Case reports

Brugada syndrome and neurally mediated susceptibility

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The risk of sudden death in patients with Brugada syndrome (BS) is still unclear. Moreover, particular clinical conditions may have a confounding effect on the diagnostic and therapeutic approach.

We report the case of a 27-year-old man with a clinical history of suspected neurally mediated syncope and typical ECG features of BS. The tilt table test showed a type I, mixed, positive response. The electrophysiological study (EPS) disclosed a peculiar ventricular irritability with the induction of a life-threatening arrhythmia. After the implantation of a cardioverter-defibrillator an episode of ventricular fibrillation during sleep at night was correctly identified and treated by the device.

The association between neurally mediated susceptibility and the typical ECG abnormalities of BS is not an unexpected event in young subjects. The misjudgment of the pathophysiological mechanism of syncopal episodes may lead, on one hand, to overlook the risk of sudden death and, on the other, to pursue inappropriate therapeutic measures. The application of a tailored diagnostic work-up based on currently available guidelines may be useful to overcome the clinical and therapeutic dilemma.

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Introduction

The Brugada syndrome (BS) is an inherited cardiac disease causing ventricular tachyarrhythmias and sudden death in patients with structurally normal hearts. According to the original description[1] this "electrical disease" is characterized by ST-segment elevation in V_1 through V_3, coved or saddleback, an apparent right bundle branch block, and rapid polymorphic ventricular tachycardia capable of degenerating into ventricular fibrillation, via a phase 2 reentry mechanism.

In spite of all the knowledge acquired over the last years on this syndrome, and the numerous publications that link the association of typical ECG features with different clinical situations, the complete clinical spectrum and the exact risk of each group of patients has yet to be defined. In this paper we report the association of a spontaneous ECG pattern of BS with neurally mediated susceptibility in a young man, and discuss the clinical and therapeutic implications of these findings.

Case report

A 27-year-old man was admitted to the emergency department after experiencing an episode of syncope in a warm and crowded classroom after prolonged standing, suggestive of a vaso-vagal faint. On admission, the patient was completely conscious and neurologically normal. Blood pressure was 120/70 mmHg and his blood chemistry showed values all within the normal range. Twelve-lead ECG showed sinus rhythm (74 b/min) and ST-segment elevation with a prominent J wave in V_1-V_2, as in the typical coved-type BS ECG pattern (Fig. 1A). He had no family history of syncope or juvenile sudden cardiac death. However, a careful clinical history revealed two other episodes of syncope after exertion in the previous 10 years, in one case in a heated swimming pool.

A specific structural cardiac disease was ruled out at echocardiography. Holter monitoring and signal-averaged ECG were unremarkable, and a maximal treadmill test showed no additional ECG changes or ventricular arrhythmias.

In order to disclose a vaso-vagal reflex and/or autonomic failure, as suggested by the previously described syncopal episodes, the patient underwent a head-up tilt test, performed according to the "Italian Protocol"[2]. He was inclined to a 60° head-up angle from the supine position. After 19 min, in the passive phase of the test, the patient developed frank syncope with unde-

tectable systolic blood pressure, followed by sinus block and a 42 b/min junctional escape rhythm on the ECG. He was then returned to the supine position and shortly thereafter he regained consciousness. A diagnosis of type I, mixed, positive response to tilt testing was made based on the trends of heart rate and blood pressure values[3].

Subsequently, the patient underwent an electrophysiological study (EPS) to test inducibility of ventricular tachyarrhythmias. When cannulating into femoral vessels, sinus bradycardia and blood pressure fall was observed, as with the tilt test, without loss of consciousness probably due to the supine position.

The intracardiac conduction intervals measurement, particularly the HV interval, revealed normal values. Programmed electrical stimulation was performed using two stimulation sites (right ventricular apex and right ventricular outflow tract) at two cycle lengths (500 and 400 ms), and delivery of a maximum of two premature stimuli. Polymorphic ventricular tachycardia, rapidly degenerating into ventricular fibrillation (Fig. 1B) that required emergency defibrillation, was induced using two extrastimuli with a coupling interval of 220 and 200 ms, respectively, during a drive cycle length of 400 ms at the right ventricular apex.

In summary, the patient was diagnosed to have BS and neurally mediated susceptibility. However, in consideration of the results of the EPS, a single-chamber cardioverter-defibrillator (ICD) was implanted. Two zones of ventricular tachycardia detection were programmed. The low-rate zone, with a detection rate of 180 b/min, was programmed with antitachycardia pacing therapy as first attempt, followed by three shocks after ineffective pacing; in the high-rate zone, with a detection rate of 210 b/min, the therapy was programmed only with shocks.

The patient presented at the scheduled follow-up after 3 months. He was free from symptoms. Nevertheless, the analysis of the stored ventricular electrograms and episode details from the ICD showed the onset of polymorphic ventricular tachycardia with a heart rate > 210 b/min during sleep at night. The arrhythmia was correctly detected and treated by the device firstly with an ineffective shock and subsequently with a second, effective shock (Fig. 2).

Discussion

The diagnosis of BS should be strongly considered in presence of the typical ECG features, with coved-type ST-segment elevation, either under baseline conditions and following challenge with a sodium channel blocker, and in absence of any structural heart disease[4]. Our patient fulfills all these criteria.

The occurrence of syncope in individuals with typical BS ECG abnormalities has a strong unfavorable prognostic impact. In the risk stratification scheme proposed by Priori et al.[5], the association of the history of "unexplained syncope" with the presence of spontaneous typical ST-segment elevation disclosed a major statistically significant increase of the risk of death by Cox regression analysis, with the occurrence of a cardiac arrest in 44% of this population in a mean observation time of 41 years. In this study the results of EPS had a poor diagnostic accuracy (38%); howev-

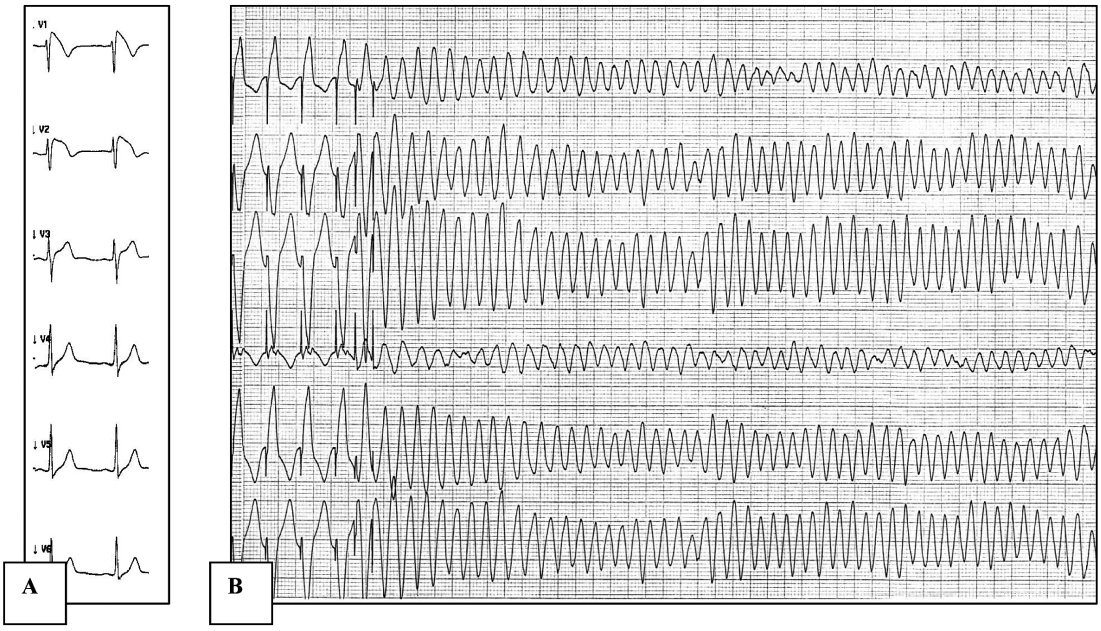

Figure 1. Panel A: *ECG on admission, precordial leads. The typical "coved-type" ST-segment elevation is evident.* Panel B: *electrophysiological study, standard limb leads. A polymorphic ventricular tachycardia "torsade de pointes" rapidly degenerating into a ventricular fibrillation was induced by means of two extrastimuli with a coupling interval of 220 and 200 ms, respectively, during a drive cycle length of 400 ms at the right ventricular apex.*

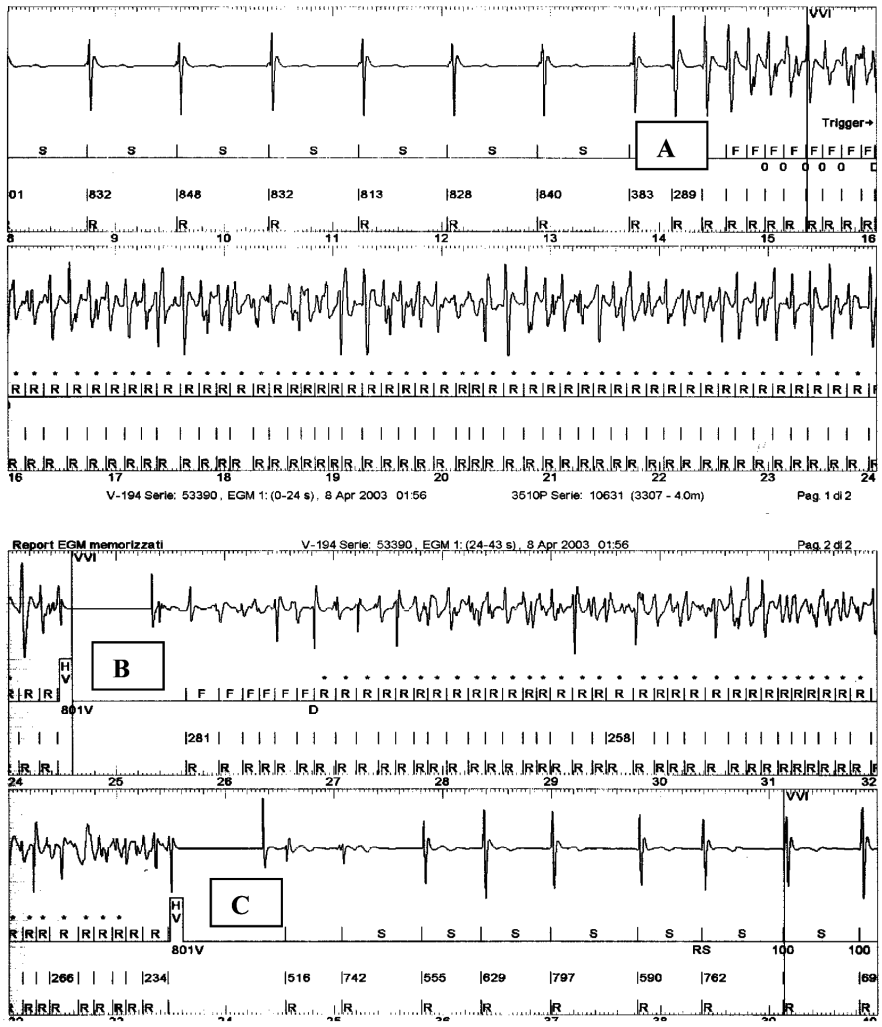

Figure 2. *Stored ventricular electrograms from the implanted cardioverter-defibrillator. Onset of polymorphic ventricular tachycardia during sleep at night* (A). *The arrhythmia was correctly detected and treated by the device firstly with an ineffective shock* (B) *and subsequently with a second, effective shock* (C).

er, the negative predictive value of the test was high (92%).

Brugada et al.[6] observed a new arrhythmic event (sudden death or ventricular fibrillation) in 16% of their patients with typical coved-type ST-segment elevation and "syncopal episodes of unknown origin", during a mean follow-up of 31 ± 41 months. Moreover they reported a high negative predictive value of the EPS in patients with and without syncope (95 and 97%, respectively).

On the basis of these data, therapy with ICD is recommended (class I) in patients with BS and "unexplained syncope", regardless of the electrophysiological findings[4,7]. When another possible cause of syncope is identified, EPS may be valuable for risk stratification. Indeed, the risk of sudden death in this setting is not defined and the implantation of an antiarrhythmic device may be inappropriate, especially in young patients.

In our case the clinical history was suggestive of neurally mediated susceptibility, in agreement with the European Society of Cardiology guidelines on syncope[3]. Therefore, our diagnostic work-up for a relatively young patient considered to perform a non-invasive and extremely safe procedure such as a tilt test before taking into account a direct ICD implantation (Fig. 3). In fact, a negative tilt test, owing to its high specificity[3,8], would have ruled out with little doubt a spontaneous neurally mediated syncope and would have led to a direct ICD implantation, without electrophysiological evaluation[4,7]. The positivity of the test made the diagnosis of a common faint possible, although not certain. It was therefore mandatory to evaluate the tendency of our patient towards life-threatening arrhythmias. Even if the usefulness of the EPS for the identification of patients with BS candidates for ICD implantation is to date controversial (class IIB) the high negative predictive value of the test[5,6] may be crucial for an accurate prognostic stratification. With respect to this issue, Samniah et al.[9] described the clinical features of a 30-year-old man with recurrent near-syncope spells, a family history of sudden death, tilt

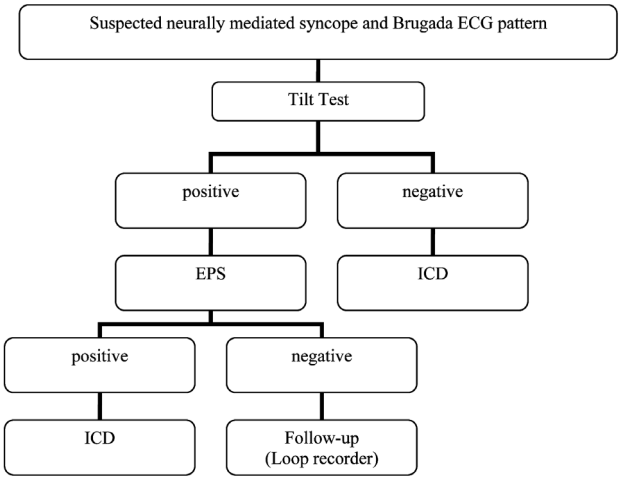

Figure 3. *Proposed diagnostic work-up in our patient with suspected neurally mediated syncope and spontaneous ECG pattern of Brugada syndrome. EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator.*

table test-induced syncope and characteristic ECG features of BS disclosed by procainamide. In this case the absence of inducible arrhythmias at EPS suggested a conservative therapeutic approach and excluded ICD implantation.

Once ventricular irritability has been excluded, the implantation of a loop recorder may be helpful to define the precise mechanism of the syncopal episode[3] as an alternative to a close clinical follow-up (Fig. 3).

In our case the induction of a sustained ventricular arrhythmia had made it very difficult to establish the real cause of spontaneous loss of consciousness; however, we believe that in the presence of two potential causes of syncope, it is reasonable to favor and treat the cause that is more life-threatening, that is an arrhythmic one, and therefore the patient received an ICD. This option was proven correct at follow-up, since the patient experienced an episode of ventricular fibrillation that was correctly identified and treated by the device.

In consideration of the high prevalence of syncopal episodes in young subjects (25-30% of patients with a mean age of 29 years)[10,11], mostly vaso-vagal in nature, the associated occurrence of the ECG pattern of BS may not be unexpected since this syndrome shows a prevalence in the apparently healthy population of 0.1% in Europe and of 0.6% in the rest of the world[12]. In these cases the identification of the exact pathophysiological mechanism leading to syncope is crucial. Indeed, the clinical misjudgment in this setting may lead, on one hand, to overlook the risk of sudden death with unacceptable consequences and, on the other, to pursue inappropriate therapeutic strategies such as ICD implantation. The application of a tailored diagnostic work-up based on currently available guidelines may be useful to overcome the clinical and therapeutic dilemma.

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