Indian Heart Journal 70 (2018) 416–420

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Brugada syndrome in patients with acute febrile illness

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ARTICLE INFO

Article history:
Received 8 June 2017
Accepted 31 August 2017
Available online 8 September 2017

Keywords:
Brugada syndrome
Brugada-type ECG pattern
India
Fever
Prevalence

ABSTRACT

Background: Brugada syndrome (BrS) is an inherited electroclinical syndrome and can be occasionally precipitated by fever. The prevalence of Brugada-type electrocardiographic patterns (BTEP) due to febrile illnesses have not been previously studied in India.
Materials and methods: Between June 2014 and December 2015, 525 consecutive patients admitted to a government hospital with acute febrile illness were retrospectively enrolled. In addition to their investigations for workup of fever, ECGs were analyzed and BTEP types 1 and 2 were noted. Daily ECGs if available were perused to document reversal.
Results: BTEP was seen in 23 (4% 95%CI: 2.9–6.5%): BTEP type 1 (Brugada syndrome) in 11 patients (2%; 95%CI 1.2–3.7%) and BTEP type 2 in 12. All patients with BrS (BTEP type1) were males; mean age and temperature were 37.7 years (SD: 17.6) and 38.8 °C (SD: 0.6), respectively. There were no significant differences in age, temperature or ECG parameters between patients with BTEP and those without. These patients neither had cardiac symptoms nor family history of sudden cardiac deaths. Bacterial infections were the commonest cause of fever in patients with BrS. All BTEP changes resolved with defervesence of fever except in one.
Conclusion: The prevalence of the fever induced BrS is higher in our study group and is comparable to estimates in Southeast Asian populations. An ECG should be considered in all febrile patients. Further studies are required for better characterization and risk stratification of these patients.

1. Introduction

Brugada syndrome (BrS) in an inherited electroclinical syndrome characterized by a predisposition towards malignant arrhythmias and sudden cardiac death.[1] More than 300 mutations and 18 genes underlying this syndrome have been described, with the most common involving the cardiac sodium channel seen in 30%.[1] *Lai tai* (death during sleep) in Thailand, *bangungut* (rise and moan in sleep) in the Philippines and *pokkuri* (sudden unexplained cardiac death) in Japan have similar features with BrS.[2] For diagnosis, ST-segment elevation in ≥1 precordial leads (V1–V3) positioned in the 4th, 3rd or 2nd intercostal spaces should be ≥2 mm.[1] Three types of Brugada-type ECG patterns (BTEP) have been described.[1] Based on 2013 and 2015 guidelines, type 1 pattern is sufficient by itself to warrant a diagnosis of BrS, while types 2 and 3 pattern requires the conversion to type 1 pattern on infusion of class I antiarrhythmic drugs *plus* one of the following: arrhythmia-related syncope, documented ventricular fibrillation, nocturnal agonal respiration, history of sudden cardiac death <45 years with negative autopsy or coved-type ECG changes in family members death[1] (Fig. 1).

The ECG patterns are, however, transient and can be induced by fever, drugs, electrolyte disturbances or mechanical compression of the right ventricular outflow tract.[3] The incidence of malignant arrhythmias in induced-BTEP is currently unclear.[4] Matsuo et al followed up 4788 asymptomatic individuals of whom 32 had BTEP for over 40 years, and found that the risk of unexpected death was significantly higher in the group with BTEP compared to those without.[5] Fever not only induces BTEP but it is also known to result in malignant arrhythmias in those with BrS. Amin et al described 24 febrile patients among 111 with BrS. Among the 10/24 who did not take paracetamol, three sustained cardiac arrest during a febrile episode. Eleven of the 24 who used paracetamol during fever had no untoward cardiac events.[6] Mizusawa et al investigated 88 asymptomatic patients of BrS. Patients were

Abbreviations: ASD, atrial septal defect; AWS, alcohol withdrawal syndrome; BrS, Brugada syndrome; BTEP, Brugada-type ECG pattern; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; LAE, left atrial enlargement; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

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http://dx.doi.org/10.1016/j.ihj.2017.08.029

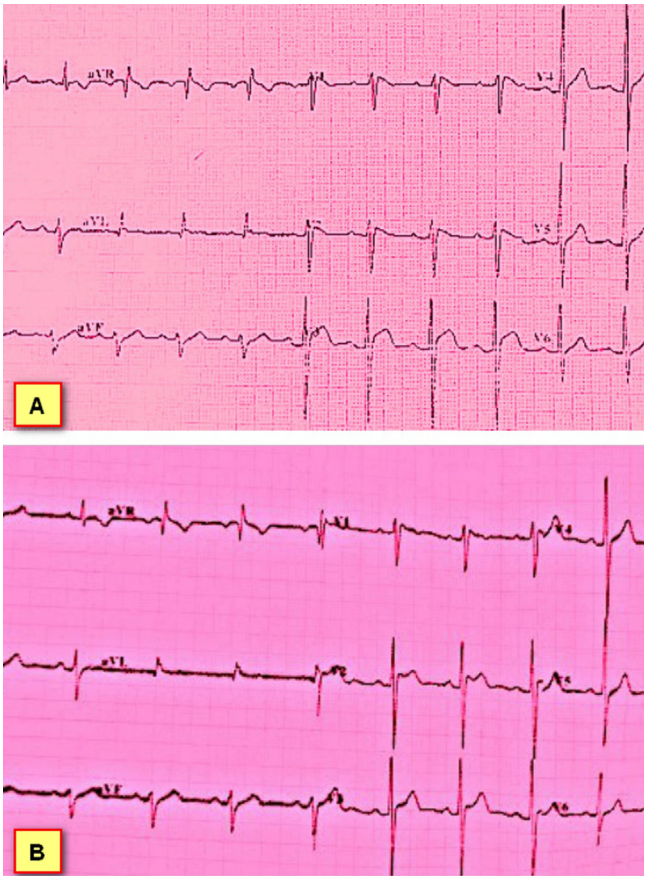

Fig. 1. [A] Type 1 BTEP in patient no 11 with scrub typhus, whose ECG changes persisted even one week after discharge. [B] Type 2 BTEP in a patient with cellulitis.

mostly male, and middle-aged. Three among the 88 developed arrhythmic events during follow-up and in one of the three patients, the event occurred during a febrile episode.[7]

There are no estimates of the prevalence of BrS from India. We hypothesized that it could be similar to that of other Southeast Asian nations, which are known to have a higher prevalence of BrS compared to the West. Moreover, as fever is known to induce BrS and predispose towards malignant arrhythmias in these individuals and febrile conditions are also common in tropical countries such as ours, we undertook this study to estimate the prevalence of fever-induced BTEP and characterize such individuals.

2. Materials and methods

With the approval of the Institute Ethics Committee, data was retrospectively collected from consecutive patients admitted in the department of General Medicine of the Indira Gandhi Medical College and Research Institute, Puducherry, between 01 June 2014 and 31 December 2015. Patients $\geq$ 13 years and whose admitting diagnosis was acute febrile illness (fever $<$ 3 weeks) were recruited. Those with history or clinical findings of heart disease or drug therapy for cardiac ailments were excluded from the study. Oral or an axillary temperature at admission, investigations such as complete blood count, renal and liver function tests, chest radiograph and electrocardiogram (ECG) were noted. A temperature beyond 37.2 °C was considered as fever. An ECG obtained in each patient by a technician using standard lead placement were analyzed by both investigators. BTEP type 1 was diagnosed as BrS. Data regarding family history of syncope, nocturnal agonal respiration, sudden cardiac deaths (including those aborted) and previous ECGs, if documented was obtained. Demographic data, past medical history, drug history and family history was also noted. Type 1 and type 2 patterns were defined according to consensus criteria. Daily ECGs in those patients with a BTEP were also read by both investigators to document resolution. All patients with BTEP had been followed up once after discharge to recheck an ECG.

2.1. Statistics

A sample size of 525 was calculated to estimate the frequency of fever induced BTEP assuming a prevalence of 2%, with a precision of 1.2% with alpha 0.05.[8] All data were entered into an Excel sheet and thence extracted and analyzed by SPSS for Windows version 22. Independent samples T-test was used to compare patients with and without BTEP. Chi-square (or Fischer's exact test) was used for categorical data. Statistical significance was defined as a p-value $<$ 0.05.

3. Results

Five hundred and twenty-five subjects with acute febrile illness were recruited for the study. BTEP (type 1, n = 11 and type 2, n = 12) was seen in 23, with none having type 3 (Table 1). Based on documentation in the case files, none of our patients had preexisting BrS. Males constituted 72% (n = 366) and 300 of the study population were from rural areas. There was no recorded history to suggest previous syncope, malignant arrhythmias, or nocturnal agonal respiration in these patients. None of them had a family history of sudden cardiac death or a record of previous

Table 1
Features of patients with BTEP or BrS, and those without.

Variable	BTEP (CI) M = 23	No BTEP(CI) N = 502	Significance	BrS(CI) N = 11	No BrS (CI) N = 514	Significance
Age (years)	35 (27.4–42.5)	36.0 (34.6–37.5)	0.75	37.7(25.8–49.5)	35.9(34.5–37.4)	0.75
Male gender (n)	22/23	357/502	0.01	11/11	368/514	0.04
Rural (n)	14/23	286/502	0.71	6/11	294/514	0.86
Alcohol (n)	4/23	110/502	0.94	4/11	111/514	0.24
Hospital stay (days)	6 (4.9–7.0)	5.5 (5.3–5.9)	0.44	6.6(5.5–7.7)	5.5(5.3–5.8)	0.07
Fever duration (days)	7.7 (4.7–10.8)	7.6 (4.7–10.8)	0.86	7.5(3.7–11.3)	7.6(7.1–8.0)	0.97
Temperature (C)	38.9(38.0–38.8)	38.3 (38.2–38.4)	0.005	38.8(38.3–39.2)	38.3(38.2–38.4)	0.03
Pulse rate (beats/min)	96 (83.7–108.2)	89.4 (87.9–94.9)	0.13	93(86.7–100.7)	89(88.8–91.1)	0.26
Systolic BP mmHg	101.3(90.3–112.4)	108.3(107–109.6)	0.03	98(75.1–122.6)	108(106.9–109.5)	0.04
ECG HR	92.14 (70.7–113.5)	88.4 (85.8–90.2)	0.16	94(83.1–105.6)	88(86.8–90.0)	0.27
ECG PR	154 (134.9–173.0)	140.7 (138.1–143.4)	0.28	153(136.6–171.1)	141(139.1–143.0)	0.13
ECG QRS	90.2 (81.3–99.2)	88.4 (87.2–89.6)	0.15	91.3(84.57–98.1)	88.2(87.3–89.1)	0.33
ECG QTc	404 (376.8–431.1)	412.6 (409.5–415.6)	0.11	411(391.0–431.5)	410(408.2–412.7)	0.93

HR-heart rate; PR- PR interval; QRS- QRS duration; QTc- corrected QT interval.

normal or abnormal ECGs. Four patients had a history of chronic alcohol consumption and alcohol abuse but had never been told by their treating physicians to have abnormal ECGs previously. None of the patients with BrS were on medications that predisposed to a BTEP. Of the patients with BTEP and fever due to known etiology, scrub typhus (n = 4), dengue and pneumonia (n = 3 each), enteric fever (n = 2) and one case each due to HIV/pleural tuberculosis, cellulitis, malaria and urinary tract infection were seen. Seven cases of BTEP were due to undifferentiated illness. BTEP was significantly associated with male sex, higher temperature, and lower systolic blood pressure (Table 1). Other ECG abnormalities detected in those with BTEP were atrial enlargement (two each of right and left) and left ventricular hypertrophy. BTEP resolved in all patients following defervescence of fever, except in one whose changes persisted even one week after discharge. He was lost to follow-up thereafter. Multivariate analyses of historical variables, examination findings, and investigations revealed no statistical difference between those with and without BTEP during fever, except with regard to duration of hospital stay (p-value < 0.01). The characteristics of the 11 patients with BrS are given in Table 2.

4. Discussion

Worldwide prevalence of Brugada syndrome is estimated to be between 0.1 and 0.5 per 1000 people.[9] The prevalence in North America ranges from 0.07 to 0.012%.[10] Among asymptomatic Filipinos and Koreans, the prevalences were 0.17% and 0.9%, respectively.[11] In Japanese atomic bomb survivors, the prevalence was 14.2/100000 person-years.[10] The prevalence rates in population studies performed in Taiwan and the Philippines were 0.13% and 0.17%, respectively.[12] Overall, in Asian populations, the estimated prevalence stands at 0.15%.[10] BTEP was seen in 0.8% of a young asymptomatic university populace in Pakistan-the only other South Asian country to have a prevalence study.[13] Patients with BrS described in various case reports have been reported across all age groups (ranges 2–80 years).[9] There are no prevalence studies from India. However, there is a wide variation in the prevalences reported by different studies, as the methodologies used for estimation were different. Also, the true prevalence of BrS is difficult to estimate as ECG is dynamic in nature and the changes are often concealed until unmasked by fever or drugs.[9]

Fever causing BTEP has been attributed to complex reasons: age (young > old), gender (male > female) and the effect of temperature on either the mutant type or wild type sodium channels leading to a reduction of sodium current, thereby delaying conduction.[8] BTEP due to fever has been described only in three studies.[8,14,15] The Turkish study had 103 febrile males as subjects, and 10 cases of BTEP type 2 were observed- hence no BrS were reported.[14] The studies from Israel and Thailand had 402 and 158 patients, respectively. Eight among the 402 (2%) and 6/158 (4%) had BrS, respectively. In our study, we found 11 patients with BrS (2%; 95%CI 1.2–3.7%). Mean ages of the Turkish and Thai cohort were 46 and 48.2 years, respectively, while our study had a lower mean age of 35 years (95% CI 27.4–42.5). The mean temperatures in all three studies were comparable. Both the Israeli and Thai study had an afebrile control, showing a higher prevalence of BrS in the presence of fever when compared to those without. The Asian predominance has been attributed to ethnicity, either due to increased prevalence of disease producing mutations in these populations, or due to its modifying effect on the mutation or due to its increased susceptibility to arrhythmias.[10] Seasonal variation of BrS-related arrhythmias have not been proved in southeast Asian countries.[8] In India, the problem could be potentially huge, considering a large young population with scope for infectious diseases/fever that could precipitate BrS. Since ECGs are not routinely performed for fever, the problem could be underestimated.

Indian studies in BrS have so far been only in the form of case reports (Table 3). A literature search revealed at least 12 such reports.[16–27] The ages ranged between 1 and 67 years, comparable to our subjects with age ranges of 13 to 65 years. Eight (66%) from these case reports were male, compared to 22 males (95%) in our study. Four had preexisting BrS and only one fever-induced BTEP has been reported. None of our patients had preexisting BrS and all of them had fever-induced BTEP. In all but one, our patients' ECG changes resolved with resolution of fever.

There is no consensus regarding the risk of malignant arrhythmias in these patients with fever-induced BTEP although there seems to be some indication that unexpected death is more frequent in this group.[4,5] Electrophysiological studies are also not known to contribute to the risk stratification. None of our patients underwent electrophysiological tests or drug testing due to the lack of facilities. All our patients were advised to avoid alcohol and sodium channel blockers and take paracetamol during fever.

4.1. Limitations

Our study is the first such from India, and we report the largest number of fever induced BTEP in a single study. However, our study suffers from some limitations. The data collection is retrospective and hence all the requisite information may not have been available. This is in comparison to the three studies from Turkey, Israel and Thailand, where data collection was prospective, and hence, the true magnitude of the problem may not be known accurately. ECG changes in BrS may not persist since they are dynamic and the once daily ECG may have missed some patients. High lead placements (V1 and V2 in 2nd or 3rd intercostal space)

Table 2
Demographic and clinical data of patients with Brugada syndrome.

Age/gender	Diagnosis	Duration Fever (d)	Alcohol, years	Temperature °C	Pulse/min	SBP mmHg	P wave	LVH	Echo
16,M	Undifferentiated	20	No		80	100	RAE	N	–
46,M	AWS; Undifferentiated	7	Yes, 20	38.9	100	130	LAE	LVH	LVH
45,M	Undifferentiated	7	Yes, 20	38.2	79	110	N	LVH	LVH
13,M	Scrub typhus	10	No	38.9	90	80	N	N	–
17,M	Enteric fever	7	No	39.0	100	100	N	N	–
37,M	Pneumonia	4	No	40.1	106	80	LAE	N	–
60,M	Pneumonia	3	Yes, 35	37.7	98	98	RAE	N	N
65,M	Cellulitis	1	No	39.4	112	140	N	N	N
26,M	Enteric fever	2	No	38.9	88	110	N	N	–
45,M	Vivax malaria	7	Yes, 15	38.3	90	130	N	LVH	LVH
45,M	Scrub typhus	15	No	38.9	88	100	N	N	–

LAE-left atrial enlargement; RAE-right atrial enlargement; LVH-left ventricular hypertrophy; AWS-alcohol withdrawal syndrome; N- normal.

Table 3
Brugada syndrome in India.

No	Reference	Age, gender	Trigger	BTEP	Outcome
1	Sastry et al.[16]	1, M	None	BrS	VT, recovered
2	Chattree et al.[17]	40, F	None	BrS	Recurrent syncope, aborted SCD; ICD placed
3	Bawaskar HS.[18]	10, M	Scorpion sting	BrS	Unmasked during recovery, with spontaneous reversal
4	Rangaraj et al.[19]	22, M	Electrocution	BrS	Recovered uneventfully
5	Nayyar et al.[20]	56, F	Aluminum phosphide poisoning	BrS	Runs of VT with LBBB; refractory shock, death
6	Kiran et al.[21]	28, F	Dothiepin	BrS	Asymptomatic, spontaneous reversal
7	Goraksha et al.[22]	14, M	Acute gastroenteritis	BrS	Presented with VF; ICD placed
8	Mehrotra et al.[23]	10, F	None	BrS	Recurrent polymorphic VT, managed with iv quinine; Associated ASD
9	Sivakumar et al.[24]	15, M	None	BrS	ICD shock causes embolization of ASD closure device
10	Boda et al.[25]	19, M	Fever	BrS	Asymptomatic, family screening positive
11	Reddy et al.[26]	59, M	None	1 & 2	VT
12	Prabhu et al.[27]	67, M	Zinc phosphide poisoning	BrS	VF in hospital, complete recovery

VF- ventricular fibrillation; VT- ventricular tachycardia; ICD-implantable cardioverter defibrillator; ASD- atrial septal defect; LBBB-left bundle branch block; SCD- sudden cardiac death.

are known to be able to pick up Brs with greater sensitivity, but this had not been performed on these febrile patients. So again, some patients may have been missed. In view of unavailability of previous ECGs or documented episodes elsewhere, whether these patients had BrS previously is unknown. Follow-up data was difficult to come by as many were asymptomatic and did not return and hence the prognostic significance in these patients is also not known. Neither a sodium-channel blocking test nor a genetic test was done in these patients, which could have enabled us to score them. According to the proposed Shangai Score System, all our patients save one, would have had 'possible BrS', while the lone patient whose ECG changes persisted after discharge could be considered to have 'probable BrS.'[1] Since most studies have used 38 °C as a temperature cut off, there is a possible risk of underestimating the prevalence of BTEP. Being a hospital-based study, our prevalence is probably an underestimate of fever induced BTEP, and thus, may not accurately reflect the prevalence in the community.

5. Conclusions

Fever induced BTEP is common in India with a prevalence similar to that of other Southeast Asian countries. Such patients may be predisposed to malignant arrhythmias during the febrile episode. Hence, ECG should probably be considered for all patients being admitted with fever. Close and regular follow-up of these patients is mandatory, since the risk of malignant arrhythmias may be high. Liberal use of antipyretics during febrile episodes may be advisable to preempt risk of arrhythmias. Follow-up will also help in the risk stratification and appropriate management of these patients as and when they become symptomatic due to fever or consumption of alcohol/sodium channel blockers. Genetic testing would give a better idea of the true prevalence of mutations causing BrS in Indian patients.

Conflicts of interest

There is no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

None.

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