Clinical Profile, Treatment Strategies, and Outcomes of Filipino Adults with Brugada Pattern Electrocardiogram and Syndrome in a Tertiary Care Hospital in Manila, Philippines

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Abstract

BACKGROUND: Brugada syndrome is an inheritable syndrome that carries an increased risk of sudden cardiac death. This study aims to delineate the natural history, clinical and electrophysiologic profile, treatment strategies, and outcomes of patients with Brugada pattern electrocardiogram (ECG) and Brugada syndrome in a tertiary care hospital in the Philippines.

METHODOLOGY: This is a retrospective observational study of patients diagnosed with Brugada pattern ECG and Brugada syndrome admitted in a single center from 2004 to 2019.

RESULTS: Twenty-three patients were included in the study. All patients were male. In both groups, the majority were nonsmokers (n = 13) and nonalcoholic beverage drinker (n = 14). In patients with Brugada pattern ECG, all presented as an incidental finding (n = 10; $P < 0.001$), whereas in Brugada syndrome, six patients presented with out-of-hospital resuscitated cardiac arrest (46.15%, $P = 0.019$). There were only three patients with a family history of sudden cardiac death. All patients had normal ejection fraction and sinus rhythm. Twenty-one patients had ST elevation (91.30%). Fourteen patients had spontaneous type 1 Brugada pattern ECG, whereas the rest were inducible to type 1 after flecainide test. Seven patients underwent implantable cardioverter-defibrillator implantation before discharge; one patient died at the time of diagnosis, and one had recurrent admission for arrhythmia. No single patient received medical management.

CONCLUSION: Clinical profile, ECG findings, and outcomes were not significantly different between the two groups of patients except for the clinical presentation upon diagnosis. Treatment strategies were guideline-directed.

KEYWORDS: Brugada pattern ECG, Brugada syndrome

INTRODUCTION

Brugada syndrome is an inheritable syndrome that carries an increased risk of sudden cardiac death. It is a rare autosomal dominant disorder caused by mutations in the cardiac sodium-channel gene SCN5A in the absence of overt structural heart disease first found in 1998.[1] Thereafter, many genes were implicated as Brugada susceptibility genes, including *GPD1L*, *CACNB2*, *CACNA1C*, *SCN1B*, *KCNE2*, *KCNE3*, *KCNE4*, and *IRX5*, as well as the sodium-channel beta subunit (*SCN3B*).[2]

The syndrome is characterized by sudden death associated with one of three electrocardiographic patterns as previously known: type 1 electrocardiographic pattern with a coved-type ST segment and an inverted T wave in V_1 and V_2; type 2 electrocardiographic pattern with a saddleback ST-segment elevated by >1 mm; type 3 pattern in which the ST segment is elevated by 1 mm. However, in the recent expert consensus conference in July 2016,[3] among the three types of ST elevation, only type 1 was considered diagnostic for Brugada syndrome. The syndrome remains associated with ventricular fibrillation and a high risk for sudden cardiac death, predominantly in younger male patients with structurally normal hearts.[1,4,5] Despite warning signs and symptoms or after resuscitated cardiac arrest, many patients with Brugada syndrome are still misdiagnosed.[6]

There are limited studies on Brugada syndrome among Filipinos, but Brugada pattern electrocardiograms (ECG) among Asians have been reported. Notably, Gervacio-Domingo et al[7] reported the prevalence of type 1 Brugada pattern ECG to be 0.2% among 3907 Filipinos. In Southeast Asia, the incidence appears to be approximately 40 per 100,000 compared with Europe, where it is a mere 1 per 100,000. The Brugada pattern ECG is rarely found in the United States (0.02% for type 1 and 0.03% for types 2 and 3, whereas it is found more commonly in Asia (0%–0.36% for type 1 and 0.12%–2.23% for types 2 to 3). There are more Brugada types 2 and 3 in Asia (1.8%–2.5% and 0.12%–2.23%, respectively) compared with the United States and Europe (0.03% and 1.5%, respectively).[7]

Patients diagnosed with Brugada pattern ECG and syndrome before and after the recent expert consensus conference[3] is unknown in our institution. This study would delineate the natural history, clinical and electrophysiologic profile, treatment strategies, and outcomes of patients with Brugada pattern ECG and Brugada syndrome in a specialty tertiary care hospital in the Philippines.

METHODS

Data of adult Filipino patients, 18 years or older, with diagnosis of Brugada pattern ECG and Brugada syndrome who were admitted at the Philippine Heart Center from 2004 to 2019 were retrospectively reviewed through chart review (using *International Classification of Diseases, 10th Revision* [*ICD-10*] codes 147.2 and 149.8). All patients who had a final chart diagnosis of Brugada pattern ECG and Brugada syndrome but with incomplete data and with concomitant condition that might produce a type 1 Brugada-like ECG were excluded (such as right bundle-branch block, pectus excavatum, arrhythmogenic right ventricular cardiomyopathy, occlusion of the left anterior descending artery or the conus branch of the right coronary artery, acute pericarditis/myocarditis, pulmonary embolism, dissecting aortic aneurysm, central and autonomic nervous system abnormalities, Duchenne muscular dystrophy, myotonic dystrophy, and prinzmetal angina). Using the definition by recent expert consensus conference[3] (Appendix A), the list of patients with Brugada pattern was finalized after ECGs were read and adjudicated by two cardiologists (one electrophysiologist). This study was approved by the Philippine Heart Center Institutional Ethics Review Board, and all procedures were performed in accordance with its ethical standards.

Descriptive statistics was used to summarize the demographic and clinical characteristics of patients. Frequency and proportion were used for categorical variables, median and interquartile range for non–normally distributed continuous variables, and mean and SD for normally distributed variables. Shapiro-Wilk was used to test the normality of the continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α level of significance. STATA 13.1 (StataCorp, College Station, Texas) was used for data analysis.

RESULTS

Thirty-three patients with final diagnosis of Brugada were admitted from 2004 to 2019. After chart review, 10 patients were excluded because of lack of ECGs; hence, 23 patients were included in the study.

Table 1 shows the demographic characteristics of the subjects. Ages ranged from 24 to 66 years (mean, 40.21 ± 11.86 years). All patients were male. In both groups, Brugada pattern ECG and syndrome, the majority were nonsmokers (n = 13 of 23 [56.52%]) and nonalcoholic beverage drinkers (n = 14 of 23 [60.87%]). In patients diagnosed with Brugada pattern ECG, all presented an incidental finding during workup (n = 10; $P < 0.001$), whereas in Brugada syndrome, six patients presented with out-of-hospital resuscitated cardiac arrest (46.15%, $P = 0.019$). There were only three patients with family history of sudden cardiac death. All patients had normal ejection fraction. Seven patients underwent implantable cardioverter-defibrillator (ICD) implantation before discharge, whereas one patient died at the time of diagnosis.

Electrocardiographic parameters were evaluated. All patients had sinus rhythm with a heart rate range of 50 to 83 beats/min (mean, 69.21 ± 9.13 beats/min). None of the patients met the criteria for fragmented QRS; only 2 fulfilled the AVR sign (8.7%), whereas 14 patients had S wave in lead I (60.87%). Twenty-one patients had ST elevation (91.30%) with a mean ST elevation of 2.52 ±1.90 mm. Fourteen patients had spontaneous type 1 Brugada ECG pattern, whereas the rest were inducible to type 1 after flecainide test. Electrocardiographic features of Filipinos with Brugada pattern ECG and syndrome are shown in Table 2.

Table 1. Baseline Characteristics of Filipinos With Brugada Pattern ECG and Syndrome

	Total (N = 23)	Brugada Pattern ECG (n = 10)	Brugada Syndrome (n = 13)	*P*
	Frequency (%) or Mean ± SD			
Age, y	40.21 ± 11.86	36.40 ± 6.94	43.15 ± 14.15	0.181
Male sex	23 (100)	10 (100)	13 (100)	—
Smoking status				0.116
Nonsmoker	13 (56.52)	7 (70)	6 (46.15)	
Previous smoker	5 (21.74)	0	5 (38.46)	
Current smoker	5 (21.74)	3 (30)	2 (15.38)	
Alcoholic drinking status				0.816
Nondrinker	14 (60.87)	7 (70)	7 (53.85)	
Previous drinker	1 (4.35)	0	1 (7.69)	
Current drinker	8 (34.78)	3 (30)	5 (38.46)	
Clinical presentation upon diagnosis				
Presyncope/syncope	4 (17.39)	0	4 (30.77)	0.104
Resuscitated cardiac arrest (out-of-hospital)	6 (26.09)	0	6 (46.15)	**0.019**
Nocturnal agonal breathing	0	0	0	—
Palpitations	2 (8.70)	0	2 (15.83)	0.486
Dyspnea	1 (4.35)	0	1 (7.69)	1.000
Fever as precipitating factor	0	0	0	—
Incidental	10 (43.48)	10 (100)	0	**<0.001**
Family history of sudden cardiac death	3 (13.64)	1 (11.11)	2 (15.38)	1.000
Ejection fraction				—
Normal (>50%)	23 (100)	10 (100)	13 (100)	
Abnormal (≤50%)	0	0	0	

ECG=electrocardiogram.
Statistically significant *p*-values are in boldface.

No single patient received medical management after a diagnosis of Brugada. Among patients with Brugada syndrome, seven had ICD before discharge ($P < 0.05$), but none from patients with Brugada ECG. One patient had recurrent admission for ventricular fibrillation, and one patient died at the time of diagnosis.

DISCUSSION

This study described the demographic profile of patients who were admitted and diagnosed with Brugada electrocardiographic pattern and Brugada syndrome in a local hospital. Treatment strategies and in-hospital outcomes were also reported.

Brugada syndrome is generally a disease of the middle-aged adult that is 8 to 10 times more prevalent in men.[3,7,8] This male sex predominance was documented in our study population having no single patient of female sex. Male sex predominance is associated with a more prominent transient outward current (I_{to}) and higher testosterone levels.[8]

Theoretically, cigarette smoking and alcoholic consumption are overlooked triggers of Brugada syndrome. Cigarette smoking is associated with risk of ventricular arrhythmia caused by augmented oxygen demand and myocardial work as a result of nicotine release into the circulation.[9] On the other hand, alcohol intoxication mimics the action of sodium-channel inhibitors (eg, flecainide), which are standard agents to unmask Brugada syndrome.[7] However, in our study, the majority of patients were nonsmokers and nonalcoholic beverage drinkers. Interestingly, five among those who were either current smokers or alcoholic beverage drinkers developed arrhythmia (ventricular tachycardia) during flecainide challenge test.

Brugada pattern ECG is distinguished from Brugada syndrome with the latter having symptoms probably secondary to ventricular arrhythmia. In our study, all 10 patients with Brugada pattern ECG presented only an incidental finding of an abnormal electrocardiographic pattern during annual check-up for work clearance, with no symptoms reported ($P < 0.001$). Among those diagnosed with syndrome, six patients presented with out-of-hospital resuscitated cardiac arrest ($P = 0.019$) and

Table 2. Electrocardiographic Features of Filipinos With Brugada Pattern ECG and Syndrome

ECG Characteristics	Total (N = 23)	Brugada Pattern ECG (n = 10)	Brugada Syndrome (n = 13)	*P*
	Frequency (%) or Mean ± SD			
Rhythm				—
Sinus	23 (100)	10 (100)	13 (100)	
Atrial fibrillation	0	0	0	
Heart rate, beats/min	69.21 ± 9.13	66.50 ± 9.94	71.30 ± 8.22	0.218
PR interval, ms	0.18 ± 0.02	0.19 ± 0.02	0.18 ± 0.02	0.087
QRS axis, degrees	50.47 ± 36.19	44.10 ± 24.79	55.38 ± 43.37	0.471
QRS duration, ms	0.08 ± 0.02	0.087 ± 0.02	0.086 ± 0.02	0.940
QTc interval	389.26 ± 39.54	383.50 ± 36.07	393.69 ± 42.9	0.552
Fragmented QRS	0	0	0	—
S wave in lead I	14 (60.87)	8 (80)	6 (46.15)	0.197
aVR sign	2 (8.70)	1 (10)	1 (7.69)	1.000
ST elevation (mm)	2.52 ± 1.90	3.20 ± 2.34	2.00 ± 1.35	0.137
Brugada pattern				0.516
Type 1 (spontaneous)	14 (60.87)	7 (70)	7 (53.85)	
Type 1 (induced)	1 (4.35)	1 (10)	0	
Type 2 (inducible to type 1)	5 (21.74)	1 (10)	4 (30.77)	
Type 3 (inducible to type 1)	3 (13.04)	1 (10)	2 (15.38)	

ECG=electrocardiogram.

Table 3. Treatment Strategies and Outcome of Filipinos With Brugada Pattern ECG and Syndrome

Treatment Strategy/Outcome	Total	Brugada Pattern ECG	Brugada Syndrome	*P*
	Frequency (%)			
Medical management (to specify what drugs were given)	0	0	0	—
ICD implantation	7 (30.43)	0	7 (53.85)	0.007
Recurrent admission for arrhythmia				1.000
Ventricular tachycardia	0	0	0	
Ventricular fibrillation	1 (4.35)	0	1 (7.69)	
Death	1 (4.35)	0	1 (7.69)	1.000

ECG=electrocardiogram; ICD=implantable cardioverter-defibrillator.

four with syncopal attacks. Identification of presenting symptom is important in the management and prognosis of patients. In a study by Probst et al,[10] the cardiac event per year was 7.7% in patients with aborted sudden cardiac death, 1.9% in patients with syncope, and 0.05% in asymptomatic patients.

In our study, only three patients had a history of sudden cardiac death among other family members. This can be explained by the fact that despite extensive knowledge on the genetic cause of Brugada, only 30% to 35% of those clinically diagnosed are genetically diagnosed; hence, a family history of sudden cardiac death at any age is not considered an independent prognostic marker for cardiac events in either asymptomatic or symptomatic patients.[11] The same divergent is reported by

Gervacio-Domingo et al,[12] wherein family history did not appear to differ between those with and those without events. All patients had normal left ventricular ejection fraction by Simpson method (>50%), and further review of echocardiographic findings showed no structural abnormalities. Murata et al[13] described Brugada as a "disease of the right ventricle" or "right ventricular cardiomyopathy"; hence, a normal left ventricular function was expected but should never be overlooked as other possible causes of ST elevation can be ruled out in our patients.

Electrocardiogram has a vital role in the diagnosis of patients. In a study by Gervacio-Domingo et al,[7] there are more Brugada types 2 and 3 in the Philippines and Asia (1.8–2.5%and 0.12–2.23%, respectively) contrary to our data, with most patients presenting spontaneous type 1 Brugada pattern (n = 14 [60.87%]). Aside from diagnosis, ECG can be used to prognosticate patients with Brugada pattern as to the numerous electrocardiographic parameters that have been associated with an increased risk of cardiac arrhythmia.[14] Atrial fibrillation was more commonly seen in Brugada syndrome than in the general population, but abnormal fragmentation of QRS and QTc prolongation to more than 460 milliseconds[14] were all not seen in our study. The presence of a significant S-wave in lead I was recently reported to confer a greater risk for VT and VF,[11] which was found in 14 of our patients; however, it was not statistically significant ($P = 0.197$). The presence of ST elevation, although not statistically significant (2.52 ± 1.90, $P = 0.137$), tells us that ST elevation among our patients was likely present only to satisfy one of the minimum criteria for the diagnosis of Brugada pattern, which is an elevation of at least 1 mm.

In our study, only one patient died at the time of diagnosis after presenting with ventricular fibrillation. To date, the only proven effective treatment strategy for the prevention of sudden cardiac death is ICD,[8] which was performed in seven of our patients with Brugada syndrome but none among patients with Brugada pattern ECG. Patients with spontaneous type I ECG consistently have twice the risk of arrhythmic events compared with patients who develop such an electrocardiographic pattern when challenged with a sodium-channel blocker.[14] Medical management with quinidine, a class I antiarrhythmic agent, is recommended in patients with VT storm or in patients with contraindication to ICD (class IIa).[8] In our study, among those with Brugada pattern ECG, no single patient received medical management, which translates to a guideline-directed treatment strategy. Only one of our patients had recurrent admission for arrhythmia (ventricular tachycardia) 2 years after diagnosis. This interval of arrhythmia recurrence from the initial presentation or diagnosis was similarly observed in a study by Adler et al,[14] with a range of 1.5 to 6 years.

The main limitation of this study is that it is retrospective and purely chart review. The sample population was also limited to admitted patients only, hence a relatively small number of participants leading to possible underestimation of the true incidence of Brugada syndrome in our institution. Documentation of cardiac events and outcomes among our patients was done only in an in-hospital basis, which could miss out long-term cardiac events and outcomes postdischarge.

CONCLUSION

This study described the demographic profile, treatment strategies, and outcomes of patients who were admitted and diagnosed with Brugada pattern ECG and Brugada syndrome in a local hospital. Except for the clinical presentation upon diagnosis that was incidental in Brugada pattern ECG patients ($P < 0.001$) and out-of-hospital resuscitated cardiac arrest in Brugada syndrome patients ($P < 0.019$), other clinical profile and electrocardiogram findings were not significantly different between the two groups. Treatment strategies were guideline-directed.

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