A case series of Brugada syndrome with a novel mutation in the ankyrin-B gene: an unusual unmasking in acute myocarditis

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Background
Brugada syndrome (BrS) is a genetically heterogeneous channelopathy that may lead to sudden death. We report a novel mutation of the ankyrin-B gene that is probably related to the occurrence of BrS in two brothers.

Case summary
First, we present the case of a 27-year-old male who was admitted to the hospital with acute myocarditis. The patient showed left ventricular dysfunction and was given carvedilol. Six days later, while asymptomatic and afebrile, the patient exhibited an electrocardiogram (ECG) with repolarization ‘saddleback’ ST changes in V2. A procainamide provocative test was performed with a response for Type 1 Brugada ECG pattern. Genetic testing revealed a novel mutation, c.5418T>A (+/-) (p.His1806Gln), in the ankyrin-B gene encoding. His 34 years old brother had an ECG J point elevation in leads V1 and V2 of 1 mm not fulfilling diagnostic criteria for Brugada ECG pattern. He also experienced arrhythmia-related syncope. Flecainide provocation test changed ECG towards a Type 1 Brugada pattern. A subcutaneous implantable defibrillator (ICD) was implanted. Patient 1 remains asymptomatic while Patient 2 experienced an appropriate ICD shock during follow-up.

Discussion
In this case series, two brothers with BrS exhibited the same mutation of the ankyrin-B gene. Ankyrin-B is associated with the stability of plasma membrane proteins in the voltage-gated ion channels. Our finding provides a foundation for further investigation of this mutation in relation to BrS. Moreover, the timing of its presentation raises concerns as to whether myocarditis or beta-blockers are associated with the presentation of BrS ECG.

Keywords
Brugada syndrome • Case series • Mutation • Electrophysiologic study • Provocation test

Learning points
- A novel mutation, c.5418T>A (+/-) (p.His1806Gln), in the ankyrin-B gene may be associated with the appearance of Brugada syndrome in two brothers.
- Myocarditis, even in the non-acute phase, and carvedilol administration can be associated with the presentation of repolarization changes on the electrocardiogram.
- Genotypic information needs to be considered in the context of clinical assessment in the diagnostic and decision-making process in inherited arrhythmic syndromes, since the same genotypic variant can have different phenotypic expressions.
Introduction

Brugada syndrome (BrS) is a common cause of sudden death in young people who have no clear structural myocardial anomalies. It is a genetically heterogeneous autosomal dominant channelopathy with variable penetrance that affects the sodium channel and interferes with the proper generation of the cardiac action potential.

The investigation of BrS genetics is currently a hot topic; however, it is more complex than the other primary arrhythmia syndromes. Although only rare variants in SCN5A have been definitively associated with BrS to date, more than 20 genes have been implicated in BrS presentation. However, at least two-thirds of individuals with a clinical diagnosis of BrS or an isolated Type 1 Brugada electrocardiogram (ECG) pattern do not have a known mutation. Notably, the majority of mutations in BrS are found in single individuals or small families.

Timeline

| Patient 1 | Event                                                                 |
|-----------|----------------------------------------------------------------------|
| Day 1     | Fever, sore throat, and chest discomfort                              |
| Day 3     | Admission to hospital with diagnosis of myocarditis                  |
|           | Initiation of carvedilol 6.25 mg × 2                                  |
| Day 4     | Increase of carvedilol to 12.5 mg × 2                                |
| Day 6     | Electrocardiogram (ECG) with repolarization ST changes in V2, similar to 'saddleback', indicative of Type 2 Brugada ECG pattern |
| 3 months  | Provocation test revealed a Type 1 Brugada ECG pattern                |
| 6 months  | Genetic testing revealed a mutation: c.5418T>A (+/−) (p.His1806Gln), ankyrin-B gene, exon 38 |
| 5 years   | No adverse events in our patients                                    |
| Patient 2 |                                                                      |
| 2 years before | Multiple presyncopal and syncopal episodes                          |
| Day 1     | ECG with elevation of J point in V1 and a concave upwards ST elevation in V2 |
| 1 month   | Provocative test revealing a Type 1 Brugada ECG pattern and an electrophysiological study with induction of ventricular fibrillation |
|           | Implantation of a subcutaneous defibrillator                         |
| 1 year    | Genetic testing revealed the same mutation: c.5418T>A (+/−) (p.His1806Gln) ankyrin-B gene, exon 38 |
| 2 years   | Experienced an appropriate implantable defibrillator shock due to ventricular tachycardia |

Case presentation

Patient 1

A 27-year-old male without significant clinical history was admitted to the hospital with sudden-onset chest pain unrelated to exercise. He had had febrile illness and sore throat for the previous 2 days. On admission, blood pressure, heart rate, and body temperature were 120/75 mmHg, 82 b.p.m., and 37.6°C, respectively. His clinical examination showed no pathological signs other than an erythematous pharynx.

The initial ECG (Figure 1A) was unremarkable. Echocardiography showed a left ventricular ejection fraction of 50% with mild hypokinesia of the posterior and lateral wall. Laboratory tests showed a white blood cell count of 11.7 × 10⁹/μL (81% neutrophils), serum C-reactive protein 41 mg/L, and high sensitivity cardiac troponin 1530 pg/mL with a maximum value that reached 2190 pg/mL on the second day of his hospitalization. The patient was diagnosed with acute myocarditis and was referred for cardiac magnetic resonance imaging (MRI), which confirmed the findings of myocarditis with the presence of contrast enhancement (Figure 2).

The patient was placed on carvedilol 12.5 mg × 2. From the second day of hospitalization, he was afebrile and asymptomatic. Four days later, and while he was still asymptomatic and afebrile with a fall in troponin levels, his ECG revealed repolarization ST changes in V2, similar to ‘saddleback’, indicative of Type 2 Brugada ECG pattern (Figure 1B). These ECG features were absent from previous ECGs, suggesting an association with either the myocarditis or the beta-blocker treatment.

The patient was not receiving any other medication that could be associated with ECG changes, while serum chemistry—apart from troponine—was normal including electrolyte levels (serum sodium 141 mEq/L, potassium 4.2 mEq/L). The ECG findings persisted, although temperature remained at a subfebrile level. The beta-blocker was discontinued and a day later the ECG returned to its previous pattern.

The patient did not report any past syncopal episodes or other symptoms that could be related to arrhythmical events. Furthermore, none of his family had any documented inherited arrhythmia-related disease nor any report of sudden death until then. The patient was put on 24-h Holter monitoring, which showed no arrhythmological findings.

Three months later, the patient repeated the cardiac MRI, which showed that the pathological findings had diminished. A provocative test with procainamide infusion (at a dose of 10 mg/kg for 10 min i.v.) was performed with a typical response for Type 1 Brugada ECG pattern (Figure 3). After that the patient was referred for an electrophysiological study (EPS) with programmed ventricular stimulation, at two right ventricular sites (apex and outflow tract) using two drive train cycle lengths up two extrastimuli at each site, which proved negative. The patient was followed up and a family screening was recommended.

Genetic testing of his immediate family focused on several genes described in the BrS research literature (ABCC9, AKAP9, CACNA1C, CACNA2D1, CACNB2, DSG2, GPD1L, KCN4, KCND2, KCND3, KCNE3, KCNE5, KCNH2, KCNJ8, PKP2, RANGRF/MOG1, SCN1B, SCN2B, SCN3B, SCN5A, SCN10A, SEMA3A, TRPM4), using next generation sequencing confirmed by Sanger sequencing. It was revealed that the patient carried a novel heterozygous variant, c.5418T>A (+/−) (p.His1806Gln), on the ankyrin-B gene, exon 38, which may be linked with a genetic predisposition for BrS. Our patient is monitored once a year in our outpatient clinic and remains asymptomatic.
Patient 2

From the family screening it was determined that the patient’s brother—34 years old—had been experiencing presyncopal and syncopal episodes, while his parents (mother aged 63 years and father 65) were asymptomatic. His brother’s ECG showed a J point elevation in leads V1 and V2 of 1 mm not fulfilling diagnostic criteria for Brugada syndrome. Further investigations were undertaken.

Figure 1 (A) Electrocardiogram of the first patient on admission for fever due to acute myocarditis. (B) Electrocardiogram of the same patient on the sixth day of admission, showing a pattern similar to Type 2 Brugada electrocardiogram pattern, with a ‘saddleback’ appearance of the ST segment in lead V2. ECG, electrocardiogram.

Figure 2 Cardiac magnetic resonance imaging confirming the diagnosis of myocarditis showing increase myocardial signal hyperintensity and late gadolinium enhancement involving the posterolateralbasal and lateral wall of the left ventricle (annotated by yellow arrows).
for Brugada ECG pattern (Figure 4). His symptoms occurred in upright and seated position and always preceded by palpitations which was suggestive of arrhythmia-related syncope.

He was admitted to the city’s arrhythmia centre, where he underwent a flecainide provocation test for BrS, during which the ECG changed towards a Type 1 Brugada ECG pattern (Figure 5). An EPS was performed with programmed ventricular stimulation. At the right ventricular apex and at a drive train cycle length of 400 ms with two extrastimuli ventricular fibrillation was induced, which was cardioverted with a 200 Joule defibrillator shock. A subcutaneous implantable defibrillator (ICD) was implanted and a conditional zone at 200 b.p.m. and a shock zone at 230 b.p.m. were programmed. In addition, he underwent a genetic examination that revealed the same mutation as his brother.
Notably, Patient 2 experienced an appropriate ICD shock during follow-up.

Discussion

We report the case of two brothers who had BrS and both exhibited the same new mutation on the ankyrin-B gene. Although the specific mutation found in heterozygosity in both siblings has not yet been shown to be responsible for certain pathophysiological consequence, it could be related to their pathologic phenotype.

BrS is one of the most common inherited channelopathies associated with an increased risk of sudden cardiac death. According to the European Society of Cardiology guidelines, diagnosis of BrS occurs either spontaneously or after provocative drug test with intravenous administration of sodium-channel blockers (such as ajmaline, flecainide, procainamide, or pilsicainide). In our case series, the two brothers were treated in different hospitals, where the choice of procainamide in one case, and flecainide in the other, had to do with the availability of the drug. However, both pharmacological approaches for provocative drug test are recommended by the current guidelines.

There is an ongoing debate regarding the value of conducting EPS for risk stratification of those patients. It should be noted that according to current ESC guidelines for the prevention of sudden death, ICD implantation should be considered in patients with a spontaneous diagnostic Type 1 Brugada ECG pattern and history of syncope (Class IIa), and may be considered in patients with a spontaneous diagnostic Type 1 Brugada ECG pattern and history of syncope (Class IIa), and may be considered in patients with a diagnostic presentation of BrS who develop ventricular stimulation (VF) during programmed ventricular stimulation (PVS) with two or three extrastimuli at two sites (Class IIb).

Although Patient 2 presented with symptoms suggestive of arrhythmia-related syncope, ECG did not fully satisfy the criteria for spontaneous Type 1 BrS. Consequently, the decision to perform EPS in Patient 2 helped further the risk stratification and re-enforced the decision of ICD implantation. It should be kept in mind that both indications have a C level of evidence, which indicates that they are not based on strong data, and studies are needed to document these recommendations.

Ankyrins are required to maintain the integrity of the plasma membranes and to anchor specific ion channels, ion exchangers, and ion transporters in the plasma membrane. Their dysfunction is implicated in numerous diseases, including arrhythmological diseases, neurodegeneration of Purkinje cells, and BrS. More specifically, ankyrin-B mutations are associated with cardiac dysfunction due to abnormal coordination of multiple ion channels and transporters, such as Na/K ATPase and Na/Ca exchanger. Ventricular myocyte express ankyrin-B and its importance in the electrophysiological properties of myocardium has been indicated by many experimental studies in the literature, given the great pathophysiological importance of ankyrin B on cellular integrity and normal function, we cannot rule out an association of this mutation with a possible myocarditis genetic predisposition.

Despite the fact that both brothers had the same mutation, they had different phenotypes and different clinical manifestations. Notably, individual genotypes can map to numerous phenotypes via developmental variations. Different degrees of expression in different individuals may be due to variation in the allelic constitution of the remaining genome. In many cases, the same mutation is not always expressed in the same way due to differences of penetrance and expressivity, partially explained by the actions of gene modifiers. This explains the fact that the same mutation was associated with different phenotypic expressions in the two siblings, in one case myopathic and in the other arrhythmogenic.

Although the knowledge of the genotype is valuable and may influence the decision-making, patient management was based on the clinical symptoms and the findings from the laboratory test since so far in the guidelines the genotype does not change the therapeutic approach in BrS.

More studies are needed to evaluate the effects of genotype on disease expression in order to use genetic testing for clinical decision-making. Consequently, the identification of this gene variant did not affect our therapeutic approach. But that could happen in the future if additional data for specific mutation support the role of genotype information in clinical decision of BrS. For now, genotype and cascade screening in family members may facilitate the detection of individuals who are at higher risk for the appearance of BrS and need a closer follow-up.
Our patient exhibited Brugada pattern on his ECG while under treatment for myocarditis. Up to now, acute myocarditis has rarely been described in BrS. Nevertheless, we know that an inflamed myocardium may be associated with the discovery of a Brugada-like ECG. In the present case, the Brugada ECG pattern appeared after the patient’s acute myocarditis had been treated and was not related to fever.

It is also of interest that the only other factor that might have been involved in the provocation of the Brugada-like ECG was carvedilol administration. Carvedilol administration followed by the appearance of the patient’s acute myocarditis had been treated and was not related to fever.

On the other hand, although beta-blocker intoxication may reveal Brugada ECG pattern, carvedilol has been proposed in the literature as an alternative for protection against malignant ventricular arrhythmias in patients with BrS. On the basis of our case, this possibility should be viewed with scepticism until well-designed studies have provided more evidence and shed further light on the matter.

We should emphasize the lack of evidence proving causation of carvedilol on the repolarization changes of ECG. In contrast, the existence of myocarditis or any other inflammatory triggering factor may be implicated in the appearance of Brugada ECG pattern. It is important to point out how different clinical manifestations can occur despite the same genetic mutation and the same mutation may exhibit not only a wide spectrum of symptoms but also a variable expressivity on the response to treatment.

Conclusions

We present a case series of two brothers who both had BrS and a novel mutation in the gene encoding ankyrin-B. Although the functional effect of the founder mutation has not yet been clarified, this mutation may provide a genetic predisposition to this syndrome. Moreover, the timing of its presentation raises concerns as to whether beta-blockers may be associated with the presentation of Brugada ECG pattern.

Lead author biography

Maria E. Marketou is Consultant in the Department of Cardiology of Heraklion University Hospital, Greece. She is an ESC Fellow. She has been working in the Coronary Care Unit and participating in various diagnostic and therapeutic procedures in the catheterization and clinical electrophysiology laboratory. She is also very active in the hypertension and cardiovascular prevention outpatients’ clinic, in addition to her regular duties for the wards in the Cardiology Clinic. Her main research interests are focused in genetics and molecular cardiology.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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