

# A case of schizophrenia comorbid for tetralogy of Fallot treated with clozapine: further considerations on a role for 22q.11.2 in the proneness for seizures

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**Abstract:** We present a case of schizophrenia comorbid for tetralogy of Fallot, without chromosome 22q.11.2 deletion or duplication, treated successfully with a combination of clozapine and antiepileptic drugs. Although clozapine by itself initially triggered convulsive seizures, we continued it with co-administration of valproate and topiramate. This combined treatment did not affect cardiac function of the patient, who experienced a favorable clinical course in terms of symptomatology and functional outcomes. To our knowledge, we provide the first report on a patient with tetralogy of Fallot, in whom 22q.11.2 was not deleted and clozapine-induced seizures were observed.

**Keywords:** schizophrenia, clozapine, tetralogy of Fallot, seizure, copy number variants

## Introduction

Tetralogy of Fallot is characterized by ventricular septal defects, aortic overriding, right ventricular outflow stenosis, and right ventricular hypertrophy. It accounts for 3%–5% of all congenital heart disease cases, with an incidence rate of 0.28 per 1,000.<sup>1</sup> Chromosome 22q.11.2 deletion has been reported in nearly 25% of patients with tetralogy of Fallot.<sup>1</sup> Likewise, ~25% of individuals with 22q.11.2 deletion have the disease.<sup>2</sup>

Schizophrenia has been reported to occur in ~25% of individuals with 22q.11.2 deletion.<sup>1</sup> Patients with treatment-resistant schizophrenia with 22q.11.2 deletion but without a history of epilepsy are prone to convulsive seizures induced by clozapine, even when relatively low doses are administered.<sup>3</sup>

The incidence of clozapine-induced seizure was reported to be ~5% (for a 1-year period), and 4%–6% to 22% over different time frames.<sup>4</sup>

Here, we describe a case of treatment-resistant schizophrenia comorbid for tetralogy of Fallot that was successfully treated with clozapine. Although clozapine initially triggered convulsive seizures, its administration was continued in combination with antiepileptic drugs. The treatment did not affect the cardiac function of the patient, who experienced a favorable clinical course. The implications for the role of 22q.11.2 copy number variants (CNVs) in clozapine-induced seizures are re-considered.

## Case report

The nature of this publication was explained to the patient, and written consent was obtained. The present case involved a 24-year-old man (birthweight 1,400 g) who was

diagnosed with tetralogy of Fallot. He did not have a history of seizures before hospitalization. His father, but not mother, also had schizophrenia (the patient has no siblings). A history of mental illness or other malformations, including heart diseases, was not evident in other members of his family. The patient underwent surgical intracardiac repair for tetralogy of Fallot at age 3, and has been receiving regular follow-up evaluations since then. The patient is a nonsmoker.

At age 19, the patient began experiencing command auditory hallucinations and thought broadcasting, and was diagnosed with schizophrenia. He was not responsive to treatment with antipsychotic drugs, including risperidone (3–6 mg/day) and paliperidone (dose unknown). He was treated with risperidone between age 19 and 20, but did not see a psychiatrist between age 20 and 21. Then, treatment with paliperidone was started when he was 21, which was continued for 1 year. He sometimes held a part-time job until age 21, when he was fired. He became withdrawn thereafter. The patient developed communication deficits and his hallucinatory and delusory behaviors became prominent. In addition, delusions of grandeur became systematic, and he repeatedly exhibited sudden violent behaviors. When the patient was 22 years old, he injured another person seriously while in a hallucinatory–paranoid state, and was hospitalized in the forensic ward.

While hospitalized, the patient was unresponsive to haloperidol (up to 12 mg/day), risperidone (12 mg/day), and olanzapine (20 mg/day). He exhibited pathological polydipsia and water intoxication, resulting in a blood sodium level of 120 mEq/L and tonic-clonic seizures. These observations indicated that the patient had treatment-resistant schizophrenia.

Twelve months after the initial hospitalization, he was transferred to our section to start clozapine therapy. The patient was 154 cm tall and weighed 47 kg. His intelligence quotient was 79, as measured by the Wechsler Adult Intelligence Scale-III. The patient's face had characteristics of velo-cardio-facial syndrome, as he had a prominent nose with a bulbous tip, malar flatness, and a small mouth.<sup>5</sup> He also exhibited hypernasal speech, short stature, and slender hands, but did not have a cleft palate or hypocalcemia.<sup>5</sup> An echocardiogram indicated a left ventricular ejection fraction of 36%, mild mitral regurgitation, moderate tricuspid regurgitation, and abnormal interventricular septal motion. Holter monitoring revealed a tendency to exhibit sinus tachycardia. Blood biochemistry analyses revealed that the brain natriuretic polypeptide level was slightly elevated at 20.6 pg/mL. Chromosomal analysis by fluorescence in situ

hybridization (FISH) revealed neither deletion nor duplication of 22q.11.2.

Clozapine treatment was started 13 months after the initial hospitalization. Its administration began at 12.5 mg, and the amount was subsequently increased by 25 mg every 2–3 days over the initial 3 weeks until it reached 200 mg. Thereafter, the dosage was increased by 25–50 mg each week, bringing the amount up to 400 mg over the first 2 months from the beginning of administration. We did not measure blood levels of clozapine. No co-administration of other antipsychotic drugs were prescribed. Then, the communicability of the patient improved drastically and auditory hallucinations and delusions stopped affecting his activities of daily living. As his violent behaviors and pathological polydipsia were alleviated, the patient was able to participate in a group therapy program consistently.

Tonic-clonic seizures were observed 2 weeks after titrating clozapine to 400 mg/day. In addition, electroencephalography showed frequent high-amplitude spike waves, mainly in the left temporo-occipital region in the basic rhythm of high-amplitude slow waves. In contrast, magnetic resonance imaging of the brain did not show abnormalities other than mild cerebellar atrophy. Therefore, the clozapine dose was reduced to 300 mg/day, and 600 mg/day of valproic acid was added.

Echocardiography 6 months after the start of clozapine revealed no significant changes in cardiac functions. In addition, the brain natriuretic polypeptide level was decreased to 10.5 pg/mL. Seven months after commencing clozapine treatment, convulsive seizures recurred. At that time, the blood concentration of valproic acid was 70.3 µg/mL, which was within the therapeutic range. Therefore, topiramate was added, and the dose was gradually increased to 200 mg/day. The convulsive seizures ceased and spike waves disappeared. The dose of clozapine was increased to 450 mg/day. Seventeen months after the start of clozapine treatment, psychiatric symptoms were stabilized, and seizure episodes were no more present. Currently, the patient is engaged in leisure activities, work, and group therapy programs.

## Discussion

To our knowledge, we report here the first case of schizophrenia comorbid for tetralogy of Fallot without the 22q.11.2 deletion, in a patient who responded well to clozapine.

Patients with schizophrenia with the 22q.11.2 deletion have been shown to respond well to a relatively low-dose clozapine, with a greater likelihood of developing convulsive seizures induced by the drug.<sup>3,5</sup> Gothelf et al<sup>5</sup> reported a case of

schizophrenia with tetralogy of Fallot with 22q.11.2 deletion, whose psychotic symptoms and violent behavior were improved by clozapine 200 mg/day. Occurrence of clozapine-induced seizures was prevented by adding valproic acid, at 600 mg/day, which induced myotonic jerks.<sup>5</sup> Mild diffuse atrophy of the cortex and cerebellar vermis was also identified in that case.<sup>5</sup> These observations may be contrasted with those of the patient (without 22q.11.2 deletion) in our report, who responded well to clozapine, but co-administration of the same dose of valproic acid (600 mg/day) by itself did not prevent seizure recurrence. Whether the mild cerebellar atrophy, observed in both cases, is associated with vulnerability to developing clozapine-induced seizures deserves further investigations.

Kushima et al identified CNVs, including 22q.11.2 or Xp.22.31 deletion, in ~9% of Japanese or Taiwanese patients with schizophrenia.<sup>6</sup> In their study, ~40% of patients with CNVs had a history of congenital or developmental phenotypes, and the incidence of treatment resistance was significantly higher.<sup>6</sup> While FISH did not reveal 22q.11.2 deletion or duplication in our patient, no other chromosomal tests were conducted. Therefore, it is unclear whether he has other types of CNVs. Convulsive seizures triggered by clozapine are reported to occur more frequently in patients with the 22q.11.2 deletion.<sup>3</sup> Future surveys should be conducted to investigate the relationships between clozapine-induced convulsive seizures and CNVs other than 22q.11.2.

Limited data exist with regard to the selection of anti-epileptic drugs for clozapine-induced epilepsy.<sup>3,4</sup> A previous report suggests the effectiveness of valproic acid for clozapine-induced epilepsy.<sup>4</sup> Gabapentin, lamotrigine, and topiramate have also been used to manage seizures in clozapine users.<sup>4</sup>

Specifically, there has been little information on the type of antiepileptic drugs effective for treating or preventing clozapine-induced seizures in schizophrenia patients with 22q.11.2 deletion and tetralogy of Fallot. On the other hand, the present case, comorbid with the cardiac anomaly but without 22q.11.2 deletion, was successfully treated with clozapine at doses that triggered seizures by co-administration with valproic acid and topiramate. Clearly, additional studies are warranted to determine which antiepileptic drugs should be recommended as an adjunctive therapy for clozapine treatment, in association with information on CNVs.

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## Disclosure

The authors report no conflicts of interest in this work.

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