

Brugada Syndrome-An Always Surprising Disease: A Case Report

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Abstract

Brugada Syndrome (BrS) is an inherited channelopathy, with an autosomal dominant transmission, incomplete penetrance and variable expressivity, associated with high risk of malignant arrhythmias and sudden cardiac death, predominantly in young men. Even though nearly 30 years of study about this syndrome has gone past, several key points still remain to elucidate: The lack of a definite consensus regarding the management of asymptomatic patients, the influence of drug challenging test, the role of genetic test, symptoms and electrophysiological study in the decision-making process, the management of apparently low risk patients, the role of epicardial ablation are only some of the topics of ongoing controversy. This case report highlights these important and still debated topics about BrS, suggesting how much is still unknown about it.

Keywords: Channelopathies; Sudden cardiac death; Brugada syndrome; Syncope; Epicardial ablation

Introduction

The Brugada syndrome (BrS) is an arrhythmogenic disease associated with an increased risk of ventricular fibrillation and sudden cardiac death (SCD). Since BrS has been described for the first time, great progresses have been overcome but risk stratification and management of patients, even more asymptomatic ones, remains challenging. We report a 60-years-old man in this case report.

Case Report

We report the case of a 60-years-old man with no previous comorbidities, except gastroesophageal reflux disease and mixed anxiety-depressive syndrome. Family history was positive for SCD, as a paternal uncle died suddenly at age 56. A paternal 1st degree cousin experienced recurrent syncope (Figure 1).

The patient suddenly lost consciousness and collapsed during a work meeting. His colleagues witnessed that his eyes rolled back, and he had seizures. External cardiac massage was provided by his colleagues, waiting for the ambulance, but any witness was able to determine presence/absence of pulse. At ambulance arrival, sinus rhythm 75 bpm was present with blood pressure 125/80 mmHg and Glasgow Coma Scale score 3, so orotracheal intubation was performed and the patient admitted to the hospital.

At hospital admission physical examination, chest radiography, complete blood cell count, metabolic profile, brain natriuretic peptide (BNP), coagulation and troponin were normal. A cerebral CT was performed and repeated after 24 hours, resulting negative for ischemic brain injury. Transthoracic echocardiography showed normal heart dimensions with preserved left ventricular ejection fraction. A patent foramen ovale was suspected and subsequently revealed by contrast enhanced transcranial Doppler and transesophageal echocardiography. Cardiac magnetic resonance showed no abnormality. Coronary angiography showed no lesions in the coronary arteries. Continuous ECG monitoring during hospital stay and a 24 hours Holter-ECG were negative for relevant arrhythmias.

Due to the initial presentation with loss of consciousness, in the absence of a certain cause, we decided to perform an electrophysiological study (EPS), which showed normal AH and HV interval, normal Wenckebach point, normal corrected sinus node recovery time.

Programmed ventricular stimulation in two different sites or the right ventricle with triple extrastimuli, also during isoproterenol infusion, revealed no inducibility of arrhythmias.

The initial electrocardiogram was suspect but not certainly diagnostic for a Brugada pattern (Figure 2). Brugada ECG pattern is dynamic and can be spontaneous or concealed, but it can be unmasked under certain circumstances as a wide range of medications, alcohol or cocaine toxicity, autonomic nervous system changes, especially increased vagal tone, a febrile state and potassium or calcium imbalances [1].

Placement of ECG precordial leads in 2nd and 3rd intercostal space increases the sensitivity in some BrS patients; therefore [2,3]. We performed an ECG by shifting right precordial leads V1-V2 in the II and III intercostal space: Although we could not identify a diagnostic Brugada type 1 ECG pattern, we noticed a slow descending arm of r' wave and an undefined transition between depolarization and repolarization (Figure 3).

Furthermore, we performed a flecainide challenge test that resulted negative. During the hospitalization, some days after the first episode of loss of consciousness our patient experienced another similar episode, this time with ECG documentation of torsades de pointes followed by ventricular fibrillation, which was promptly treated with DC-shock, followed by the restoration of sinus rhythm and return of spontaneous circulation.

The patient received an ICD in secondary prevention and was then discharged home (Figure 4). Following genetic counselling and specific informed consent for molecular genetic testing, 51 genes associated with primary arrhythmic disorders were analyzed in the patient using PED MASTR Plus assay (Multiplicom - www.agilent.com). With

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this tool, 952 indexed amplicons (300-400bp) of the coding regions of the selected genes were produced for next generation sequencing (NGS) by ILLUMINA-Miseq (www.illumina.com); data were filtered and analyzed with the support of Sophia Genetics DDMRR (https://dropgen.sophiagenetics.com). MAF filter was 1%. KCNQ1 exon 9 and

SCN2B exon 4, not included in the PED assay, were analyzed by Sanger sequencing (ABI PRISM® 3130). Regions with high rumor or depth of coverage less than 20X were specifically covered by Sanger sequencing as well. Multiple ligation probe amplification (MLPA) was conducted for SCN5A and for the *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* genes using

No.	Detection Time	Type	Details	Prediction PP/RR	Pre-termination PP/RR
	Nov 14, 2016 3: 35: 54 PM	Follow-up	--	--	--
6	Nov 9, 2016 10: 10: 43 AM	VF	Duration: 20 s; Shocks delivered: 1	828/832	735/732
5	Nov 8, 2016 11: 01: 21 AM	VF	Duration: 16 s; Shocks aborted: 1	691/194	923/918
4	Oct 27, 2016 9: 37: 22 AM	VF	Duration: 21 s; Shocks delivered: 1	517/243	878/879
3	Oct 22, 2016 10: 11: 44 AM	VF	Duration: 24 s; ATP: 1; ATP One Shot: YES; Shocks delivered: 1	728/245	965/965
	Oct 19, 2016 2: 14: 45 PM	Follow-up	--	--	--
2	Oct 17, 2016 6: 18: 49 PM	VF	Duration: 22 s; ATP: 1; ATP One Shot: YES; Shocks delivered: 1		
	Oct 10, 2016 2: 32: 05 PM	Follow-up	--	--	--
	Oct 3, 2016 9: 58: 22 AM	Follow-up	--	--	--

Table 1: Patient's ICD window with five episodes correctly classified as VF, 4 of them appropriately treated with DC-shock, one spontaneously aborted.

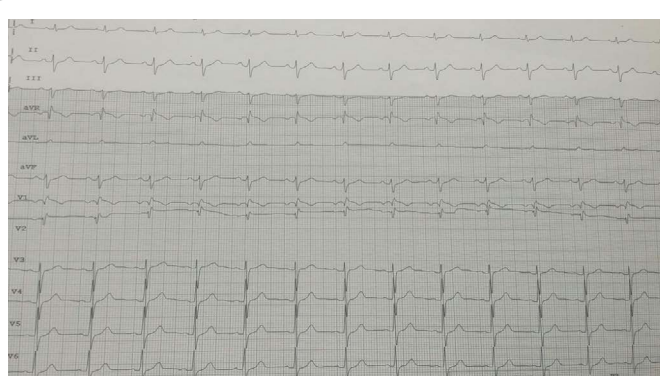
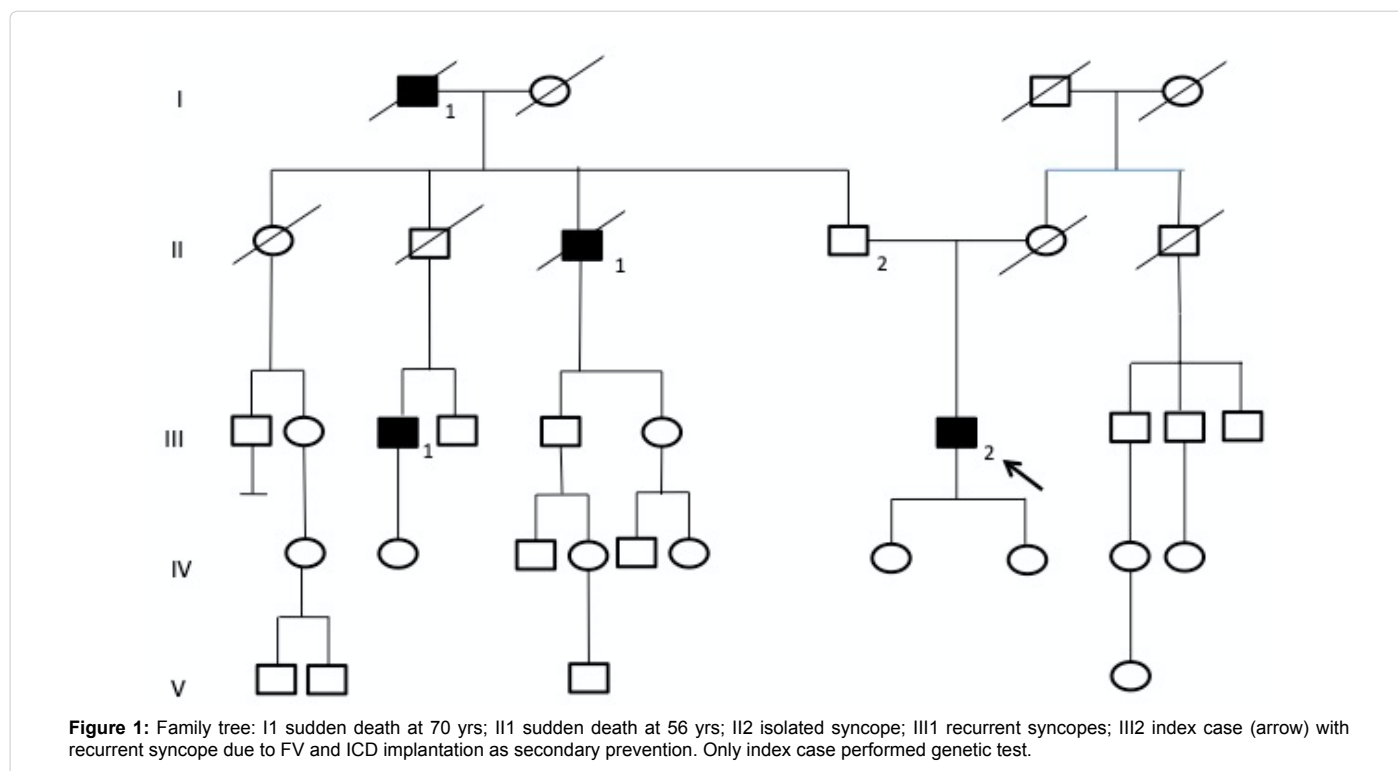


Figure 2: Patient's 12-lead ECG at time of presentation.

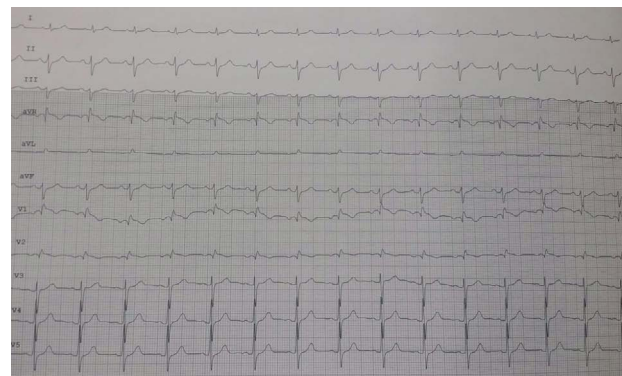


Figure 3: A 12-lead ECG with v1-v2 placement in the 2nd intercostal space.



Figure 4: A dual chamber implantable defibrillator (ICD) was implanted.

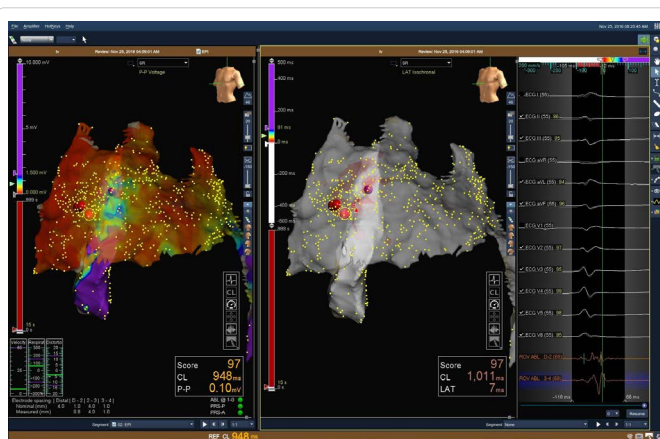


Figure 5: Cardiac mapping defined areas of low voltage and delayed fragmented electrograms in the area of right ventricular outflow tract (RVOT) followed by epicardial ablation of the substrate. Small red dots are tagged sites at which radiofrequency energy was applied.

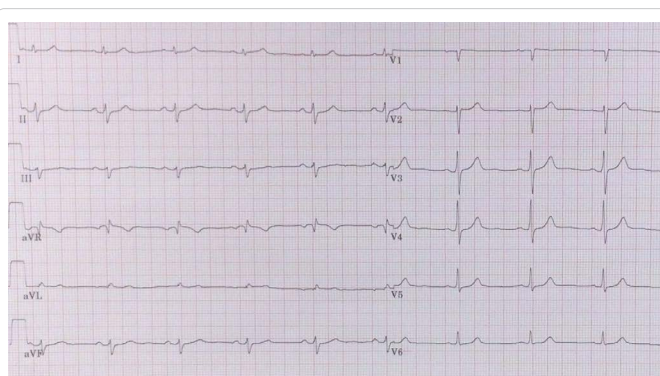


Figure 6: ECG normalization after epicardial ablation.

SALSA MLPA probe mix P108-B2 and SALSA MLPA P114 Long-QT probe mix respectively, according to manufacturer instructions (MRC Holland, <http://www.mlpa.com>).

The NGS analysis of 51 genes associated with primary arrhythmic disorders in the index case identified a total of 273 variants. Following quality and population frequency filters applications, no pathogenic variants were identified in Brugada syndrome related genes. MLPA

analysis was negative for dosage imbalances in the analyzed genes, excluding gene rearrangements as a possible substrate of the arrhythmic phenotype reported.

Despite of the negative result of genetic tests, the pattern of disease segregation in the pedigree could be compatible with an autosomal dominant mode of inheritance with variable penetrance and expressivity (see family tree). The performed NGS analysis cover 18 genes associated with Brugada syndrome (*SCN5A*, *GPD1L*, *SCN1B*, *SCN2B*, *SCN3B*, *RANGRF*, *SLMAP*, *PKP2*, *CACNA1C*, *CACNB2*, *CACNA2D1*, *TRPM4*, *KCNE3*, *KCNH2*, *KCNJ8*, *KCNE5*, *KCND3*, *HCN4*), with an expected diagnostic sensitivity not exceeding 30%.

In the next month our patient experienced 5 FV episodes recorded and efficiently treated by the ICD (Table 1). Multiple ICD shocks, although appropriate, could be not only dangerous, having pro-arrhythmic effects or causing myocardial injury but also psychologically devastating. In this case, medications such as quinidine, restoring normal doming of the action potential, could be an effective option in order to reduce ventricular arrhythmias, but the adverse effects often preclude its use especially for younger patients, who may need these medications for long term [4]. Since our patient didn't tolerate quinidine treatment, we opted for epicardial ablation. Thus, we performed cardiac mapping to accurately define areas of low voltage and delayed fragmented electrograms, followed by ablation with normalization of Brugada pattern (Figures 5 and 6). After 17 months of follow-up, there were no either arrhythmic events or ICD therapy.

Discussion

For many people with BrS, death could be the first clinical manifestation, that means that they would experience their first and potentially lethal arrhythmic event without being protected by ICD. Therefore, identification of patients at high risk of SCD who need ICD is very important but still unresolved and new parameters to be used as a risk-stratifier are strongly necessary.

Our case report describes how clinical diagnosis and therapeutic management can be difficult in Brugada syndrome.

The first clinical presentation of our patient was a "syncopal seizure", probably due to cerebral hypoperfusion during ventricular tachyarrhythmias that could trigger convulsions. Therefore, it is important to consider both epilepsy and arrhythmia during clinical evaluation of seizures. Fauchier et al., described an incidental diagnosis of BrS in a patient with a long-standing history of epilepsy [5-8].

At the initial presentation, our patient could be considered at low risk patient (no clear spontaneous coved pattern, negative drug test, negative EPS, no previous history of syncope) except for the familial history of SCD. However, the patient had another syncope with documented ventricular arrhythmia during the hospital stay and a trans venous ICD was implanted. Moreover, during follow up he had 6 episodes of ventricular fibrillation effectively treated by ICD.

Although we performed an extended genetic analysis covering 18 brugada syndrome genes and 51 total genes associated with inherited cardiac arrhythmias, in order to better identify complex genotypes and possible overlaps syndromes, we could not identify any mutation in this patient. This is not unexpected considering that known genes account for around 25-30% of Brugada syndrome patients. Furthermore, complex models of inheritance are emerging with digenic-polygenic contribution needed for a fully manifest phenotype (Gualandi et al., mutation load). Whole exome/genome sequencing should be an

approach to find new gene mutation associated to Brugada syndrome in this family for the following study.

Conclusion

Our case suggests as clinical presentation of Brugada syndrome can vary greatly and diagnosis and management may be challenging. Therefore, in our opinion, research should focus on the understanding of the complex inheritance and incomplete penetrance as well as on how the interaction between different genes does impact on the phenotype, in order to allow a more reliable pre-symptomatic detection and to optimize risk stratification towards a personalized management of Brugada syndrome.

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