Proarrhythmogenic effects of lamotrigine during ajmaline testing for Brugada syndrome

Kevin M.W. Leong, MBBS, MRCP,* Henry Seligman, MBBS, MRCP,† Amanda M. Varnava, MD, FRCP*†

*From the *Imperial College Healthcare NHS Trust, London, United Kingdom, and †West Hertfordshire Hospitals NHS Trust, Watford, United Kingdom.*

Introduction

Sodium channel blockade (SCB) with a class Ia or Ic antiarrhythmic agent (eg, ajmaline or procainamide, respectively) is used in the unmasking and diagnosis of Brugada syndrome (BrS). SCB is performed frequently as part of family screening or in symptomatic patients with a suggestive electrocardiogram (ECG), and concurrent medications known to potentiate arrhythmias or contraindicated in BrS are withheld prior to testing.[1] Lamotrigine (LTG) is currently not contraindicated in BrS or known to be potentially arrhythmic during testing with SCB agents. We report a case illustrating its arrhythmogenic potential and the implications of its concurrent usage during such testing in clinical practice.

Case report

A 60-year-old woman was referred following the sudden death of her paternal half-brother (proband) at 62 years of age and a diagnosis of BrS in the proband's daughter. Our patient had a lifelong history of collapses and was worked up by a neurologist 14 years earlier, given the increasing frequency of these occurrences. These were described as episodes of loss of consciousness preceded by olfactory hallucinations and/or abdominal discomfort. Her electroencephalogram reported epileptiform activity in both her temporal lobes and she was subsequently diagnosed with temporal lobe epilepsy. She was then commenced on lamotrigine 125 mg twice daily and levetiracetam 1.5 g twice daily, which reduced these episodes to once every other month.

She underwent various cardiac investigations for a family history of sudden arrhythmic death, which included a Holter monitor and echocardiogram that showed no abnormality. In addition to the family history above, there had been multiple deaths involving 3 second-degree relatives (on the paternal side) between the ages of 40 and 60 years, with myocardial infarction and epilepsy as the presumptive etiologies (Figure 1). Given our patient's family history and intermittent episodes of loss of consciousness, she had a loop recorder implanted, which had not revealed any dysrhythmias during her epileptic episodes. She was subsequently referred for an ajmaline test in light of a finding of a pathogenic mutation for BrS in her niece.

Prior to ajmaline testing, a clinical decision was made to continue both her antiepileptics to maintain seizure control, as neither drug was on the list of recommended (class I) drugs to avoid in confirmed BrS.[1] Ajmaline was delivered at an infusion rate of 1 mg/kg over 5 minutes with continuous monitoring via a 15-lead ECG performed in our cardiac day unit. Baseline ECG showed no evidence of a type I BrS pattern and a narrow QRS duration of 116 ms (measured in V_1) (Figure 2A). After 3 minutes of infusion, coved ST elevation >2 mm was observed in the precordial leads with a QRS of 144 ms (Figure 2B). This was immediately followed by gross broadening of the QRS and the development of bigeminy (Figure 2C) as the ajmaline infusion was being stopped. A gradual resolution to baseline ECG appearance was then observed over the following 10 minutes. The patient was not hemodynamically compromised at any point.

The response observed on ECG to SCB may have been related to the patient's underlying condition and/or to the additive inhibitory effects of LTG on voltage-gated sodium channels. To clarify the potential false-positive result, she was counseled for a repeat ajmaline test off LTG. Two weeks after the patient had been fully weaned off LTG, a repeat ajmaline test at the same dosing level and infusion rate produced a type I BrS pattern at 4 minutes with no gross broadening of the QRS or electrical alternans (Figure 3). To complete her risk stratification, she underwent an electrophysiological catheter study with programmed electrical stimulation, which was negative. Our patient and the proband's daughter were genotyped and found to carry a pathogenic SCN5A mutation (neucleotidic change c.361C>T p.Arg121Trp) for BrS. This was also found in one of the proband's sisters on

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KEY TEACHING POINTS

- Epilepsy may coexist with Brugada syndrome (BrS) as part of a cardiocerebral channelopathy.
- Sodium channel blockade (SCB) testing is required to look for underlying BrS, although guidance regarding which antiepileptic medications should be withheld is limited.
- Lamotrigine is potentially proarrhythmogenic during SCB testing in those with BrS, or may cause a false-positive result. A decision to withhold the drug prior to testing should be discussed and considered.

downstream cascade screening, which would make the proband an obligate carrier. None of the family members has had an ECG revealing a spontaneous type I BrS pattern. To date, no arrhythmias have been detected via our patient's loop recorder and the patient has been maintained on levetiracetam and topiramate for her epilepsy.

Discussion

LTG is used in the treatment of epilepsy and reduces neuronal hyperexcitability via its inhibitory effects on voltage-gated sodium channels.[2] Although thought to have a preferential effect on neuronal sodium channels, LTG has reportedly caused a type I Brugada phenocopy on ECG following SCB testing during BrS work-up.[3,4] In both these case reports, the type I Brugada pattern could not be elicited following a repeat SCB test off LTG. In those with underlying loss of sodium channel function, as in our patient with BrS, the additive SCB effects of LTG were sufficient to cause a proarrhythmic change, as evidenced by the development of bigeminy (Figure 2C). It is unclear if the proarrhythmic response observed has a dose-dependent relationship, as this is the first case to report the effects of LTG during ajmaline testing in a patient with underlying BrS. It is worth noting that the BrS phenocopy has been previously elicited on ECG during an ajmaline challenge at LTG doses ranging from 100 mg to 275 mg twice daily in individuals without BrS.[3,4] Levetiracetam binds to neural synaptic vesicle proteins that modulate release of neurotransmitters, and is not likely to have contributed to the findings.

The BrS ECG pattern can be intermittent and provoked by other variables, such as fever, vagal stimulation, electrolyte imbalance, and certain medications. By implication, an individual's proarrhythmic state may also be subject to such variables, resulting in different outcomes on 2 different test days. As far as possible, this was controlled for by there being no differences in the aforementioned factors, with the

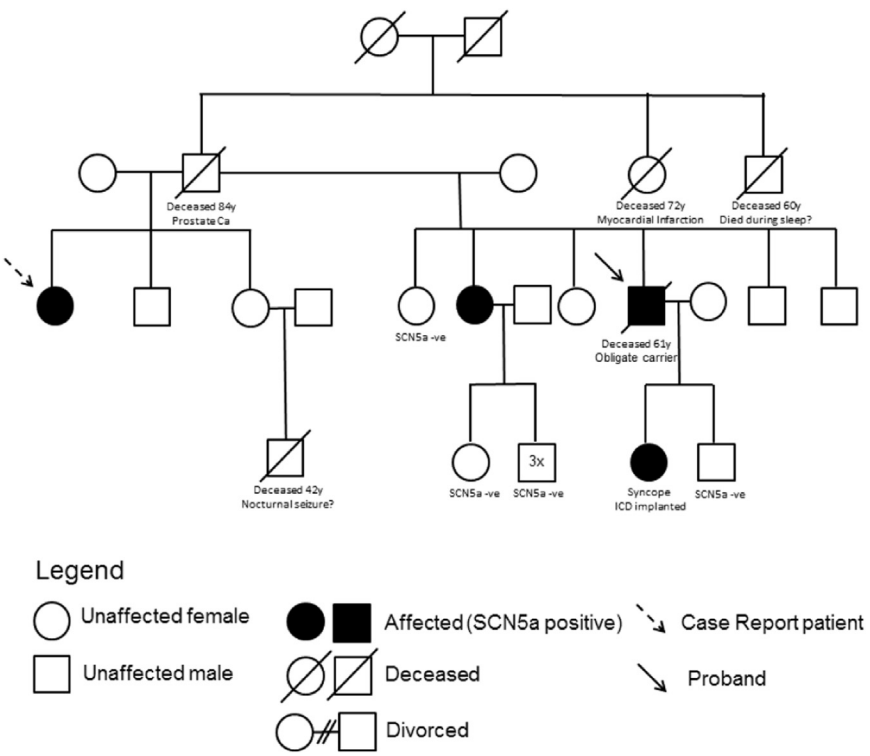

Figure 1 Family tree of case report patient (*dashed arrow*) and proband (*solid arrow*). None of the affected (*shaded*) patients had a spontaneous type I Brugada pattern on electrocardiography.

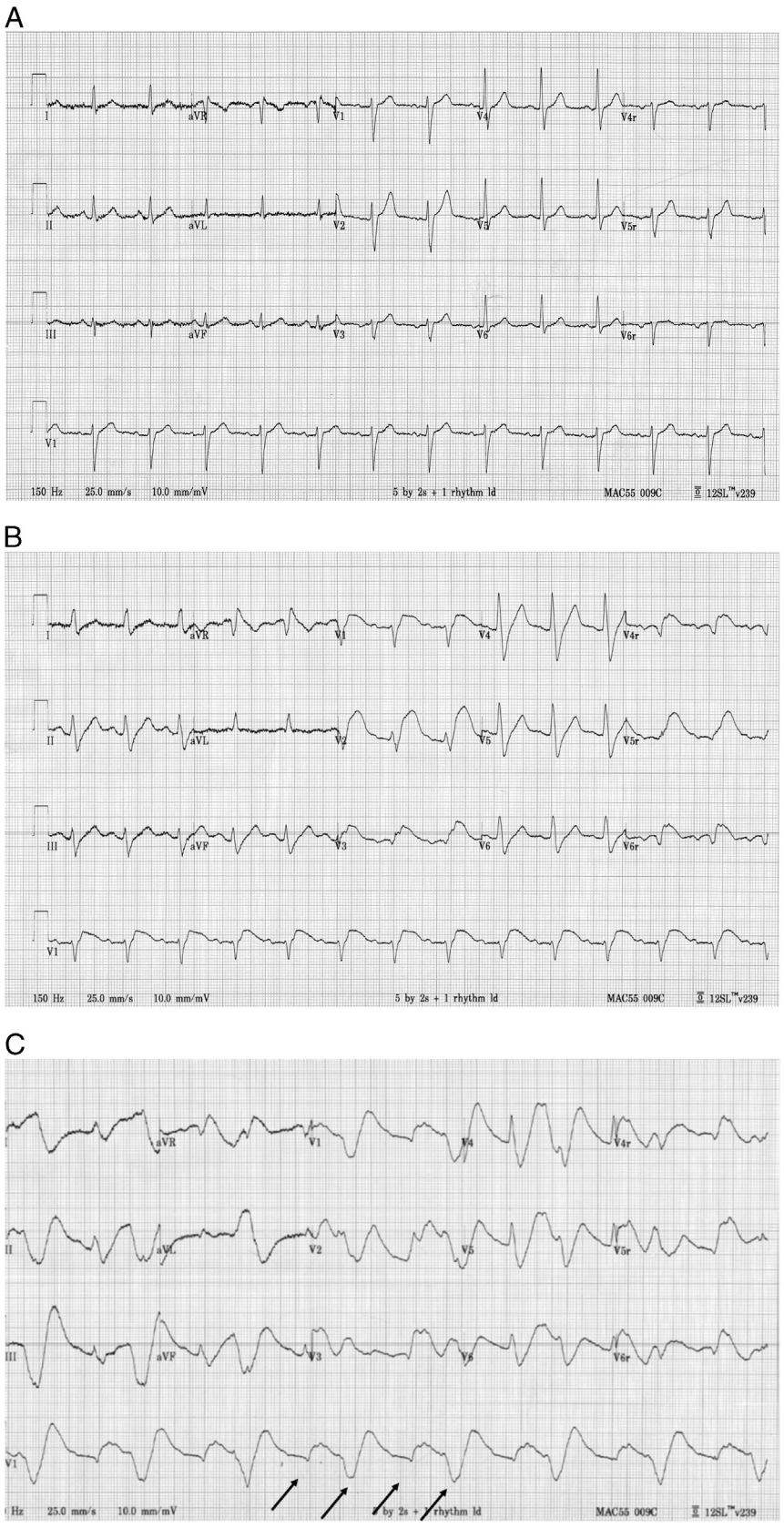

Figure 2 **A:** The 15-lead surface electrocardiogram (ECG) at baseline. Electrodes at V_4R and V_5R were positioned at the left and right second intercostal space, respectively. V_3 and V_6R were positioned at the left and right third intercostal space, respectively. All other electrodes were positioned in their conventional spaces. QRS duration in lead V_1, 116 ms. **B:** The 15-lead ECG with ajmaline testing while the patient was on lamotrigine at 3 minutes. Manifestation of type I pattern in precordial leads and QRS broadened to 144 ms (V_1). Ajmaline infusion stopped at this point. **C:** The 15-lead ECG with ajmaline testing while the patient was on lamotrigine at 3 minutes, 10 seconds. Marked prolongation of QRS complex (measuring 210 ms in V_1). Bigeminal heart rhythm with alternating QRS morphologies indicated by arrows.

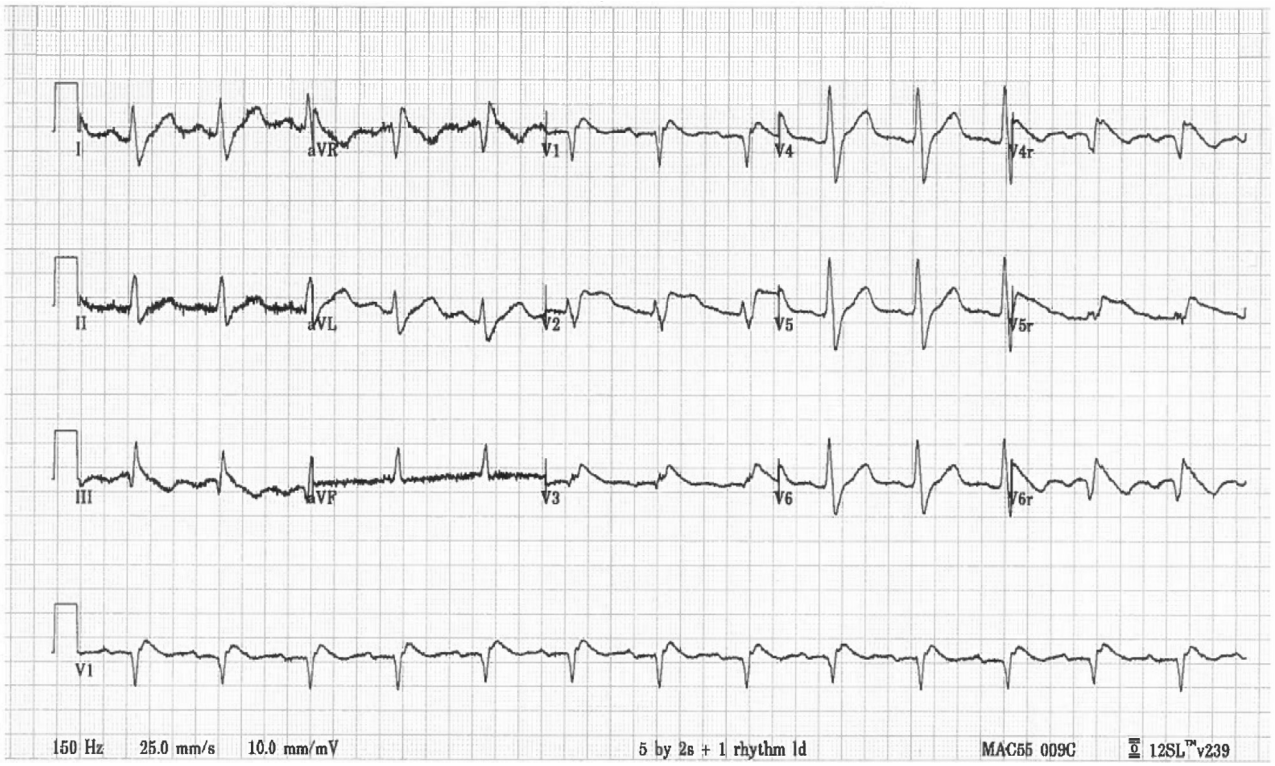

Figure 3 The 15-lead electrocardiogram with repeat ajmaline testing while the patient was off lamotrigine at 4 minutes. Type I BrS pattern in leads V_1, V_2, V_3, V_4R, V_5R, and V_6R with no alternans. QRS duration measured at 146 ms in V_1.

exception of the patient's being off LTG on the second test. Although variable autonomic tone may be a confounding factor, the patient was fasted and relaxed and the test was carried out at the same time of day on both occasions.

The SCN5A mutation (nucleotidic change c.361C > T p. Arg121Trp) found in this family is a single-nucleotide variant on cytogenetic location 3p22.2, which encodes sodium voltage-gated channel alpha subunit 5 in the myocardium. Although associated with BrS, it is not known to increase susceptibility to fatal ventricular arrhythmias, to our knowledge.[5] The genotypic impact on susceptibility to ventricular arrhythmias during an SCB challenge is of interest, especially given the observation that such events occur at higher frequency during SCB test in patients with SCN5A mutations.[6] Given this first case report, it is unclear if the proarrhythmic effect seen with lamotrigine during ajmaline testing can also be observed in individuals with other types of mutations, bearing in mind the variable nature of the genotypic-phenotypic relationship in BrS.

Medications that have a class I recommendation to avoid in confirmed cases of BrS are summarily withheld in those undergoing work-up. Little guidance exists on whether other medications not within this category should also be withheld with SCB testing. The decision is usually undertaken on a case-by-case basis, factoring the need to control other competing comorbidities and the evidence available on the proarrhythmic potential of the drug in question. LTG has had the most plausible effect in this case, as none of the proarrhythmic changes were observed in its absence on repeat testing, other situational factors being similar and despite a longer period of infusion/larger dose given. To further support this notion, there are reports in the literature where overdoses of LTG have led to QRS prolongation, complete heart block, and broad complex tachycardia.[7–9] In addition, LTG, when compared with the SCB effects of flecainide, has shown similar reductions in the maximum rate of depolarization of the action potential in guinea pig Purkinje fibers.[9] The combination of LTG and ajmaline is an important drug interaction to note, given the frequent usage of LTG in epileptic management and the reported coexistence of epilepsy and BrS as part of a cardiocerebral channelopathy syndrome.[10]

Conclusion

We report the first case of LTG's proarrhythmic potential in the setting of SCB testing and the implication this has on working up suspected BrS cases. Consideration should be given to withholding the drug prior to testing and this course should be discussed with the patient and his or her responsible physicians.

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