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Brugada-Type Electrocardiographic Changes Induced by Antipsychotics in a Patient with Resistant Schizophrenia: A Case Report

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Abstract | **Case Report**

Brugada syndrome (BrS) is a cardiac channelopathy caused by loss-of-function mutations in the *SCN5A* gene, leading to decreased sodium current and risk of malignant ventricular arrhythmias. Several psychotropic drugs, particularly antipsychotics with sodium channel–blocking properties, have been implicated in unmasking or inducing Brugada-type electrocardiographic (ECG) patterns. We report the case of a young man with treatment-resistant schizophrenia who developed a type-1 Brugada ECG pattern while receiving chlorpromazine, which normalized after drug withdrawal. These effects may be potentiated by high plasma concentrations, drug interactions, or predisposing *SCN5A* variants. Epidemiological studies suggest that patients with schizophrenia may present a higher prevalence of Brugada-like ECG patterns, possibly related to shared ion channel and autonomic dysfunction. Management of schizophrenia in patients with BrS requires careful antipsychotic selection and collaboration between psychiatry and cardiology to minimize arrhythmic risk. Drugs with minimal sodium channel–blocking activity are preferred alternatives. Regular ECG monitoring is recommended during treatment with sodium channel–blocking psychotropics, especially in resistant or poly-treated cases. Early recognition of drug-induced Brugada phenocopy allows safe continuation of psychiatric care while preventing fatal cardiac events.

Keywords: Brugada syndrome, SCN5A, psychotropic drugs, sodium channel, chlorpromazine, schizophrenia.

INTRODUCTION

Brugada syndrome (BrS) is an inherited or acquired cardiac channelopathy characterized on the surface electrocardiogram (ECG) by coved ST-segment elevation in the right precordial leads (type-1 Brugada ECG pattern) and an associated risk of ventricular fibrillation and sudden cardiac death. Although classically linked to pathogenic variants in SCN5A and related genes, Brugada-type ECG changes may also be drug-induced or unmasked by external factors, including certain antiarrhythmics, psychotropic agents and metabolic disturbances [1,2].

Psychotropic medications particularly agents with sodium-channel blocking or membrane-stabilizing properties have been repeatedly implicated in the emergence or exacerbation of Brugada-type ECG patterns. Case reports and reviews have documented reversible type-1 ECG changes temporally associated with tricyclic antidepressants, some antipsychotics (including older phenothiazines and, in rarer reports, clozapine), lithium, and other drugs that alter cardiac ion currents; these observations support a pharmacologic mechanism that reduces inward sodium current (I_Na) or otherwise perturbs repolarization, thereby exposing a latent arrhythmogenic substrate [1,3–6].

Patients with schizophrenia constitute a clinically vulnerable population for cardiac adverse events for several reasons: frequent exposure to psychotropic polypharmacy; higher prevalence of cardiac risk factors and unhealthy lifestyles; and emerging evidence that a subset may harbor intrinsic electrophysiologic vulnerability (higher prevalence of Brugada-like ECG traits reported in some cohorts) [2,4,7]. These converging risks motivate careful cardiac assessment (including baseline and serial ECGs) when initiating or modifying antipsychotic therapy, particularly with agents known or suspected to affect sodium channels [3,4,8].

Despite accumulating evidence implicating psychotropic agents in drug-induced Brugada patterns, the literature contains relatively few contemporary

reports explicitly linking chlorpromazine a widely used phenothiazine with membrane-stabilizing properties to Brugada-type ECG changes at therapeutic doses ; most data regarding phenothiazines are derived from pharmacologic studies, older case reports of overdoses, and aggregated lists of potentially unsafe drugs for BrS patients [1,3,5,9]. Because chlorpromazine remains in use in many clinical settings and antipsychotic polypharmacy is common in treatment-resistant cases, clinicians should remain alert to the possibility of a drug-induced Brugada phenotype and promptly involve cardiology when suggestive ECG changes arise.

CASE PRESENTATION

We report the case of a 28-year-old man followed in our department for schizophrenia, diagnosed in 2019, comorbid with a substance use disorder involving daily tobacco use (approximately one pack per day) and occasional cannabis and alcohol consumption. He did not have hypertension, diabetes, abnormal triglycerides, high-density lipoproteins or low-density lipoproteins, was not overweight and did not have a personal or family history of cardiovascular disease, sudden cardiac death, or arrhythmia. There was no personal or family history of syncope, presyncope or arrhythmias. He has had multiple antipsychotic trials including olanzapine, risperidone and quetiapine.

During his first psychiatric hospitalization in 2025, baseline investigations including physical examination, complete blood count, serum electrolytes, liver and renal function tests, thyroid profile, and resting electrocardiogram (ECG), blood pressure, heart rate and temperature. were within normal limits. The patient was initially treated with risperidone (8 mg/day) without clinical improvement, followed by amisulpride (800 mg/day) and chlorpromazine (300 mg/day).

Given the lack of satisfactory response to two antipsychotic trials of adequate dose and duration, the diagnosis of treatment-resistant schizophrenia was established. A pre-clozapine evaluation was subsequently initiated. Electroencephalography (EEG) and blood test showed no abnormalities; however, a routine pre-treatment ECG unexpectedly revealed a coved-type ST-segment elevation in leads V1–V2, compatible with a type-1 Brugada-pattern ECG (*figure 1*), in the absence of any clinical symptoms such as syncope, chest pain, or palpitations.

Given this incidental finding, the initiation of clozapine therapy was withheld, and a cardiology consultation was requested. The cardiology team concluded that the ECG changes were suggestive of a Brugada-type pattern, most likely drug-induced. As a precaution, chlorpromazine was discontinued, while amisulpride (800 mg/day) was maintained and aripiprazole (15 mg/day) was added.

The patient remained clinically stable from both psychiatric and cardiovascular perspectives. A repeat ECG performed after discontinuation of chlorpromazine demonstrated complete normalization of the ST-segment elevation, supporting the hypothesis of drug-induced Brugada-type ECG changes rather than a primary genetic Brugada syndrome.

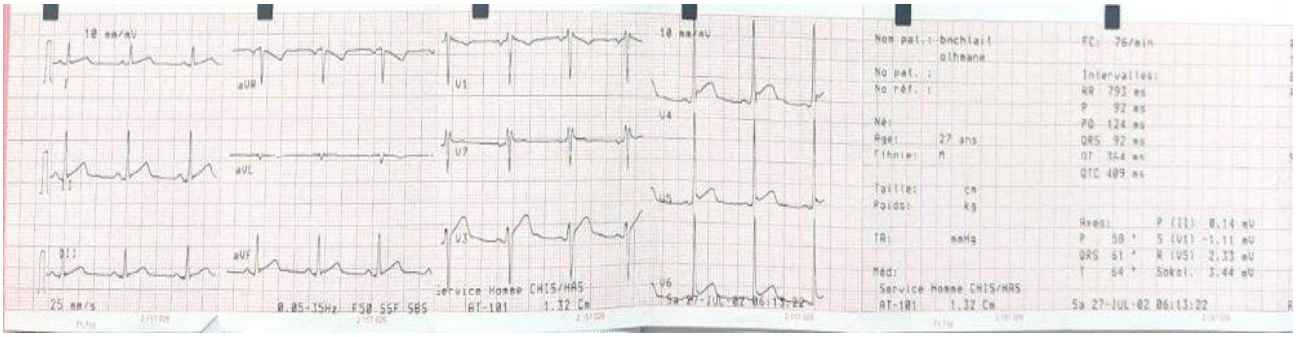

Figure 1

DISCUSSION

Prevalence and association of schizophrenia and Brugada syndrome

Patients with schizophrenia (SCZ) represent a population at markedly increased cardiovascular risk, including higher rates of sudden cardiac death (SCD). A landmark cross-sectional study found a Brugada-type ECG pattern in 11.6% of patients with schizophrenia compared to only 1.1% in matched non-schizophrenic controls, indicating a significantly elevated prevalence of Brugada ECG markers in SCZ [7]. A more recent case-control study involving recent-onset schizophrenia spectrum disorders found a suspect Brugada ECG in 8.5% of cases versus 1.5% of controls [10]. Genetic analyses further suggest a modest but significant causal liability of schizophrenia on Brugada syndrome, with Mendelian randomisation indicating $\beta \approx 0.14$ ($p \approx 0.009$) for SCZ liability increasing Brugada risk [11]. Thus, the association appears robust and not fully explained by confounders such as sodium-channel blocking medication or comorbidities. Some authors hypothesise shared pathophysiologic mechanisms (ion-channel dysfunction, autonomic dysregulation, inflammation) between schizophrenia and Brugada syndrome [12,13]. This heightened prevalence has important clinical implications for screening and monitoring.

Types of Brugada syndrome and the drug-induced form

Brugada syndrome is classified as a genetic channelopathy typically autosomal dominant with variable penetrance primarily involving loss-of-function mutations in SCN5A and other ion-channel genes. The hallmark ECG is the type-1 "coved" ST-segment elevation (≥2 mm) in leads V1–V2, often with a terminal negative T-wave. Two other phenotypes exist: type-2 (saddle-back ST elevation) and type-3 (less prominent ST changes) [14]. Importantly, not all patients with a Brugada ECG pattern have the inherited form; many represent drug-induced or unmasked Brugada ECG where the substrate may be latent or absent and the trigger is external (drug, fever, metabolic disturbance) [15,16]. Experimental data demonstrate that blockade of I_Na (sodium current) and/or I_Ca (L-type calcium current) in right ventricular epicardium produces loss of the action potential dome, exaggerated to outward current and ST elevation with propensity to phase-2 re-entry and ventricular tachyarrhythmia [15]. In clinical practice, drug-induced Brugada patterns have been documented with sodium-channel blockers (e.g., flecainide, pilsicainide) as well as with certain non-antiarrhythmic agents (e.g., metoclopramide) [20]. The risk of malignant arrhythmia in purely drug-induced forms is thought to be lower than in primary congenital Brugada syndrome, but remains incompletely defined [17,18].

Psychotropic agents and Brugada-type ECG changes

Psychotropic agents are increasingly recognised as potential precipitants of Brugada-type ECG changes. A scoping review of Brugada syndrome in schizophrenia outlined how antipsychotic and antidepressant drugs that affect sodium or calcium channels may unmask Brugada patterns and contribute to SCD risk independent of QT prolongation [14]. Indeed, a comprehensive table of psychotropic-induced Brugada-pattern ECGs lists numerous case reports involving tricyclic antidepressants, mood stabilisers (e.g., lithium, carbamazepine) and older antipsychotics [17]. For example, a case of carbamazepine-induced Brugada-type ST elevation in a patient with schizophrenia demonstrates the plausibility of ion-channel modifying psychotropics causing this phenomenon [7]. Moreover, also antipsychotics as quetiapine and clozapine may unmask this feature [9,21,22].

In mechanistic pharmacology data, antipsychotics such as chlorpromazine exhibit sodium-channel blocking effects (IC_{50} for I_Na block reported ~1.47 μM) in heterologous systems, highlighting a plausible arrhythmogenic pathway. Thus, when patients with schizophrenia on polypharmacy receive antipsychotics with sodium-channel blocking potential (especially in combination), the risk of unmasking a Brugada-type pattern is heightened [23].

While direct case-report literature explicitly linking chlorpromazine to Brugada syndrome is limited, the pharmacological profile of chlorpromazine (phenothiazine class) supports its plausibility as a trigger in predisposed individuals. Chlorpromazine's sodium channel blockade (alongside other ion-channel effects) places it on risk tables for drug-induced I_Na and I_Ca blockade leading to Brugada phenocopies [23,24]. In our case, the temporal relationship between chlorpromazine administration (300 mg/day) and the incidental detection of coved ST elevation (type-1 pattern) in V1-V2, followed by normalization of ECG after chlorpromazine withdrawal, strongly supports a drug-induced Brugada phenotype. Moreover, the absence of symptoms, negative family/personal cardiac history and normalization of ECG argue against a full congenital Brugada syndrome and favour the phenocopy model. This highlights the importance of recognising chlorpromazine (and other antipsychotics) as potential precipitants in at-risk individuals.

Management of resistant schizophrenia in context of Brugada syndrome

The management of treatment-resistant schizophrenia (TRS) in patients with Brugada syndrome (BrS) presents a major therapeutic challenge due to the potential proarrhythmic risk of most effective antipsychotics, particularly clozapine. *Clozapine* remains the gold standard for TRS, yet its known propensity to inhibit cardiac sodium channels ($Na_v1.5$) and to unmask Brugada-type ECG patterns necessitates extreme caution [25]. Baseline and serial ECG monitoring are mandatory prior to and during treatment, especially during dose escalation. In patients with confirmed BrS or previous drug-induced Brugada patterns, alternative strategies should be considered, such as low-dose atypical antipsychotics with minimal sodium channel blockade (e.g., olanzapine, quetiapine, or aripiprazole), in combination with psychosocial and cognitive-behavioral interventions [26]. Where clozapine use is unavoidable, co-management with cardiology and electrophysiology teams is essential, along with avoidance of concomitant sodium channel–blocking agents and electrolyte monitoring [27.28]. Implantable cardioverter-defibrillator (ICD) therapy may be discussed in high-risk cases. Recent reports highlight that individualized pharmacovigilance, pharmacogenetic screening for SCN5A variants, and the use of therapeutic drug monitoring (TDM) can reduce cardiac risks while maintaining psychiatric stability [29]. A multidisciplinary approach integrating psychiatry, cardiology, and clinical pharmacology remains the cornerstone of safe and effective management.

In our patient, chlorpromazine was discontinued while continuing amisulpride (800 mg/day) and adding aripiprazole (15 mg/day), leading to ECG normalization and maintained psychiatric stability.

From the cardiology standpoint, the decision to implant an ICD in a patient with drug-induced Brugada pattern must be individualized. Current consensus suggests that asymptomatic patients with only drug-induced type-1 ECG changes and no arrhythmic events generally do not require ICD implantation; the focus remains on removal of the trigger and monitoring [30,31]. However, in schizophrenia patients' additional factors (substance use, polypharmacy, autonomic instability) may modify arrhythmic risk and warrant closer surveillance (ECGs, Holter monitoring). Multidisciplinary collaboration between psychiatry and cardiology is critical.

Clinically, our case reinforces that patients with schizophrenia are a high-risk group for Brugada ECG abnormalities both congenital and drug-induced and that antipsychotics may trigger or unmask such abnormalities. Pre-emptive ECG screening, minimization of sodium-channel–blocking psychotropics, and careful monitoring during drug switches are recommended. From a research perspective, further large-scale prospective studies are needed to quantify arrhythmic risk in schizophrenia patients with Brugada ECG patterns, and to stratify the risk associated with specific psychotropic agents. Pharmacogenomic profiling (e.g., SCN5A variant screening) may help identify vulnerable individuals.

LIMITATIONS

Our discussion and inference are limited by the paucity of direct case reports involving chlorpromazine and Brugada syndrome, as most literature focuses on other psychotropics or tricyclic antidepressants. Moreover, we did not perform a sodium-channel provocation test or genetic testing for SCN5A variants in our patient ; hence we cannot definitively exclude a latent congenital substrate. Nevertheless, the unequivocal temporal association, ECG normalization after withdrawal, and absence of symptoms increase the likelihood of a drug-induced phenomenon.

CONCLUSION

In summary, this case highlights the interplay between treatment-resistant schizophrenia, antipsychotic polypharmacy, and unmasked Brugada-type ECG changes. It underscores the importance of cardiac vigilance in psychiatric settings and provides a blueprint for safe management: baseline ECG, avoidance of high-risk agents, early cardiology referral, and multidisciplinary coordination. As the evidence base grows, psychiatrists and cardiologists must work together to balance psychiatric efficacy with cardiac safety.

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