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Letter to the Editor

Clozapine-associated Brugada syndrome necessitating its discontinuation in an older adult with schizophrenia

1. Introduction

Brugada syndrome (BrS) is an inherited arrhythmia disorder associated with fatal complications such as ventricular fibrillation and sudden cardiac death (SCD) (Argenziano and Antzelevitch, 2018; Kabra et al., 2020). Antipsychotics have long been known to increase the risk of cardiac arrhythmias and SCD, with atypical antipsychotics proving no safer than typical antipsychotics (Murray-Thomas et al., 2013; Ray et al., 2009). Two prior reports have linked clozapine initiation with the development of the Brugada electrocardiogram (ECG) pattern; one was a cross-sectional study (Blom et al., 2014) in which ECG normalization following dechallenge was not assessed; the other was a case report of a middle-aged adult (Sawyer et al., 2017). We aim to add to the body of evidence by describing clozapine-associated BrS (with clinical symptoms) in an older adult with schizophrenia.

2. Case report

A 60-year-old male, a manual labourer, with chronic schizophrenia presented with an acute exacerbation of symptoms. He had type 2 diabetes and dyslipidemia and denied any substance use history. Family history of syncope, SCDs, presyncope, or arrhythmias was negative. Three years ago, following failed trials of oral olanzapine and risperidone, he was initiated on clozapine (up to 50 mg/day), following which he developed two syncopal episodes within a month. He discontinued the medication on his own and did not seek any further evaluation or treatment.

For his current relapse, we initiated him on clozapine 25 mg nightly (the patient or family did not disclose the prior history of syncopal attacks) and increased it to 50 mg daily after five days on an outpatient basis. Within a week of (re)initiating clozapine, he again developed three syncopal episodes accompanied by retrosternal chest pain and inability to lie down; each episode occurred at night and lasted approximately 1–2 min.

We admitted him to the coronary intensive care unit for a detailed evaluation. ECG showed sinus rhythm; heart rate was 58/minute with T-wave inversion in V1 and V3 (modified Brugada lead) (Fig. 1A). ECG taken 30 min (Fig. 1B) and two hours (Fig. 1C) following a flecainide challenge test showed a consistent type 1 Brugada pattern with coved ST-segment elevation ($\geq$ 2 mm) and T-wave inversion in V1 and V3 leads; the pattern resolved following flecainide cessation (Fig. 1D). He was afebrile, and his blood tests, including serial troponins, echocardiogram, chest X-ray, and Holter ECG were unremarkable.

Given the typical ECG changes, presence of clinical symptoms (syncope), and clear temporal correlation with clozapine initiation, we diagnosed clozapine-associated BrS. Clozapine was immediately stopped, risperidone was initiated at 1 mg per day and gradually titrated up to 3 mg per day, along with trihexyphenidyl 2 mg. Serial ECG showed progressive normalisation; V1 and V3 abnormalities normalised 4 days after cessation of clozapine. He was discharged at this point. At six-month follow-up, he remained asymptomatic with no further syncopal attacks, and serial monthly ECGs were within normal limits.

3. Discussion

The present case highlights the need for cardiac evaluation and monitoring during initiation and titration of clozapine, particularly in older adults. International guidelines and consensus statements recommend a baseline ECG for QTc interval check and, if indicated, an echocardiogram before initiating clozapine (Correll et al., 2022; Wagner et al., 2023). However, a prior survey of practicing psychiatrists from India showed variations in clozapine prescribing practices in the Indian setting (Shrivastava and Shah, 2009). Because the index patient was not drug naïve (to clozapine) and because the prior history of syncopal

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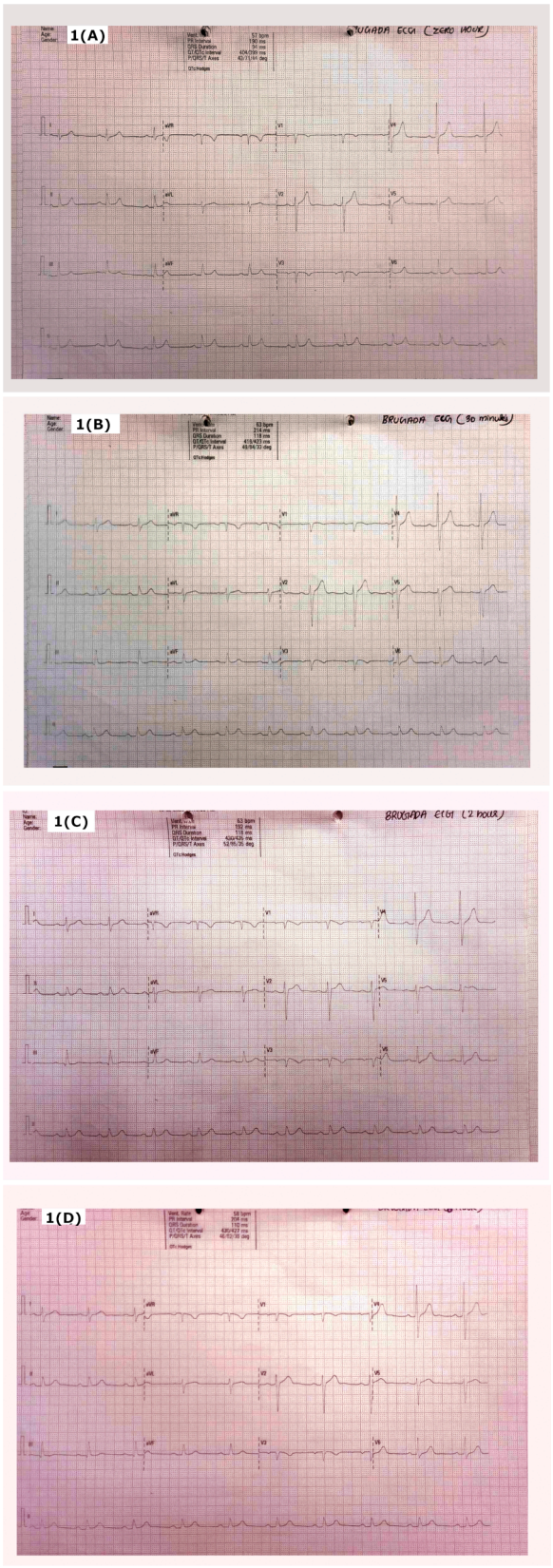

Fig. 1. Electrocardiogram monitoring before and after flecainide challenge.

episodes was unavailable, a baseline ECG was not obtained.

The rapid onset of Brugada pattern ECG following clozapine initiation and prompt reversal of changes after drug cessation strongly support a drug-induced adverse reaction. Whereas risk factors and clinical symptoms of clozapine-associated myocarditis are well documented, much less is known about cardiac arrhythmias with clozapine, not associated with myocarditis. In the index case, rechallenge was unsuccessful and did not attenuate the risk of arrhythmia.

The cardiovascular side effects of psychotropic medications, including Brugada-type ECG changes, are ascribed to blockade of ventricular sodium and calcium channels (Postema et al., 2009). However, the most serious side effect of psychotropics, namely QT prolongation, is typically caused by potassium channel blockade (Mackin, 2008). Whenever a patient on clozapine, and more broadly other psychotropics, presents with symptoms of arrhythmia such as sudden syncope, shortness of breath, or chest discomfort, BrS must be a differential diagnosis (Steinfurt et al., 2015).

The prevalence of BrS is increased in patients with schizophrenia (11.6%); this may also partly explain the increase in SCD in this group (Blom et al., 2014). However, to what extent antipsychotics contribute to this increased prevalence remains unclear. In the study by Blom and colleagues (Blom et al., 2014), more than half of those with a Brugada-pattern ECG were not on a sodium-channel blocking antipsychotic. This raises questions about whether ion channel dysfunction is intrinsic to the pathobiology of schizophrenia. Future studies must examine this possibility and the possibility of additive sodium channel blockade with antipsychotics in individuals with schizophrenia.

Sawyer et al. (2017) described a middle-aged adult with clozapine-associated BrS who also had some risk factors for cardiac disease, such as smoking, sedentary lifestyle, and poor dietary habits, but no metabolic risk factors, as in the index case. This patient developed Brugada-pattern ECG changes at the end of week 2, when on 125 mg clozapine. The index patient had more acute ECG changes at a lower clozapine dose.

To conclude, our report highlights the need for routine, serial ECG monitoring in patients initiated on clozapine. The presence of clinical symptoms of arrhythmia and typical Brugada-pattern ECG changes must prompt immediate discontinuation of clozapine and selection of an alternative antipsychotic that interacts less with sodium channels. Rechallenge may not be beneficial, as shown rather fortuitously in the index case. Fig. 2 outlines a practical algorithm for the evaluation and management of a patient with suspected clozapine-associated Brugada pattern ECG changes. Given the unclear causal evidence linking antipsychotics with BrS in schizophrenia, there is a need for adequately powered studies to confirm this association and elucidate risk factors for BrS in schizophrenia. This will help personalize antipsychotic prescriptions in this group.

CRediT authorship contribution statement

Vikas Menon: Writing – original draft, Methodology, Data curation, Conceptualization. **Pattath Narayanan Suresh Kumar:** Writing – original draft, Methodology, Data curation, Conceptualization. **Rohith Suresh:** Writing – review & editing, Conceptualization.

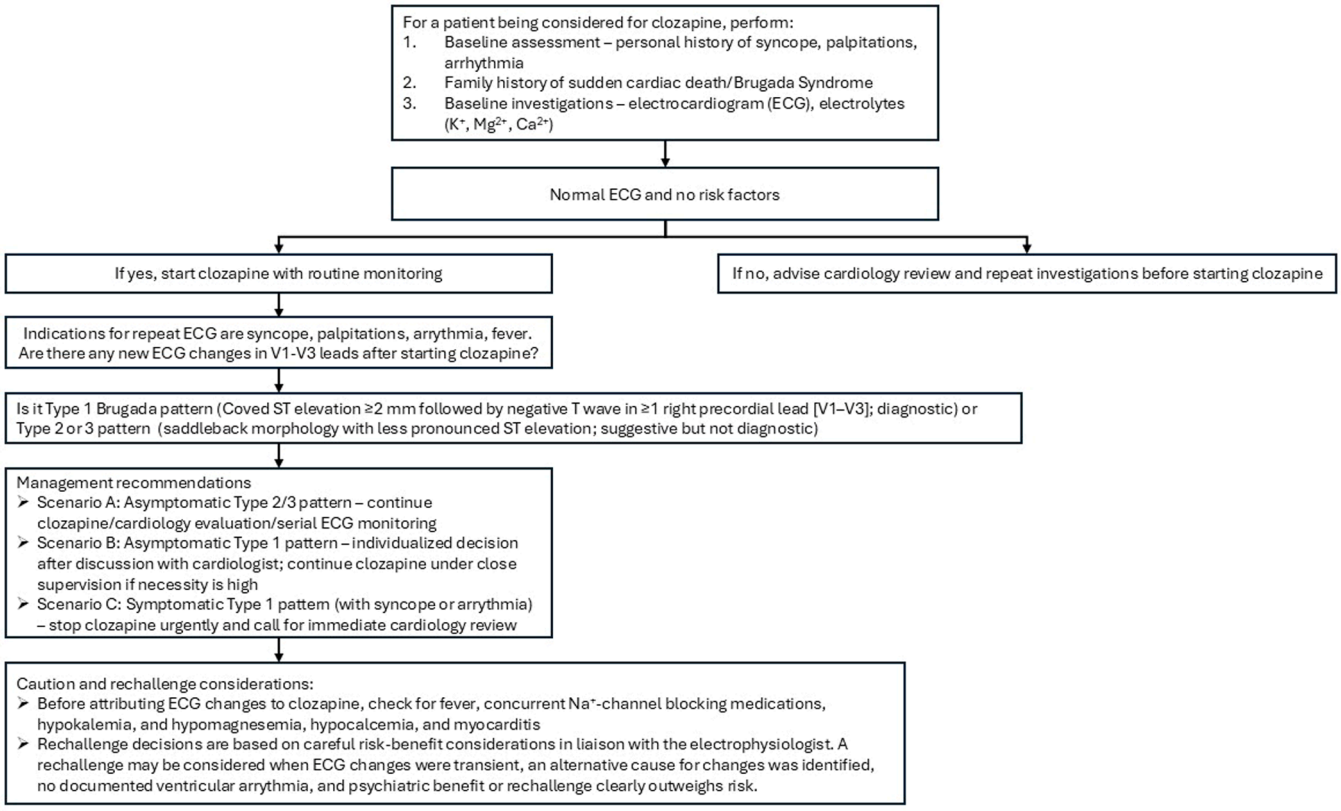

Fig. 2. Approach to evaluation and management of a patient with suspected clozapine-associated Brugada pattern changes in the electrocardiogram.

Informed consent statement

Written informed consent for publication of this report has been obtained from the patient.

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Declaration of Competing Interest

The authors declare no conflicts of interest relevant to the contents of the manuscript.

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