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Ethnic differences in patients with Brugada syndrome

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ABSTRACT

Background

There is limited information on ethnic differences between patients with Brugada syndrome (BrS) with arrhythmic events (AEs).

Objectives

To compare clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic characteristics between White and Asian BrS-patients with AE.

Methods

SABRUS is a multicenter survey from Western and Asian countries, gathering 678 BrS-patients with first documented AE. After excluding patients with other (n=14; 2.1%) or unknown (n=30; 4.4%) ethnicity, 364 (53.7%) Whites and 270 (39.8%) Asians comprised the study group.

Results

There was no difference in AE age onset (41.3±16.1 years in Whites vs. 43.3±12.3 years in Asians, P=0.285). Higher proportions of Whites were observed in pediatric and elderly populations. Asians were predominantly males (98.1% vs. 85.7% in Whites, P<0.001) and frequently presented with aborted cardiac arrest (ACA) (71.1% vs. 56%, P<0.001). Asians tended to display more spontaneous type 1 BrS-ECG (71.5% vs. 64.3%, P=0.068). Family history of sudden cardiac death (FHSCD) was noted more in Whites (29.1% vs. 11.5%, P<0.001), with higher rate of SCN5A mutation carriers (40.1% vs. 13.2% in Asians, P<0.001), as well as more fever-related AEs (8.5% vs. 2.9%, 0.011). No difference was observed between the two groups regarding prior history of syncope and ventricular arrhythmia inducibility.

Conclusions

There are important differences between Asian and White BrS-patients. Asian patients present almost exclusively as male adults, more often with ACA and spontaneous type 1 BrS-ECG. However, they have less FHSCD and markedly lower SCN5A mutation rates. The striking difference in SCN5A mutation rates should be tested in future studies.

Key Words: Brugada Syndrome; arrhythmic event; White; Asian; *SCN5A* mutation

Introduction

Brugada syndrome (BrS) is a cardiac disease entity often caused by an inherited ion channelopathy associated with a propensity to develop life-threatening ventricular tachyarrhythmias and sudden cardiac death (SCD) in ostensibly healthy patients, mostly males in their 4th decade of life[1]. Although BrS was first described in Europe[2,3] it was probably recognized, although not fully characterized, much earlier in multiple Southeastern Asian countries as mainly responsible for many mysterious cases of unexpected, usually nocturnal SCD occurring mainly in young males[4-10]. Similar series of SCD were reported in Southeast Asian immigrants living in the United States[11].

The worldwide prevalence of Brugada-ECG is estimated to be 0.5 cases in every 1,000 subjects, but it is endemic in Asian and Southeast Asian countries, especially in Japan, the Philippines and Thailand, reaching 3.7 in 1,000[12].

Over the past 3 decades, extensive research has allowed the understanding of the characteristics, pathophysiology and management of BrS. However, there is no study comparing Whites and Asians with BrS and AEs.

SABRUS is a multicenter survey of first AEs documented in 678 BrS patients from multiple Western and Asian countries[1,13,14]. The present study sought to compare the clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic characteristics of White and Asian patients participating in SABRUS.

Methods

Center selection and patient recruitment

As detailed elsewhere[1,13,14] a total of 678 BrS-patients were recruited from 10 Western (415 patients, 61.2%) and 4 Asian countries (263 patients, 38.8%) ranging from 7 to 105 patients

per center. After excluding patients with other (n=14; 2.1%) or unknown (n=30; 4.4%) ethnicity, 634 patients comprised the study group.

The study was approved by the Research Ethics Boards of all participating institutions.

Data acquisition.

Anonymous patient information was retrospectively collected concerning the following: 1) gender; 2) age at time of the first AE; 3) mode of AE documentation (group A or group B, see next); 4) ethnicity (White, Asian, other or unknown); 5) proband status; 6) family history of SCD; 7) prior history of syncope ; 8) presence of spontaneous or drug-induced type 1BrS-ECG; 7) inducibility of sustained ventricular fibrillation (VF) at EP study (EPS) and 9) results of genetic testing for the presence of *SNC5A* mutation.

Definitions.

Arrhythmic events: Defined as any sustained ventricular tachyarrhythmia documented during initial aborted cardiac arrest (ACA) (group A) or triggering appropriate ICD-shock therapy after prophylactic implantation of an ICD (group B).

Patient groups according to indication for ICD-implantation: Group B patients were subdivided by their indication for prophylactic ICD-implantation as stated in the 2015 Expert Consensus Statement[15]:

- Group B1: Class IIa indication.

- Group B2: Class IIb indication.

- Group B3 included those patients implanted with an ICD that subsequently proved to be justified (i.e. triggering appropriate ICD-shock therapy for AE) despite not complying with the IIa/IIb indications. These patients were further divided into 2 subgroups according to their

EPS results: a) Group B3a: no inducible arrhythmia at EPS; b) Group B3b: EPS was not performed.

Genetic analysis: Mutations were analyzed using the Sanger sequencing method. All *SCN5A* mutations were categorized using the ACMG criteria and classified by their known pathogenicity. Most of the *SCN5A* mutations were identified as pathogenic (56.34%) and likely pathogenic (23.24%). Detailed distribution of the mutations has been previously reported[14].

Statistical analysis.

Differences in means were assessed using a Wilcoxon Rank Sum test. Ratio differences were examined by a Chi-square test or a Fisher's exact test as appropriate. All results are shown as n (%) or mean (SD) as appropriate. Results were considered significant when $P<0.05$. All statistical analyses were done using R version 3.5.0, Vienna, Austria.

Results.

The demographic, clinical, ECG, EPS and genetic findings of the patients according to their ethnicity are presented in **Table 1.**

Demographics. Out of the 634 study patients, 364 (57.4%) were White and 270 (42.6%) were Asian. Seven Asian patients belonged to Western countries and no Whites originated from Asian countries.

Gender distribution. The proportion of females in the present cohort was higher amongst Whites (14.3% vs. 1.9% in Asians, $P<0.001$). Asian patients were predominantly males (98.1% vs. 85.7% in Whites, $P<0.001$).

Age at time of AE. No difference was observed in the mean age at time of AE between Whites (41.3±16.1 years) and Asians (43.3±12.3 years, $P=0.285$). The vast majority of patients were 16 to 70 years old in both groups (91.2% in Whites vs. 98.9% in Asians,

P<0.001), however the difference was significant due to the small proportion of pediatric (<16 years) and elderly (> 70 years) patients from the Asian population. In the pediatric group, 25 of 26 patients with known ethnicity were White (16 males and 9 females) while there was a single Asian male patient. Of the elderly group, 7 were White (4 males and 3 females) and the 2 Asians were males.

Mode of AE documentation. Asian patients more commonly presented with an ACA (group A, 71.1%) as opposed to Whites (group A, 56%) (P<0.001). The profile of Asian patients in group A differed from Whites in the following characteristics (**Supplemental Table 1)**; they were mostly males (97.9% vs. 87.3% , P<0.001); were older (41.7±11.9 vs. 37.8±17.1 years old, P<0.01); had less family history of SCD (12.8% vs. 24.5%, P<0.01); had more often a spontaneous type 1 BrS-ECG (72.9% vs. 60.3% , P=0.011); were less often *SCN5A* mutation carriers (11.3% vs. 40.1%, P<0.001) and presented less with fever during the AE (3.5% vs. 12.2% respectively, P=0.01).

In group B, Asians had a trend towards being implanted prophylactically with an ICD more frequently because of class IIa indication (53.8% vs. 41.2% in Whites, P=0.09) as opposed to Whites who had a trend towards being implanted prophylactically because of class IIb indication (33.8% vs. 21.8% in Asians, P=0.082).

A similar proportion of patients in both groups were implanted prophylactically with an ICD even though they did not have a guideline indication (group B3) (25% of Whites and 24.4% of Asians). No difference was observed when dividing into subgroups of those who had a negative EPS (group B3a) to those who did not perform an EPS (group B3b), although there were slightly more Whites in the B3b group (60%) and more Asians in the B3a group (57.9%).

Proband status. Of the 588 study patients with known information regarding their proband status, 509 were probands and 79 were diagnosed during family screening. The proportion of probands in Whites (83.2%) was significantly higher than in Asians (76.3%, P=0.008).

Clinical history. A significant higher difference in screening for family history of SCD was noted in Whites compared to Asians (95.6% vs. 83% respectively, P<0.001). Nevertheless, out of the patients who had a family screening performed, Whites had more family history of SCD as compared to their Asian counterparts (29.1% vs. 11.5%, respectively, P<0.001). No difference was observed in the proportion of patients with a prior history of syncope regarding ethnicity (40.9% of Whites vs. 37.4% of Asians, P=0.414). Fever during AE was noted more frequently in Whites than Asians (8.5% vs. 2.9% respectively, P=0.011).

ECG. There was a trend towards more frequent spontaneous type 1 BrS-ECG in Asian patients (71.5%) compared to Whites (64.3%) (P=0.068). As mentioned above, when classifying patients by their mode of AE documentation, the difference reached statistical significances in the ACA group alone (72.9% vs. 60.3% respectively, P=0.011) **(Supplemental Table 1).**

EPS. EPS was performed in a comparable proportion of Whites and Asians (59.6% and 56.7%, respectively, P=0.507). The rate of VF induction was similar in both groups (61.8% in Whites and 65.4% in Asians, P=0.549).

Genetic testing. Genetic testing was performed in a similar proportion of White and Asian patients (71.2% and 70.4%, respectively, Table 1), with a total of 449 patients tested. The mean *SCN5A* mutation was found much higher in the White population compared to Asians (40.1% vs. 13.2% respectively, P<0.001) (**Table 1)**. Dividing the mutations by their pathogenicity, revealed that out of the total patients with *SCN5A* mutations, Whites had

significantly more pathogenic mutations than Asians (90% vs. 66.7% respectively, P<0.0001) **(Supplemental Table 2).**

Mean S*CN5A* mutation rates in Asian countries were 8.1% in South Korea, 12% in China, 12.5% in Taiwan and 14.3% in Japan. These rates were lower than the mean mutation rates found in each of the Western countries (range from 22.2% in Israel to 69.2% in the UK) (**Table 2, Figure 1)**. Since some Western countries also included Asian patients or patients with different ethnicity (in contrast to Asian countries which exclusively included Asian patients), we calculated *SCN5A* mutation rates in Whites for each country. This did not change substantially the results **(Supplemental Table 3).**

We also compared *SCN5A* mutation rates from Western and Asian countries in probands only **(Supplemental Table 4, Supplemental Figure 1).** The mean mutation rate in Western countries was 39% (ranging from 0% in Canada to 69.2% in the UK) and 10.2% in Asian countries (ranging from 0% in South Korea to 13.9% in Japan). The difference was highly significant (P<0.0001).

Discussion

The present study is the first to compare the clinical, ECG, EP and genetic characteristics of BrS patients with first AE according to their ethnicity (White vs. Asian).

Similarities between Whites and Asians.

Age at AE onset. The SABRUS population did not demonstrate any significant difference in the mean age at AE onset in Whites and Asians (early 4th decade). Interestingly the vast majority of decedents in Asians with sudden unexpected nocturnal death syndrome (SUNDS) have been found to be aged 20 to 40 years (mean≈ 33 years) [10] i.e. much younger than the Asian SABRUS population at the time of their first AE. This issue has been previously discussed[1].

Prior history of syncope. In our cohort, a similar proportion of White and Asian patients had a history of syncope (≈40% in both groups). These figures are in-between the rate of prior syncope in SABRUS patients presenting with an ACA (63%) and that in those exhibiting an AE after a prophylactic ICD implantation (25%)[14]. It is noteworthy that contrasting with BrS, SUNDS patients usually do not exhibit prior syncope[10,16] possibly explaining the occurrence of sudden death at a younger age than SABRUS patients.

VF inducibility at EPS. The proportions of patients undergoing EPS in our study were similar in Whites and Asians (≈60%). VF inducibility rates were likewise comparable (61.8% and 65.4% for Whites and Asians, respectively). To our knowledge such figures cannot be compared to previous published studies in which only arrhythmia inducibility rates in BrS patients who presented with ACA were reported while the present data also included information on patients who exhibited an AE after a prophylactic ICD implantation.

Differences between Whites and Asians

Gender and ethnicity. Male predominance is a well-known characteristic of BrS**.** Although males predominated in both ethnic groups this predominance was more marked in the Asian group (98.1% vs. 85.7% in Whites, P<0.001). This was associated with a male-to-female ratio in Asians ≈9-fold higher than in Whites, as previously reported[1,17,18]. One can speculate that this is due to less family screening; however there are other possible explanations. The presence of modifier genes in Asians but not in Whites[19] could play a role. These modifier genes in Asians affect the phenotype and could have sex specific effects[20]. Another possible explanation might come from female susceptibility to triggers and/or the prevalence of triggers that might differ between genders of Asian or White origin[21]. Another issue might be a selection bias by preoccupation with ACA male victims who might more easily present with a Brugada phenotype as opposed to their female equals. Finally, whether there is less rigorous Brugada investigations in Asian females might be another confounder.

In our previous SABRUS studies[1,13] we postulated that females with BrS are protected by estrogen contributing to the sex difference observed in the syndrome and AEs. This difference could account for the very low number of females with BrS and AEs observed in our Asian SABRUS cohort. Future studies should be encouraged to attest this hypothesis.

Age distribution. In our study we noted that at the extreme age groups of patients with known ethnicity the proportion of Asian patients was very low, comprising only 1 (3.8%) of 26 pediatric patients and 2 (22%) of 9 elderly patients. The reason for this finding is unclear.

Mode of arrhythmia presentation. Our study showed that a higher proportion of Asian patients presented with ACA (71.1% vs. 56% in Whites, P<0.001). Whether this actually reflects a more malignant clinical presentation or a better management of out-of-hospital cardiac arrest in Asians is unknown. It is noteworthy however, that SUNDS mostly strikes without prior warning symptoms that would support the first explanation.

Family history of sudden cardiac death. A family history of SCD was noted more frequently in the White group (29.1% vs. 11.5% in Asians, P<0.001). Interestingly only rare people who succumb to SUNDS have a family history of SCD[10]. In addition, a significantly higher family history of SCD was observed in White patients despite the fact they were more frequently probands than Asians (29.1% and 11.5%, respectively, P<0.001). One would expect that more probands would have correlated with a lower incidence of family SCD history. Incidentally, a sub-analysis showed that in Asians an *SCN5A* mutation was more frequently observed when a family history of SCD was surprisingly absent (28.6% vs. 10.8%, P=0.03); in contrast such relationship was not observed in Whites (43.8% vs. 38.4%, P=0.481 when a family history of SCD was present or absent, respectively). A plausible explanation of this finding could be that Whites have higher mutation prevalence because more family screening

is performed in Whites. However, as opposed to Asians, most of these patients are probands, suggesting that in Whites the disease is probably more genetic in its basis.

Fever. Whites had more fever related AE compared to Asians. This issue was discussed in length in our previous paper[22].

Prevalence of spontaneous type 1BrS-ECG. In a meta-analysis by Shi et al. [23] which focused on the healthy worldwide population, a higher prevalence of spontaneous type 1 BrS-ECG was found in the Asian population; the overall prevalence of type 1 BrS-ECG pattern was estimated to be 0.08% in Asian countries, and 0.001% in Western countries. Results from the largest series of BrS with ACA have shown a prevalence of type 1 BrS-ECG ranging from 28% to 50% in Western countries and from 80% to 95% in Asian countries (**Supplemental Table 5)** [24-28]. Our results are in agreement with these studies showing that most of the SABRUS patients with ACA displayed a type 1 BrS-ECG in both ethnic groups, yet Asians had a statistically significantly higher prevalence of this ECG pattern (72.9% vs. 60.3% in Whites, P=0.011) **(Supplemental Table 1**). Bezzina et al. [19] suggested that this might be due to the presence of common sodium channel promoter haplotype in Asian but not in White subjects. Interestingly, in the same study[19] the Asian cases consisted of 94% males, which confers this association to be more relevant for Asian males.

Genetics. The newest striking discovery of the present study is the higher *SCN5A* mutation rates found in Whites (40.1% vs. 13.2% in Asians, P<0.001), with a similar difference observed when studying probands only (39% vs. 10.2% respectively, P<0.001). Even after classifying the study patients by their country of origin, those from Southeast Asia had a lower mutation rate as compared to any Western country **(Table 2, Supplemental Table 4**). The low mutation rate found in our Japanese SABRUS patients (14.3%) was similar to that reported by Yamagata et al. [29] (17.8%) in a large cooperative Japanese series. A very low

SCN5A mutation rate (7.5%) was found by Juang et al.[30] after pooling results obtained in 6 studies involving 178 BrS patients of the Han population of China. A similar low *SCN5A* mutation rate (12-12.5%) was found in our SABRUS patients from China and Taiwan.

The only exception in Asia was noted in the Thai population. Out of a population of 40 BrS patients including 29 with ACA, Makarawate et al.[31] found higher *SCN5A* mutation rates (32.5% in the whole population). Unfortunately, we were unable despite great efforts to recruit any Thai center in our SABRUS cohort[1]. However, according to Dr K. Nademanee (personal communication) the *SCN5A* mutation rate in BrS patients in Thailand is around 12%, i.e. similar to the mean rate found in our Survey in Asian patients (13.2%).

The lower prevalence of *SCN5A* mutations in Asian BrS patients suggests that the *SCN5A* gene is not the major pathogenic gene involved in the Asian population compared to the White population[32]. It may perhaps similarly be related to epi-genetic factors, e.g. a higher incidence of peri-myocarditis in Asians.

Study limitations.

By study protocol, only centers which have published series of BrS patients with AEs were invited to cooperate in SABRUS[1] and therefore the contribution by country is not sufficient to represent the actual prevalence of affected patients in this country (i.e. China). In addition, our study did not include patients from 2 countries (Thailand and Philippines) where BrS / SUNDS are considered to be a leading cause of sudden death in young men[1,32]. Also, the very low number of females and pediatric patients in Asian centers must be taken into consideration. Another important limitation is the high rate of unknown proband status in Asian patients, thus our conclusions regarding this subject should be taken with caution.

Conclusion.

To our knowledge, this is the first study comparing patients of White and Asian origin exhibiting BrS and AEs. There are important differences between these 2 ethnic populations. Asian patients present almost exclusively as male adults, more often with ACA and spontaneous type 1 BrS-ECG. However, they have less family history of SCD and markedly carry less *SCN5A* mutations than Whites. Whether this striking difference in *SCN5A* mutation rates plays a role in other important differences observed between Whites and Asians should be explored in future studies.

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Figure legends

Figure 1. Mean *SCN5A* mutation rate in each of the Western and Asian countries participating in SABRUS. Mutation rates for each country participating in SABRUS was calculated for the whole study group (634 patients) according to patients with genetic analysis performed (449 patients). Mean mutation rate for the total cohort was 29.5%, for Western countries was 40.1% and for Asia countries 12.4%, with a statistical difference between Western and Asian countries ($p<0.0001$).

Table 1. Patients characteristics according to ethnicity.

		White	Asian	P value
Number of patients		**364**	**270**	
Patient Age at AE (year)	Age range	41.3±16.1	43.3±12.3	0.285
	Patients<16 years	25 (6.9)	1 (0.4)	<0.001
	16≥ Patients ≤70	332 (91.2)	267 (98.9)	
	Patients>70 years	7 (1.9)	2 (0.7)	
Gender	Male	312 (85.7)	265 (98.1)	<0.001
	Female	52 (14.3)	5 (1.9)	
Mode of AE documentation				
	Group A	204 (56.0)	192 (71.1)	<0.001
	Group B	160 (44.0)	78 (28.9)	
	Group B1	66 (41.2)	42 (53.8)	0.09
	Group B2	54 (33.8)	17 (21.8)	0.082
	Group B3	40 (25.0)	19 (24.4)	1
	Subgroup B3a	16 (40.0)	11 (57.9)	0.313
	Subgroup B3b	24 (60.0)	8 (42.1)	
Proband Status				
	Proband	303 (83.2)	206 (76.3)	0.008
	Not Proband	60 (16.5)	19 (7.0)	
	Unknown	1 (0.3)	45 (16.7)	<0.001
Family history of SCD				
	Yes	106 (29.1)	31 (11.5)	<0.001
	No	242 (66.5)	193 (71.5)	
	Unknown	16 (4.4)	46 (17.0)	<0.001
History of syncope				
	Yes	149 (40.9)	101 (37.4)	0.414
	No	215 (59.1)	169 (62.6)	
Presence of fever during AE	Yes	29 (8.5)	6 (2.9)	0.011
	No	312 (91.5)	203 (97.1)	
	Unknown	23 (6.3)	61 (22.6)	<0.001
Spontaneous type-1 BrS-ECG				
	Yes	234 (64.3)	193 (71.5)	0.068
	No	130 (35.7)	77 (28.5)	
VF inducibility				
	EPS performed	217 (59.6)	153 (56.7)	0.507
	Inducible	134 (61.8)	100 (65.4)	0.549
	Not inducible	83 (38.2)	53 (34.6)	
Presence of *SCN5A* mutation				
	Testing done	259 (71.2)	190 (70.4)	0.900
	SCN5A mutation	104 (40.2)	25 (13.2)	<0.001
	No *SCN5A* mutation	155 (59.8)	165 (86.8)	

Abbreviations in the Mode of AE documentation: as detailed in the Methods section.

Table 2. *SCN5A* mutation rates in SABRUS according to country

A. In Western countries

Country	Patients with AE (%)	Patients with genetic analysis	SCN5A mutation rate %	Asian Patients	Unknown Ethnicity
France	130 (19.2)	117	44 (37.6)	1	30
Italy	84 (12.4)	46	19 (41.3)	1	0
Belgium	48(7)	31	9 (29)	1	3
Spain	35(5.2)	21	11 (52.4)	0	0
Netherlands	32(4.7)	30	14 (46.6)	2	2
Israel	32(4.7)	9	2 (22.2)	0	1
UK	20(3)	13	9 (69.2)	2	5
Germany	17(2.5)	15	7 (46.7)	0	2
Denmark	10(1.5)	10	3 (30)	0	0
Canada	7(1.1)	7	2 (28.6)	0	0
Total	415	299	120 (40.1)	7	43

B. In Asian countries.

Country	Patients with AE (%)	Patients with genetic analysis	SCN5A mutation rate %	White Patients	Unknown Ethnicity
Japan	119 (17.5)	84	12 (14.3)	0	0
South Korea	79 (11.6)	37	3 (8.1)	0	0
Taiwan	40 (5.9)	40	5 (12.5)	0	0
China	25(3.7)	25	3 (12)	0	0
Total	263	186	23 (12.4)	0	0