the substantial higher risk of fever related AE in children aged 0-5 is also demonstrated by the disproportionally higher percentage of fever related AE in that age group. Finally, the number of Asians, females and elderly patients is limited; therefore our results regarding these subgroups should be taken with caution and further validated by larger cohorts. Also, the current cohort includes only 1 elderly female with fever related AE (while in the literature we found 2 more cases), thus we can affirm that the risk of females for fever related

AE is very low during their reproductive years, however whether their risk increases after menopause needs to be studied further.

Conclusions

Around 6% of AE in BrS patients are associated with fever. The risk of fever-related AE in BrS markedly varies according to age group, gender and ethnical origin of patients. Taking these factors into account may help in the clinical management of BrS patients with fever.

Acknowledgements: We thank Dr. Tomer Ziv-Baran for statistical analysis support.

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Table 1: Comparison between Brugada syndrome patients with arrhythmic event related or unrelated to fever.

	Fever-related AE n=35	AE not related to fever n= 553	P value
Male Gender (%)	28 (80)	508 (92)	0.03
Age, years			
median (IQR)	25 (3-46)	43 (34-52)	<0.001
range	0.3-76	0.3-84	
Group A (%)	28 (80)	328 (59)	0.02
Probands (%)	23/33 (70)	441/507 (87)	0.02
Ethnicity (%)			0.009
Caucasian	29 (83)	312 (56)	
Asian	6 (17)	203 (37)	
Others	0 (0)	38 (7)	
Family history of SCD (%)	6 (17)	122 (22)	0.34
Spontaneous type 1 Brugada (%)	24 (66)	377 (68)	0.96
History of syncope (%)	14 (40)	224 (41)	0.95
Positive EPS (%)	9/19 (47)	210/330 (64)	0.15
SCN5A mutation (%)	14/28 (50)	118/379 (31)	0.04
VF storm (%)	6 (17)	44 (8)	0.12

AE=arrhythmic event; SCD=sudden cardiac death; EPS=electrophysiological study; VF=ventricular fibrillation, IQR=interquartile range.

Group A is defined as patients with documented aborted CA in whom the BrS diagnosis was made during work-up performed after CA.

Figure legends

Figure 1A: Patient age distribution. Patients with (left panel) or without (middle panel) fever-related AE are shown. The percentage of patients with fever-related AE in each age group is presented on the right panel. The highest percentage of fever-related AE is observed during childhood (0-15 years) with another rise in percentage in the elderly (age >70)

Figure 1B: **Age distribution in males and females**. Patients with (left panel) or without (middle panel) fever-related AE are shown. The percentage of patients in each gender with fever-related AE in each age group is presented on the right panel. Since the only females in age groups 16-26 and 60-70 were 16 and 70 years old, respectively, there are no cases of females with fever-related AE between ages 17-69.

Figure 2: Flowchart. Flowchart describing total BrS patient population and how patients were divided into subgroups with and without fever-related AE (see text).

Figure 3: Estimated arrhythmic event rate per 1000 fever days in each age group. The circles represent the estimated rate and the whiskers represent the 95% CI. The estimated risk in children aged 0-5 is higher than any other group in both genders. When looking at the estimated event rate of all patients (marked in black), there is no overlap of any estimation including its 95% CI with that of 0-5 years old age group.

Figure 1A

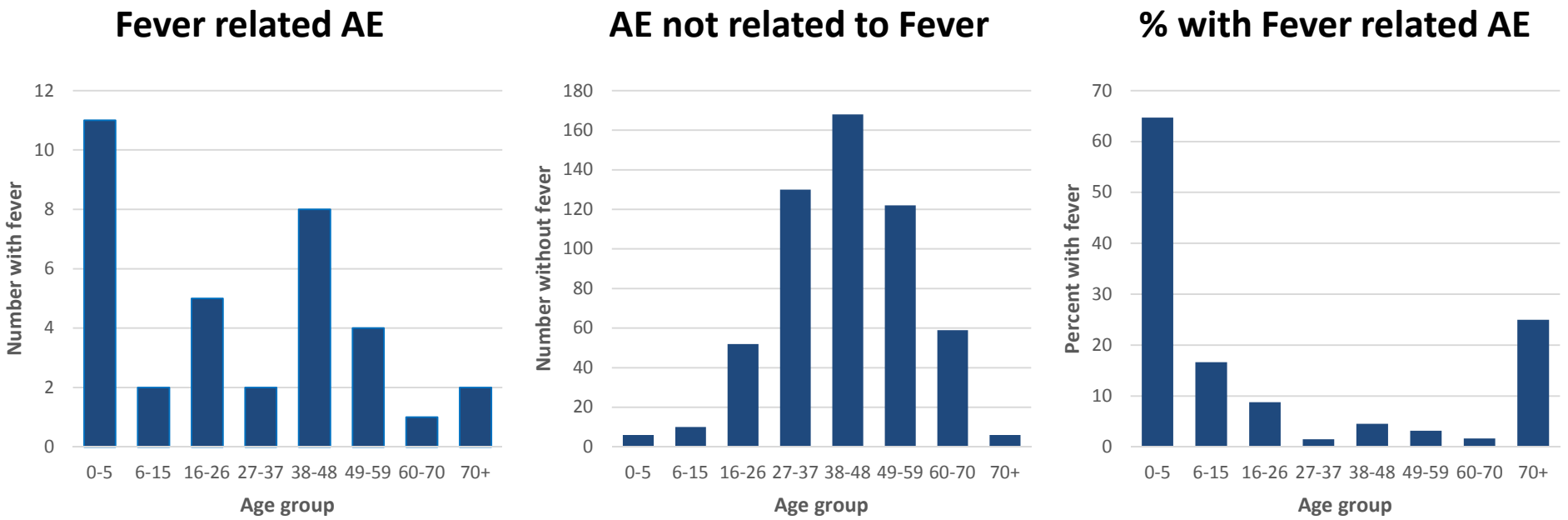

Figure 1B

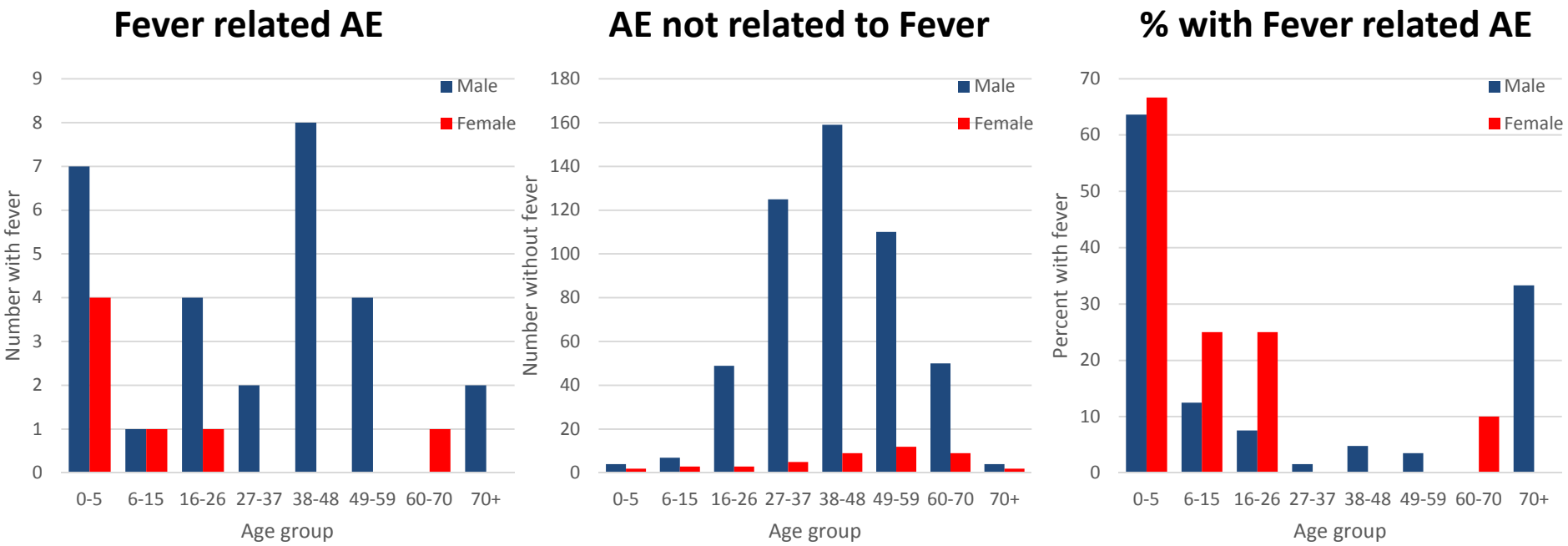

Figure 2

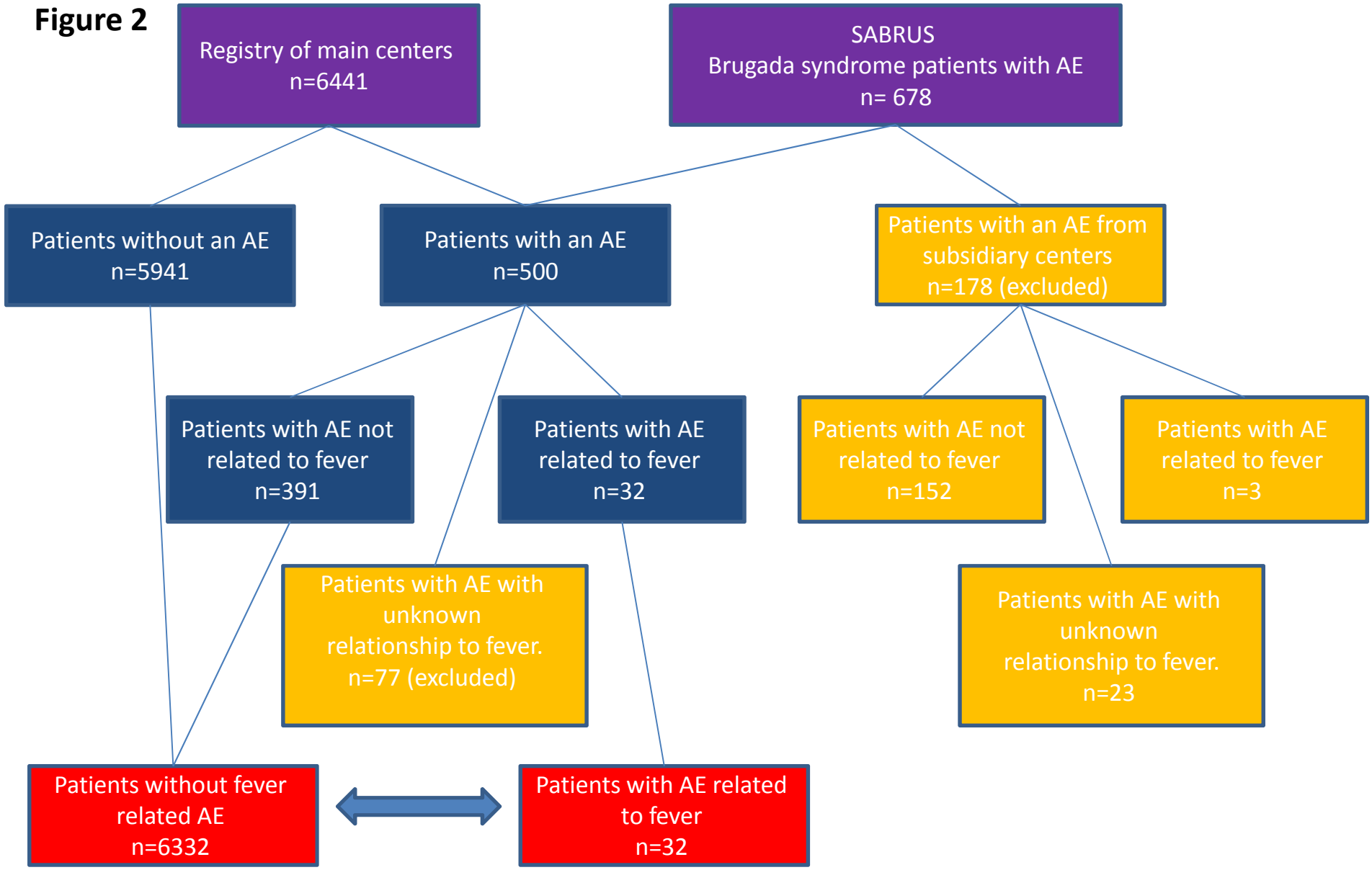

Figure 3