Gender differences in patients with Brugada syndrome and arrhythmic events: Data from a survey on arrhythmic events in 678 patients

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Gender Differences in Patients with Brugada Syndrome and Arrhythmic Events: Data from the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS) in 678 Patients.

ABSTRACT

Background
Information on gender differences in patients with Brugada syndrome (BrS) and arrhythmic events (AE) is limited.

Objectives
Compare clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic characteristics of males and females in a large cohort of BrS patients who experienced their first AE.

Methods
The multicenter Survey on AE in BrS (SABRUS) collected data on the first AE in 678 BrS patients including 619 (91.3%) males and 59 (8.7%) females aged 0.27 to 84 (mean 42.5±14.1) years old at the time of the AE.

Results
Females and males presented their AE at similar ages (42.1±21.2 vs. 41.9±14 years, respectively); however after excluding pediatric patients, females were older than males (49.5±14.4 vs. 43±12.7 years, respectively, P=0.001). Higher proportions of females were observed in the pediatric and elderly populations. In Asians, male/female ratio of AE was ≈ 9 fold higher than in Caucasians. Females less frequently showed a spontaneous type 1 ECG (31% vs. 59%, P<0.001) or arrhythmia inducibility at EP study (34% vs. 64%, P<0.001). An *SCN5A* mutation was more frequently observed in females (47.6% vs. 27.8% in males, P=0.007). A higher proportion of females (35% vs. 24% in males) underwent prophylactic ICD implantation that subsequently proved to be justified despite not complying with current guidelines (P=0.25).

Conclusions
This study confirms that females display less common risk factors for AE. It shows for the first time the complex relationship between gender distribution and patient ethnicity with the age at onset of AE as well as higher *SCN5A* mutation rates in females.

Brugada syndrome (BrS) is an inherited arrhythmic disorder that exposes patients with ostensibly normal hearts to sudden cardiac death (SCD) (1). The prevalence of the disease among these patients is relatively low with only 62 cases of aborted cardiac arrest (CA) gathered from 4 European countries in the FINGER BrS registry (2).

Despite its autosomal dominant mode of transmission, BrS is surprisingly uncommon in females. Only small series of females with BrS and aborted CA have been previously reported including 7 patients in FINGER (2) and 9 patients during a 20-year experience in the Pedro Brugada's laboratory (3). An even lower number of female patients with AE (up to 4) have been reported after prophylactic ICD implantation or follow-up of BrS patients without ICD (4-7). In addition the prevalence of all 3 types of Brugada-ECG pattern worldwide is 0.9% for males and 0.1% for females with higher figures in Asia (1.9% for males and 0.2% for females) (8).

We recently reported the results of a multicenter international survey on AE in BrS (SABRUS: the Survey on Arrhythmic events in BRUgada Syndrome) which gathered data from multiple Western and Asian countries on a large cohort of 678 BrS patients with their first ever documented AE, including 59 females (9). In addition we collected data from a large registry of 6441 BrS patients (including 1715 females) followed in the main SABRUS centers (9).

The present study sought to compare the clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic characteristics of males and females in the SABRUS patient population with first documented AE.

METHODS

CENTER SELECTION AND PATIENT RECRUITMENT

As detailed elsewhere (9) a systemic Medline search was conducted (excluding meta-analyses and case reports) by one investigator (A.M) who located and contacted the academic EP centers having the largest experience in the diagnosis and management of BrS. Briefly, 23 (85%) out of 27 centers contacted agreed to participate. The centers were requested to state whether their data originated from a single or from multiple institutions and to provide a list of these institutions in order to prevent any duplication in data collection.

A total of 678 patients were recruited from both 10 Western (415 patients, 61.2%) and 4 Asian countries (263 patients, 38.8%) ranging from 7 to 105 patients by center. Sixteen centers (69.5%) reported their sole experience and 7 (31.5%) collected the experience of multiple institutions. The French center that coordinated FINGER (2) provided data from 20 French institutions. All centers except two, declared no age limitation at patient recruitment.

The study was approved by the Institutional Committee on Human Research at the Tel Aviv Sourasky Medical Center.

DATA ACQUISITION.

Anonymous patient information was retrospectively collected using a predefined questionnaire regarding the following: 1) gender; 2) age at the time of the first AE; 3) mode of AE documentation (Group A or Group B, see below); 4) ethnicity (Caucasian, Asian, other or unknown); 5) proband status; 6) family history of SCD; 7) prior history of

syncope ; 8) presence of spontaneous or drug-induced Brugada-ECG type 1; 7) inducibility of sustained ventricular tachyarrhythmia (VF) at EP study (EPS) and 9) results of genetic testing for the presence of *SNC5A* mutation.

In addition all 23 main SABRUS centers were requested to provide the gender and age distribution of the entire BrS population followed at their own centers (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 showing that only 1.7% of the patients from Western countries had an Asian origin while no patient from Asian countries was Caucasian (9).

DEFINITIONS.

Arrhythmic events: AE was defined as any sustained ventricular tachyarrhythmia documented during initial aborted CA (group A) or triggering ICD therapy (group B).

Patient groups according to mode of AE documentation: Group A: Patients with documented aborted CA in whom the diagnosis of BrS was made *a posteriori;* Group B: Patients with an *a priori* diagnosis of BrS who received a prophylactic ICD and in whom an AE triggering appropriate ICD therapy was documented during follow-up.

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

Patient groups according to indication for ICD implantation: Group B patients were further subdivided by their indication for a prophylactic ICD implantation as stated in the 2013 HRS/EHRA/APHRS Expert Consensus Statement (10) as follows:

- Group B1: Patients with spontaneous type 1 Brugada-ECG presenting with syncope judged likely to be caused by ventricular arrhythmia (Class IIa indication).
- Group B2: Patients with a spontaneous or drug-induced type 1 ECG with inducible VF by programmed ventricular stimulation (Class IIb indication).
- Group B3: Patients implanted with an ICD that subsequently proved to be justified despite not complying with the above indications; these patients were further divided into 2 subgroups according to the EPS results: a) Group B3a: patients with no arrhythmias inducible at EPS; b) Group B3b: patients in whom EPS was not performed.

STATISTICAL ANALYSIS.

Differences between ages of different groups 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. Scale variables are presented as mean ± SD and nominal variables as N (Percentage). Statistical significance was defined as $P<0.05$. All calculations were performed using SPSS version 24 (IBM, Armonk, NY, USA).

RESULTS

The demographic, clinical, ECG, EPS and genetic findings of the patients in respect to gender are presented in Table 1 .

Demographics. Out of a total of 678 patients included in SABRUS, 619 were male (91.3%) and 59 (8.7%) were female aged 0.27 to 84 years old. The vast majority (94.2%) of patients were 16 to 70 years old while the pediatric (age < 16 years) and the elderly groups (> 70 years) comprised 4.3% and 1.5% of the survey group, respectively.

Gender distribution. Gender distribution markedly varied in respect to patient age group at time of AE (Figure 1A). The male to female (M/F) ratio was 10.4 for the whole group ranging from 25.2 in the 27-37 age group to 1.9 and 2.0 in the pediatric and elderly groups, respectively. The proportion of females was highest among the pediatric (17% of females vs. 3% of males, $p<0.001$) and the elderly groups (5% of females vs. 1% of males, $p<0.05$) while that of males was highest between ages 16-70 years (96% males vs. 78% females, $P<0.001$) (Table 1). In the pediatric group (n=29), there was a similar proportion of males and females in the 6-15 years group (42 and 40%, respectively) and in infants $\leq$ 5 years (58 and 60%, respectively). One of the 2 oldest study patients aged 84 years old was a female.

Age at time of AE. Analysis of the whole study population showed that the age at the time of the AE was abnormally distributed with no significant difference between males (41.9±14.0 years) and females (42.1±21.2 years) ($P=0.225$) (Tables 1 and 2A). Filtering out the pediatric patients from the entire cohort resulted in a normal age distribution with females being significantly older than males (49.5±14.4 vs. 43±12.7 years respectively, $P=0.001$) (Table 2B). Similar marked gender related differences in age were observed in several subgroups in patients aged $\geq$16 years: group A, Caucasians, probands, prior history of syncope, spontaneous type1 Brugada-ECG and *SCN5A* mutation carriers (Table 2B). In the pediatric group the ages of males and females at the time of AE were similar (6.2±4.9 and 5.8±6.2 years, respectively, $P=0.636$) (Table 2C); however, the presence of spontaneous type 1 ECG was associated with earlier onset of AE in the pediatric group in females as compared to males (Table 2C).

Mode of AE documentation. Most SABRUS patients belonged to group A (n=426, 62.8%) while the remaining 252 (37.2%) belonged to group B (Table 1).There was no gender difference in the proportion of patients in each group, with similar rates of males (63%) and females (61%) in group A.

Ethnicity. In SABRUS there were 364 (53.7%) Caucasians, 270 (39.8%) Asians and 44 (6.5%) patients who had another or unknown ethnic origin. Compared to males, females were more frequently Caucasian (88% vs. 50%) and markedly less frequently Asian (8% vs. 43%) (P<0.001). The M/F ratio was higher in Asians (n=53) than in Caucasians (n=6) (Table 1) with a peak ratio in the 38-48 year age group for Asians and in the 27-37 year age group for Caucasians (Figure 2A). Of note, in the pediatric group, 25 of 26 patients with known ethnicity were Caucasian (16 males and 9 females) while there was a single Asian male; in the elderly group, 7 were Caucasian (4 males and 3 females) and the 2 Asians were male.

Proband status. Of the 678 study patients 542 (79.9%, 496 males and 46 females) were probands and 88 (13%, 76 males and 12 females) were diagnosed during family member screening. The proportions of probands in Caucasians and Asians were 83.5 and 91.5%, respectively, with no significant gender difference between the various age groups. (Supplemental Figure 1).

Clinical history. A family history of SCD was noted in a similar proportion of patients of females (29%) and males (21%) (P=0.287) (Table 1). The 3 highest proportions of family history of SCD (40-50%) were noted in females (Supplemental Figure 2). A prior history of syncope was noted in a higher proportion of females (47%) than males (38%) but the

difference did not reach statistical significance (P=0.168) (Table 1, Supplemental Figure 3).

ECG. A spontaneous type 1 Brugada pattern was significantly more frequently observed in males (69%) than females (41%) (P<0.001) (Table 1). This difference was maintained up to 59 years of age at time of AE (Supplemental Figure 4); after age 60 years, a similar high incidence (≈ 65%) of spontaneous type 1 Brugada-ECG was observed in both genders.

EPS. EPS was performed in a similar proportion of females and males (66% and 58%, respectively, P=0.246). The rate of VF induction was significantly lower in females (36% vs. 66%, P<0.001) (Table 1) regardless of the patient age at time of AE (Supplemental Figure 5).

Genetic testing. Genetic testing was performed in a similar proportion of female and male patients (71% and 72%, respectively). An *SCN5A* mutation was found more frequently in females (47.6% vs. 27.8% in males, P=0.007) (Table 1). This higher mutation rate in females was noted in all age groups with the highest figures (70% and 60%) observed in the pediatric and the 60-70 years age group, respectively (Figure 3). Of note the highest mutation rate in males (66.7%) was also found in the pediatric group. Both females and females had most of their mutations classified as pathogenic or likely pathogenic with no significant difference between genders (Y% vs. X% in females and males, respectively, P=0.338).

Table 3 shows the main demographic, clinical, ECG and EP differences between 443 males and 42 females who underwent genetic testing in respect to the presence of an

SCN5A mutation. In non-mutation carriers, age at time of AE was similar for males and females (42.0±13.1 and 43.9±19.1 years, P=0.249); on the other hand, in mutation carriers, females were younger than males by ≈ 5 years (33.7±24.7 vs. 38.4±15.8 years) but the difference was not statistically significant (P=0.643). After exclusion of the patients aged <16 years, females were similarly and markedly older than males (by ≈ 7 years and 8 years) in both the non-mutation and mutation carriers, respectively (Figure 3).

Data from the registry. Data on patient gender and age distribution were provided by 22 of the 23 main SABRUS centers. Of note, only 5 of these 22 main centers were from Asian countries while the majority were from Western countries. The registry comprised 6441 patients (73.4% males and 26.6% females) (Supplemental Table 1). Of the overall registry population, 71% belonged to the 27-59 year age group and 88.4% originated from Western countries (i.e were assumed to be of Caucasian origin). The involvement of Asian patients was very low at extreme ages (1% and 2% for the pediatric group and the elderly groups, respectively) while it ranged between 7.8 to 12.9% in the other age groups. The M/F ratios were the highest (3.8-3.9) in the 27-48 year age group and the lowest at the extreme age groups (1.2 and 1.8 in the pediatric and elderly group, respectively) (Figure 1B). In Western countries the M/F ratio ranged from 1 in both the pediatric and elderly groups to 3 in the 27-48 year age group. In Asian patients it ranged from 10 in the 49-59 year age group to 86 in the 27-37 year age group (Figure 2B).

Indications of prophylactic ICD implantation. There was no difference between the proportions of males (37%) and females (39%) who underwent prophylactic ICD

implantation (Group B). Interestingly a higher proportion of females (8 of 23, 35% vs. 55 of 229, 24% of males) belonged to Group B3, i.e. underwent prophylactic ICD implantation that subsequently proved to be justified despite not complying with current guidelines indications (Table 1); however, this difference did not reach statistical significance (P=0.25).

DISCUSSION

The present study compares the clinical, ECG, EP and genetic characteristics of male and female patients with BrS and a first documented AE. In previous studies such a comparison was challenging due to the small number of female patients with AE. Of note the prior largest comparative study by Sacher et al. (4) involving 11 European centers comprised 50 males (33 with aborted CA) and only 8 females (3 with aborted CA). SABRUS collected the largest cohort of male (n=619) and female (n=59) BrS patients with AE ever reported that enables a more accurate assessment of gender differences.

CONFIRMATORY STUDY RESULTS.

The results of our study confirmed several known characteristics of the female gender (4,6,7): a) the rarity of AE; b) the lesser expressivity of the type 1 ECG pattern; c) the lower inducibility rate of VF at EPS.

AE in BrS females. In SABRUS, only 59 (8.7%) of the 678 BrS patients with a documented AE were females accounting for an M/F ratio of 10.4. This contrasts with the higher proportion of females (26.6%) with Brugada-ECG type 1 (spontaneous or drug-induced) collected in the registry accounting for an M/F ratio of 2.75. These data confirm the rare

occurrence of AE in BrS female patients despite the non-negligible prevalence of the disease in that population. Sieira et al. (7) from the Pedro Brugada group reported the highest AE rate in females (6 of 23, 26%) in a series of 542 BrS patients (42% females). They explained their large female cohort by a proactive search of BrS and an exhaustive familial screening program performed at their institution.

Spontaneous type 1 Brugada-ECG. Several prior studies demonstrated the lower prevalence of spontaneous type 1 Brugada-ECG in females regardless of their clinical presentation (asymptomatic, syncope or aborted CA) (2,4,6,7). In a study of 58 BrS patients with AE, Sacher et al. (4) found a spontaneous type 1 ECG at baseline in 36 men (72%) but in only 2 women (25%) (P=0.02). Sieira et al. (7) also found a low incidence rate (1 of 7, 14%) of spontaneous type 1 Brugada-ECG in females with AE. In contrast, in PRELUDE (5) all 3 BrS females who exhibited an AE after prophylactic ICD implantation had spontaneous type 1 Brugada-ECG. In SABRUS a spontaneous ECG type 1 pattern was observed in 69% of males and 41% of females with AE ($p<0.001$). Although our results confirm the lower female prevalence of spontaneous type 1 Brugada-ECG, the relatively high figure of 41% in females has never been reported previously and could have important prognostic implications.

VF inducibility rate. Previous studies comparing inducibility rate of VF in males vs. females in all clinical settings of BrS have consistently shown a lower inducibility rate in females (4,6,7). In SABRUS, a similar lower percentage of VF inducibility was observed in females (36% vs. 66% in males, $p<0.001$). These results likely explain the greater

proportion of females (75%) compared to males (49%) in our B3a subgroup of patients who exhibited AE after prophylactic ICD implantation and were non inducible during EPS.

NEW STUDY FINDINGS.

Gender and age at onset of AE. Our study showed that gender distribution markedly varied in respect to patient age group at time of AE with a higher proportion of females among the extreme age groups contrasting with a higher proportion of males between ages 16-70 years. Similar results were observed in the registry. In our previous paper (9), we hypothesized on the possible role of low estrogen activity that regulates the expression of Ito channels and decreases the propensity for arrhythmias in pre-pubertal and post-menopausal females (9). In addition, the fact that our results showed that in age group >16 years females exhibited their AE much later (by >6 years) than males might also be related in part to the relative protective effect of estradiol on arrhythmias during female life.

Gender and ethnicity. SABRUS also showed for the first time that gender distribution of AE was markedly dependent on patient ethnicity. The M/F ratio of AE in Asians (n=53) was ≈ 9 fold higher than in Caucasians (n=6). Interestingly analyzing the registry of the 22 main SABRUS centers showed a similar M/F risk ratio (n=8) with M/F ratios of 19.2 and 2.4 in Asians and Caucasians, respectively. However, this result markedly contrasts with the similar M/F ratio (≈ 9) of all Brugada-ECG patterns in both ethnic populations (8). Further analysis of gender differences in Caucasian and Asian patients is necessary to assess whether this could be translated to a lower AE risk in Asian females.

Earlier onset of AE in pediatric females. We found that the presence of spontaneous type 1 Brugada-ECG was associated with an earlier onset of AE in the pediatric group in females as compared to males (Table 2C). This finding suggests that in the pediatric population, a spontaneous type 1 ECG pattern in females might represent a significant arrhythmic risk factor.

Gender and presence of *SCN5A* gene mutations. The most interesting finding in our present study relates to major gender differences in genetic characteristics. Previous studies disputed genetic findings as risk factors for an AE. The latest meta-analysis by Wu et al. (11) indicated that an *SCN5A* gene mutation did not increase the risk for future cardiac events but the female population included in this meta-analysis was too scarce for enabling any analysis in respect to gender. In contrast a recent Japanese study involving 97% of males showed that *SCN5A* mutation was a significant predictor of cardiac events in BrS *probands* (12). In our study which involved 91.3% of males and 79.9% of probands, an *SCN5A* mutation was found more frequently in females (47.6%) than in males (27.8%) (P=0.007). Moreover, this was observed in all age groups at time of AE. In our male SABRUS patients the *SCN5A* mutation rate was slightly higher than that obtained in a large cohort of asymptomatic BrS male patients from 4 of the largest centers cooperating in SABRUS (27.8% vs. 20.8%, P<0.001) (Table 4). However in our female SABRUS patients the *SCN5A* mutation rate was markedly higher than in asymptomatic BrS female patients (47.6% vs. 26.6%, P<0.001) (Table 4). Therefore, the relatively high mutation rates observed in our female cohort with AE would suggest that

the presence of an *SCN5A* mutation could represent an important risk factor for AE in the female patient population and to a lesser extent in male patients.

The results of SABRUS identified for the first time a significant group of patients (the B3 group) who did not comply with the classical Class IIa and IIb indications for prophylactic ICD implantation but in whom the indication for ICD was a posteriori justified. This group comprised 25% of group B patients and a greater albeit not statistically significant proportion of females (35% vs. 24% of males) mainly due to the fact it included a subgroup of patients with negative EPS in which females largely predominated. The fact that 5 (63%) of the 8 females of group B3 were *SCN5A* mutation carriers (Table 3) would suggest important additional value of genetic testing for deciding upon prophylactic ICD implantation in females that should be assessed in prospective studies.

The profile of high risk female BrS patients. The present study provides a comprehensive profile of female BrS patients with a documented AE and emphasizes the differences from the classically known high risk male profile. The model of risk stratification in BrS recently proposed by Sieira et al. (14) does not include gender or genetic status and thus is unlikely to be suitable for female gender. In addition, its application will probably result in misidentification of high risk female patients because the latter have a lower incidence of spontaneous type 1 Brugada- ECG and a lower inducible arrhythmia rate, two major factors in determining patient eligibility for prophylactic ICD implantation.

Clinical implications.

Arrhythmic risk stratification of BrS patients is not an easy task in males and even more so in females. The present study shows for the first time that approximately half (47.6%) of BrS females with AE carried *SCN5A* mutations contrasting with only 27.6% of their male counterparts. Whether the presence of an *SCN5A* mutation in a female without a previous history of CA should be taken into account when considering the implantation of a prophylactic ICD will deserve further studies. In any case the results provided by SABRUS should prompt for proactive search of BrS, especially in females, as performed in Pedro Brugada's laboratory.

Study limitations.

In addition to study limitations listed elsewhere (9), it is worthwhile emphasizing that despite the relatively large female cohort patient (n=59) as compared to previous reports, our results from genetic testing derived from only 42 (71%) patients.

Taking into account the rarity of AE in females with BrS, especially in Asia, a large international registry of genetic testing in females with and without AE is warranted.

A history of sinus node dysfunction was found by the Pedro Brugada group to represent a significant predictor of AE (14,15). This parameter was not assessed in our study.

Conclusion

This is the largest study that compared demographic, clinical, ECG, EPS and genetic findings in males and females patients with BrS and AE. Besides confirming previously known differences, it shows for the first time the complex relationship between gender distribution and patient ethnicity with age at onset of AE as well as a possible worse prognosis associated with the presence of *SCN5A* mutation in females. It is important

that all these factors will be taken into account in future studies on arrhythmic risk stratification in BrS.

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