International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Cardiac arrest and Brugada syndrome: Is drug-induced type 1 ECG pattern always a marker of low risk?☆,☆☆

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ARTICLE INFO

Article history:
Received 4 July 2017
Received in revised form 27 October 2017
Accepted 31 October 2017
Available online xxxx

Keywords:
Sudden death
Brugada syndrome
Brugada type 1 ECG pattern
Aborted cardiac arrest

ABSTRACT

Background: Patients diagnosed as affected by Brugada syndrome (BrS) on the basis of a drug-induced type 1 ECG pattern (type1) are regarded as at low risk for cardiac arrest. We tested whether this assumption matches reality.
Methods: The study population included 26 patients from our group and 217 patients from three studies published between 2002 and 2013, all of them with aborted cardiac arrest (ACA) and in whom a previously unrecognized type1 (spontaneous or drug-induced) was discovered after the event, thus leading to the diagnosis of BrS.
Results: Among our 26 patients, a drug-induced type1 was detected in 11 (42%) and only 1/11 showed a spontaneous pattern during follow-up; of 6 patients with syncope before ACA, 4 (67%) had only a drug-induced pattern. ICD shocks rates were similar in both spontaneous and drug-induced groups (57% and 45%). Early on, year 2002, the percentage of drug-induced type1 after ACA was much lower (14%) and has progressively increased to approximately 50%.
Conclusions: If drug-induced type1 carries low arrhythmic risk, it should seldom be the only marker for BrS after an ACA. In studies on patients after an unexpected ACA, a drug-induced type1 leads to the diagnosis of BrS more often than anticipated. This contrasts with prospective studies focusing on patients already diagnosed as BrS and which consider drug-induced type1 as a marker of low risk. Contrary to current views, it is possible that not all patients with a drug-induced BrS type1 are at low risk of future events.

1. Introduction

In the world of Internet and of Facebook the expression "went viral" has become a most common one. During the last 25 years something similar has progressively happened with Brugada Syndrome (BrS). All over the world cardiologists who never saw a case in their life, now encounter BrS patients all the time and make one diagnosis of BrS after another. This is not small potatoes. BRS is one of those arrhythmogenic disorders of genetic origin which is associated with risk for sudden cardiac death and, due to the lack of certainly effective pharmacological therapies, it is all too often managed with an implantable cardioverter defibrillator (ICD). As the rate of appropriate discharges by ICDs in these patients is very low, the problem for risk stratification and proper management is a serious one [1,2].

The identification of the not many BrS patients at high risk is challenging and still elusive. Among patients who have been diagnosed as being affected by BrS, those who show the spontaneous type 1 ECG pattern (type1) are considered at risk of sudden death (SD) or of aborted cardiac arrest (ACA) due to life-threatening ventricular arrhythmias [3]. Although this event is relatively rare, it has a heavy emotional impact as it affects rather young individuals, apparently healthy and thought to have a long life expectancy. Conversely, the drug-induced pattern has always been regarded as a marker of low risk for cardiac events, as witnessed by the fact that no guidelines recommend active therapy in this case [3]. This concept has constantly been reinforced by the fact, unavoidable given the current practice, that the drug test is almost always performed in asymptomatic patients.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ *Acknowledgement of grant support*: This study was supported by the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement 733381.
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https://doi.org/10.1016/j.ijcard.2017.10.118
0167-5273/

In our own personal experience we have serendipitously, but repeatedly, observed events questioning this dominating concept. Indeed, in our management of survivors of cardiac arrest [4], eventually diagnosed as affected by BrS, we have encountered an unexpected number of subjects in whom the post-event diagnosis was indeed BrS, but it was based solely on the observation of a drug-induced type1. The initial puzzlement has prompted the plan of going beyond anecdotal observations and of more formally testing the possibility, hitherto not considered, that the presence of a positive drug test might not always be taken as a marker of low risk. We then performed an observational retrospective study with a predefined focus on those BrS individuals presenting with a most severe phenotype, i.e. having suffered from an unexpected aborted cardiac arrest (ACA) which subsequently led to the diagnosis of BrS.

2. Methods

2.1. Study population

2.1.1. Eligibility criteria and data sources

To address the specific clinical question of interest, the main patient characteristic for inclusion was a clinical presentation with ACA, either as first event or preceded by syncope, followed by a diagnosis of BrS based on Consensus-driven criteria [3,5].

The study population comprised two distinct sources of information: 1) our Italian cohort, which provided unpublished data on 26 BrS patients who survived an ACA, consecutively enrolled in 2010–2016 at our centers; and 2) the international literature. As to the literature including major BrS registry cohorts, we explored one public electronic database (PUBMED) and considered for inclusion only those studies published after year 2000 including >15 subjects retrospectively diagnosed as previously unrecognized BrS on the basis of a type1 ECG, spontaneous or drug-induced. To avoid double counting, we excluded all reports involving patients who subsequently became part of larger studies. After exclusion of the ineligible ones, only three large studies were accepted for the analysis [6–8]. In the entire population, we assessed the following potential risk factors: spontaneous type1, familial SD, positive electrophysiologic study (EPS), and *SCN5A* mutations. The assessment of the EPS results was limited by the non-homogeneity of the protocols used, as some studies adopted aggressive protocols (e.g. triple extrastimuli and/or premature ventricular beats reaching the ventricular refractory period), while others used less aggressive stimulation protocols. Not every study had all these risk factors available. At variance with the three published studies, we also report data on the prevalence of nocturnal ACA and the prevalence of previous syncope before ACA. The three selected studies contributed 1823 BrS patients, of which 217 (12%) fulfilled the requirement of having suffered an ACA. With the 26 Italian patients, the study population totals 243 subjects in whom a previously unrecognized type1 ECG (spontaneous or drug-induced) was discovered after ACA.

2.2. Statistical analysis

Descriptive statistics summarizing study patients characteristics were expressed as counts and percentages for categorical variables, which were compared by chi-square test. Continuous variables, presented as mean and standard deviation were compared by ANOVA. A $p < 0.05$ was considered statistically significant. SPSS Statistics version 23 (IBM Co, Armonk, NY) was used for computation.

3. Results

The characteristics of all BrS patients included in the study, subdivided by cohort, are reported in Table 1. The vast majority of the 243 patients with a prior ACA were males (223, 92%) and aged ≥40 years on average at time of their event or diagnosis. A family history of SD was present in 24%, ranging from 10%–38%. A spontaneous type1 ECG was documented in 69% and a drug-induced type1 ECG in 31%. Among those who underwent EPS (157, 65%), sustained ventricular arrhythmias were induced in 101 (64%). A relatively small number of subjects in only two cohorts, including ours, underwent genetic testing, which successfully identified a *SCN5A* mutation in 24%.

Compared with the early results of the 2002 study by Brugada et al. [6], a significant and clinically meaningful, difference was observed in the reported prevalence of the diagnostic ECG pattern. The percentage of drug-induced type1 ECG trended significantly higher over the time, increasing from 14% in the early period, to 29% in the Asian cohort [7], up to 50% in the Finger study population [8]. This higher frequency of drug-induced pattern was confirmed also among the 26 Italian cases (11, 42%).

In comparison with the other earlier BrS cohorts, a significantly smaller percentage of our patients underwent EPS (5 of 26, 19% vs 58%, 74% and 76%); in 4 of these 5 subjects the test was positive. A nocturnal ACA occurred in 7/26 (27%) patients. Only 6/26 (23%) had a syncope preceding ACA and, importantly, four of them (4/6, 67%) had a drug-induced type1, when they were tested following the ACA. During a mean FU of 72 ± 41 months, only 1 of the 11 BrS patients in the drug-induced group showed a spontaneous type1. It is worth noting that all our 26 patients were reassessed at a scheduled 6-month interval visits, and were therefore regularly monitored. The only exception was represented by 2 patients who were hospitalized because of a permanent brain damage post–ACA. At each visit the patients had a complete clinical assessment and ECG recording, mostly performed exploring the high intercostal spaces ($n = 21$) and less frequently with 12 lead 24-h Holter monitoring ($n = 7$), according to the practice of each participating center. The ICDs were also periodically interrogated. Therefore, we believe that both quality and frequency of the periodic assessments of these patients suggest, even though cannot prove, that if a spontaneous pattern had emerged, it would have probably not been missed. By contrast, a spontaneous type1 was confirmed in 12 of the 15 subjects

Table 1
Characteristics of BrS patients with a presenting ACA in the different study subgroups.

Year of publication	Italian cohort	Brugada	Probst	Takagi	*P§*
	2017	2002	2010	2013	
Enrollment period	2010–2016	early cases −2001	(<2005–2009)	(2002−2011)	
ACA, n	**26**	**71**	**62**	**84**	
Males	23 (88.5%)	61 (86%)	55 (89%)	84 (100%)	0.008
Age (yrs)	40 ± 11	41 ± 16	44 ± 14	49 ± 13	0.001¶
Familial SD	9 (35%)	23 (38%)	6 (10%)	20 (24%)	0.02
Drug-induced Type 1	11 (42%)	10 (14%)	31 (50%)	24 (29%)	<0.001
Spontaneous Type 1	15 (58%)	61 (86%)	31 (50%)	60 (71%)	
EPS, n	5(19%)	54(76%)	36 (58%)	62 (74%)	<0.001
Inducibility	4 (80%)	44 (81%)	16(44%)	37 (60%)	0.003
SCN5A	3/14 (21%)	NA	12/49 (24%)	NA	1
Follow-up duration, months	72 ± 41	54 ± 54	54 ± 32	46 ± 35	0.05
Arrhythmic events** during follow-up, n (%)	13/26 (50%)	44 (62%)	22 (35%)	27 (32%)	0.001
Mean event rate per year, %	8.3	13.7	7.7	8.4	

Data are absolute (n) and relative (%) frequencies out of the total number of patients with ACA; mean ± SD or median and interquartile range (Q1-Q3).
§ from global χ [2] and ANOVA test.
EPS: electrophysiological study.
NA: not available.
** VF, SCD, ICD shock.
¶ For the French study, originally reporting median and IQR values, estimation of the sample mean and SD was derived according to Wan X et al. *BMC Medical Research Methodology* 2014, 14:135 with the caveat that these approximation methods could not be accurate.

Please cite this article as: P. Delise, et al., Cardiac arrest and Brugada syndrome: Is drug-induced type 1 ECG pattern always a marker of low risk? Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.10.118