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CASE REPORT
Arrhythmias/Electrophysiology

A case report of a young patient with both Brugada and long QT3 syndrome: between the hammer and the anvil

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Background Brugada syndrome (BrS) is an inherited disorder associated with increased risk of ventricular arrhythmias and sudden cardiac death. The most common genetic alteration is a loss of function mutation of SCN5A gene. Several mutations in SCN5A gene were found to be associated with an overlap phenotype of both BrS and long QT3 (LQT3) syndrome.

Case summary We report of a 29-year-old man with familial LQT3 syndrome that was diagnosed at age 6 during evaluation of syncope. He has been treated for several years with Flecainide. Now presented with recurrent episodes of syncope. Electrocardiogram (ECG) upon admission was notable for Brugada type 1 pattern that was attenuated after Flecainide was discontinued. Genetic analysis revealed SCN5A 1790D>G mutation that is associated with overlap of LQT3 and BrS. Due to recurrent syncope and difficult management of both LQT3 and BrS, an implantable cardioverter-defibrillator was implanted together with beta-blockers treatment. The patient was discharged home with no evidence of Brugada type 1 pattern on his ECG. He had no further syncope or arrhythmias during 6 months of follow-up.

Discussion There are few reports describing the phenotypic overlap between LQT3 and BrS. Despite the confirmed genetic link between both syndromes, their management strategy is controversial. In particularly, the treatment with sodium channel blockers for LQT3 syndrome may increase the risk for arrhythmias in patients with coexisting BrS. The present case demonstrates the link between LQT3 and BrS and the difficult dilemma in the management of these patients.

Keywords Brugada syndrome • Long QT syndrome • Implantable cardioverter-defibrillator • Case report

Learning points

- Physicians should be aware of possible genotype–phenotype overlap between long QT3 (LQT3) syndrome and Brugada syndrome (BrS) caused by specific SCN5A gene mutations.
- Flecainide should probably be restricted or used cautiously and with the back-up of an implantable cardioverter-defibrillator in patients with combined LQT3 syndrome and BrS.
- Overlap syndromes provide a challenge in diagnosis, treatment, and clinical management.
- Genetic analysis is an essential tool for diagnosis and planning the management of such combined syndromes.

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Introduction

Brugada syndrome (BrS) is an inherited disorder associated with increased risk of ventricular arrhythmias and sudden cardiac death. The syndrome is inherited in an autosomal dominant manner with incomplete penetrance. The most common genetic alteration is a loss of function mutation of SCN5A gene, encoding the α-subunit of the cardiac sodium channel (Nav1.5).[1] This gene is also associated with other hereditary arrhythmias such as long QT3 (LQT3) syndrome with a gain of function of the Na channel, sinus node dysfunction, and cardiac conduction disease.[2–5] The SCN5A-D1790G mutation was found to be associated with an overlap phenotype of both BrS and LQT3 syndrome. Thus far, only several cases describing this unusual phenotype have been reported.[6–10]

In the following case, we report of a young patient that was diagnosed in childhood with LQT3 syndrome and now presented with recurrent syncope and Brugada electrocardiogram (ECG) pattern.

Timeline

1996	The patient was diagnosed with long QT3 syndrome at age 6 during evaluation of syncope, and Flecainide was initiated.
2015	Genetic analysis revealed that the patient and two family members had SCN5A 1790D>G mutation.
November 2019	He was hospitalized in another hospital with syncope and prolonged QT after discontinuation of Flecainide.
December 2019	Current admission in our institute was due to recurrent syncope. Electrocardiogram was consistent with type 1 Brugada pattern. Due to recurrent syncope and difficulty in medical management of both Brugada and long QT syndromes, an implantable cardioverter-defibrillator was implanted together with beta-blockers treatment. The Brugada pattern resolved after discontinuation of Flecainide.
June 2020	During 6 months of follow-up, the patient remained asymptomatic, without evidence of further arrhythmias or syncope.

Case presentation

A 29-year-old man with known familial LQT3 syndrome was admitted to our department with recurrent episodes of syncope. He was diagnosed with LQT3 syndrome at age 6 during evaluation of syncope. Initially, he was treated with Metoprolol and subsequently with Flecainide since his QT interval remained prolonged despite beta-blockers treatment. Baseline ECG (*Figure 1*) demonstrates typical features of LQT3 syndrome including prolonged ST-segment, late onset of T-wave and prominent U-wave (lead C2 and C3).

Three weeks before admission, he was hospitalized in another hospital due to syncope following discontinuation of Flecainide. Electrocardiogram revealed prolonged QT interval of more than 500 ms. Treatment with Flecainide was reinitiated with adequate QT shortening and he was discharged home after refusing an implantable cardioverter-defibrillator (ICD) implantation.

His present admission was due to recurrent syncope despite Flecainide treatment. He felt dizziness and then collapsed. Physical examination was unremarkable. Blood pressure was 119/73 mm/Hg in supine position, with no evidence of orthostatic hypotension. Heart rate was 58 b.p.m., temperature was 36.6°C, and saturation was 99% in room air. Laboratory tests including potassium, sodium, calcium, and magnesium levels were all within normal range. Unexpectedly, ECG showed typical findings of Brugada type 1 pattern with right bundle branch block and ST-elevation in V1–3 leads (*Figure 2*). Echocardiography revealed normal left and right ventricular size and function without any valvular disorder. Due to recurrent syncope, difficulty in medical management of both Brugada and long QT syndromes, and relative bradycardia attributed to the medical treatment and LQT3 (*Figure 1*), a dual-chamber ICD was implanted. Notably, subcutaneous ICD was not chosen due to the need for atrial pacing. Finally, he was discharged with Propranolol sustained release 80 mg daily, and the ICD was programmed to DDD pacing mode at a rate of 70 b.p.m., to facilitate QT shortening. The successful combination of atrial pacing and beta-blockers treatment resulted in a QTc interval of 450 ms and only a subtle Brugada ECG pattern (*Figure 3*).

Genetic analysis was positive for SCN5A 1790D>G mutation, which is associated with the overlap syndrome of LQT3 and BrS.[11] The patient's mother and a brother were also found positive for this specific mutation (*Figure 4*). The mother's ECG was remarkable for prolonged QTc interval of 460–480 ms, and appearance of Brugada type 2 pattern after Flecainide initiation, and the brother's ECG was significant for sinus bradycardia, prolonged QTc of 470 ms and alternate Brugada pattern. During 6 months of follow-up, our patient remained asymptomatic, without evidence of further arrhythmias or syncope.

Discussion

There are only few reports describing the phenotypic overlap between LQT3 and BrS. Bezzina *et al.*[12] were the first to describe such phenotypic overlap in a Dutch family with insertion mutation of 1795insD. Veltmann *et al.* [13]described mutations leading to simultaneous manifestation as LQT3 and BrS and Priori *et al.*[14] showed the possibility of Brugada type 1 pattern after administration of Flecainide in a subset of patients with LQT3.

Despite the confirmed genetic link between both syndromes, there are significant differences in their management. Expert consensus document recommends to avoid triggers such as fever, alcohol consumption, and specific medications including sodium channel blockers that may enhance lethal arrhythmias in patients with Brugada.[15] Importantly, Quinidine and Isoproterenol are the treatment of choice to prevent and suppress ventricular arrhythmias in BrS. On the other hand, the recommendations for LQT focus on the use of beta-blockers as a first line of treatment, whereas sodium channel blockers such as Flecainide and Mexiletine can be useful, as add-on therapy for LQT3 patients. The use of ICD for primary and secondary prevention in both syndromes is also discussed in detail.[15]

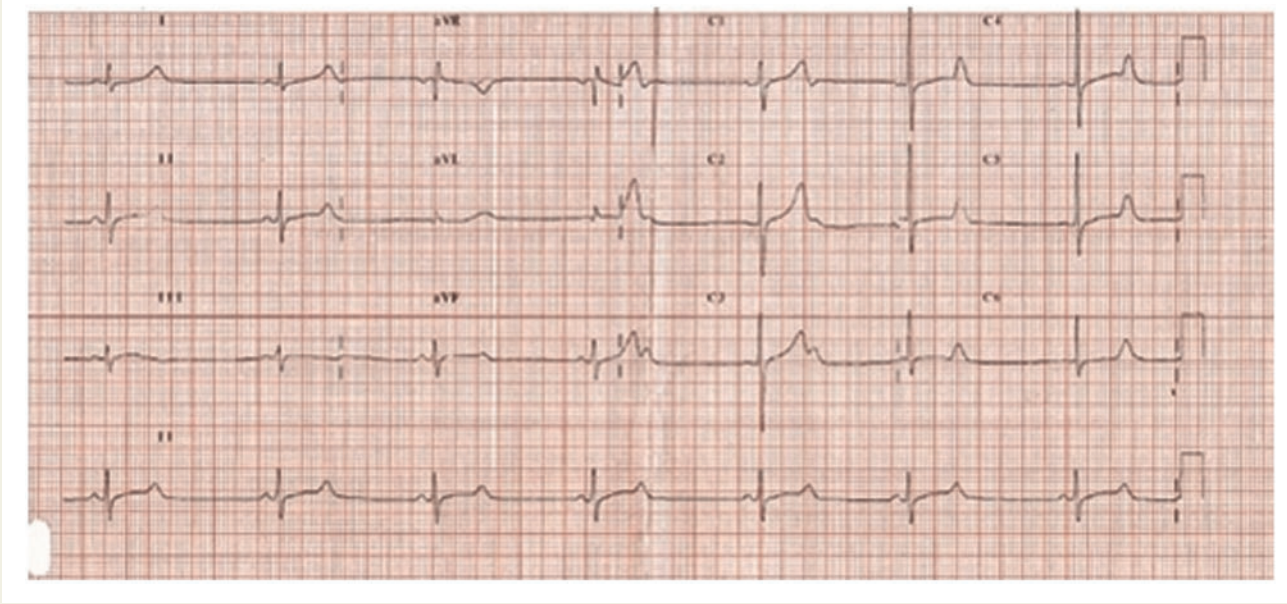

Figure 1 Baseline electrocardiogram demonstrates prolonged QT interval with QTc of 490 ms, prolonged ST segment, late onset of T-wave and prominent U-wave (lead C2 and C3) which are typical of long QT3 syndrome.

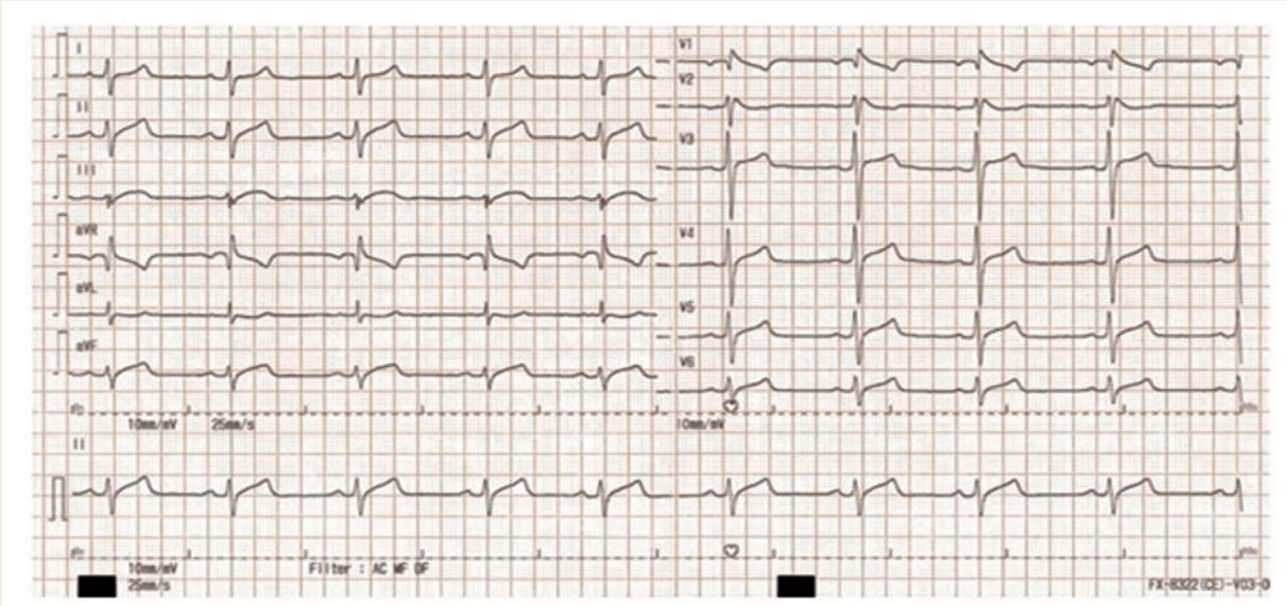

Figure 2 Electrocardiogram after administration of Flecainide 100 mg twice daily. Note the appearance of Brugada type 1 pattern in the right precordial leads and shortening of the QT-interval compared with the baseline electrocardiogram. QTc: 426 ms; PR: 188 ms.

Administration of sodium channel blockers may shorten the QT interval in patients with LQT3 but exacerbate ST-segment elevation in patients with BrS. This provides a challenge in the treatment of patients with simultaneous manifestations of LQT and Brugada, particularly due to the increased risk of malignant arrhythmias resulting from sodium channel blockers.

In our patient with diagnosed LQT3, the use of Flecainide unmasked the presence of BrS. Mexiletine could potentially serve

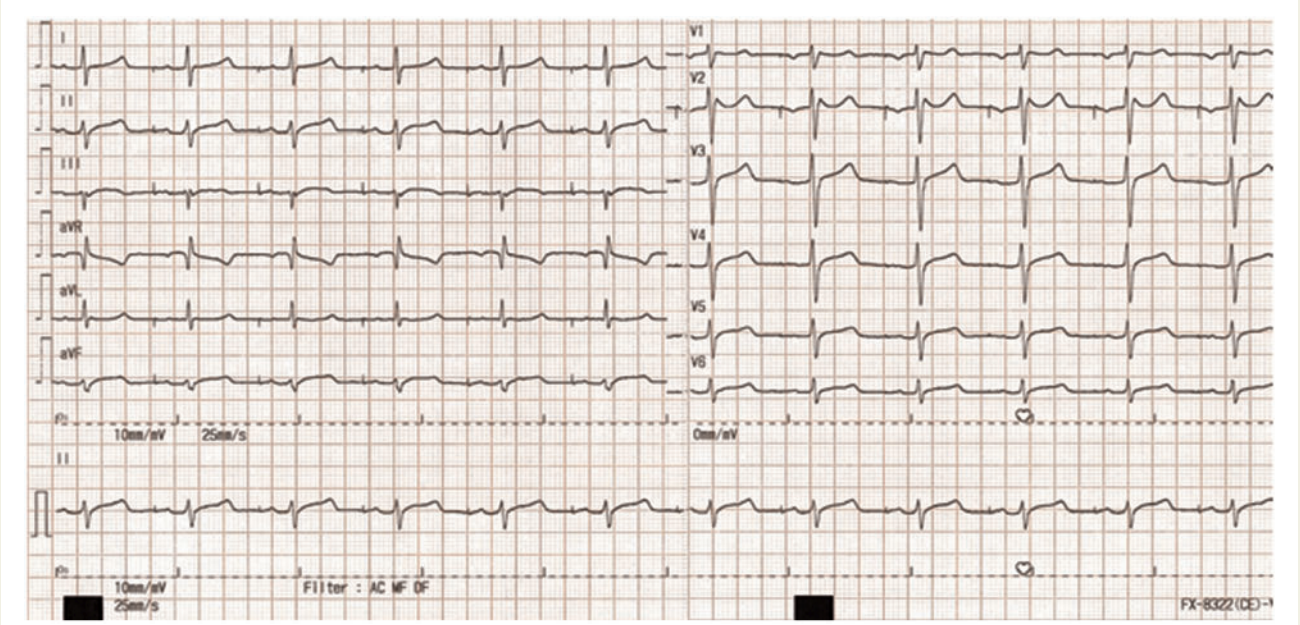

Figure 3 Electrocardiogram after implantable cardioverter-defibrillator implantation and discontinuation of Flecainide. On treatment with propranolol 80 mg daily. QTc: 450 ms; PR: 200 ms.

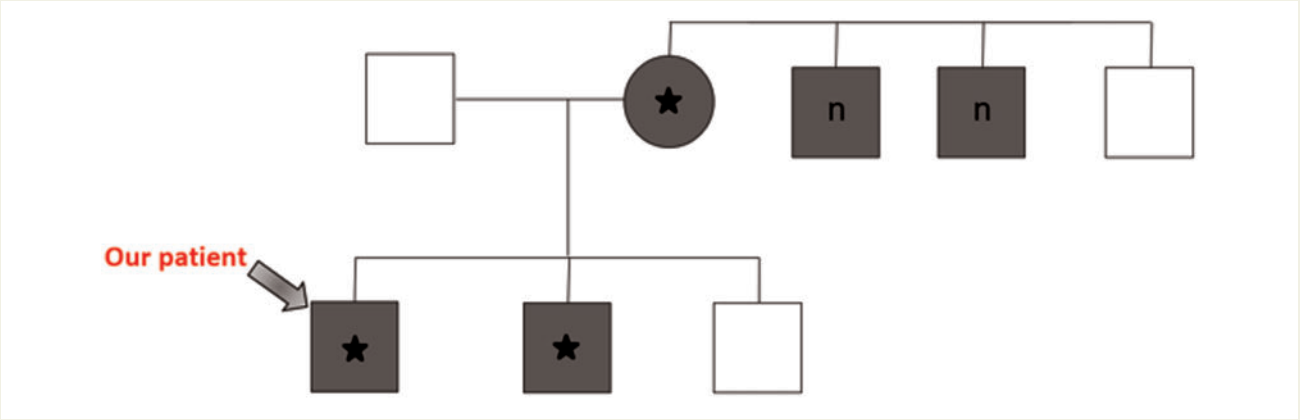

Figure 4 The family pedigree. Our patient is marked with an arrow. 'n': Positive phenotype. Genetic testing was not performed. (Asterisk) Genetic analysis consistent with SCN5A D1790G mutation.

as a second line of treatment in LQT3 without aggravation of Brugada pattern, although we have not tried it in our case. Ultimately, in the presence of overlap syndrome, recurrent syncope, and difficult medical management, we decided to proceed with ICD implantation together with beta-blockers treatment and atrial pacing.

This case demonstrates the link between LQT3 and BrS and the difficult dilemma in the management of these patients. One should be aware of the possibility of phenotypic combined inherited arrhythmogenic syndromes caused by number of mutations in SCN5A gene. The recognition of such conditions may change the management strategy and influence the prognosis of these individuals.

Lead author biography

Dr. med. Ala Abu Dogosh was born in Beer-sheva, Israel, in 1988. He graduated in 2014 from Ulm university in Germany. He is in his final year of residency in the Department of Cardiology at Soroka University Medical Center.

Supplementary material

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

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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.

Conflict of interest: The authors have no conflict of interest to declare.

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