

Clozapine-induced myocarditis in an adolescent male with DiGeorge Syndrome

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Abstract

DiGeorge Syndrome (22q11.2 deletion syndrome) is a chromosomal disorder associated with both congenital heart malformations and schizophrenia, which is often treatment-resistant and may warrant treatment with clozapine. Clozapine-induced myocarditis (CIM) is a rare complication of clozapine therapy, with a reported incidence ranging from 0.015% to 3%. Fulminant CIM has a nonspecific presentation in both adult and pediatric populations and a mortality rate approaching 50%. Few cases of pediatric CIM have been documented in the literature. This report highlights a case of CIM in an adolescent male with DiGeorge Syndrome whose clinical course was characterized by a subtle, nonspecific presentation and resolution with supportive care.

Keywords: clozapine, myocarditis, clozapine-induced myocarditis, pediatric, DiGeorge Syndrome

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Introduction

DiGeorge Syndrome (DGS; 22q11.2 deletion syndrome) is a genetic disorder typically diagnosed in childhood characterized by congenital heart defects, neonatal hypocalcemia, and immune deficiency. Additionally, the deletion in 22q11.2 is a well-established genetic risk factor for the development of psycho-cognitive disorders^{1,2} and schizophrenia, with a lifetime incidence approaching 27%.³⁻⁵

Clozapine, an atypical antipsychotic, has demonstrated clinical efficacy for treatment-resistant schizophrenia in

adults and at least 8 patients with DGS.^{3,6-9} Reported use in pediatric populations, however, is more limited. Clozapine is associated with development of agranulocytosis and metabolic risk; however, it also carries a black box warning for myocarditis, cardiomyopathy, and mitral valve incompetence.¹⁰ Clozapine-induced myocarditis (CIM) often presents initially with nonspecific signs of infection that progress to pronounced tachycardia, elevations in troponin and C-reactive protein, and eventual left ventricular dysfunction.¹¹

The risk of CIM has historically ranged from 0.015% to 0.188%, although recent literature indicates an incidence approaching 3%.¹²⁻¹⁴ These rates may remain underestimated, however, because of under-diagnosis and subsequent underreporting. Sagar et al¹⁵ suggest histopathological confirmation for definitive CIM diagnosis; however, this may not be clinically feasible for all patients. Retrospective analysis has shown patients with DGS may possess elevated risk for noncardiac adverse effects of clozapine, including seizures.¹⁶ Although the association of congenital cardiac malformations with DGS may theoretically increase the propensity of CIM,

limited literature exists to characterize this risk.¹⁶ As CIM has been associated with an estimated mortality rate approaching 50%, such cases underscore the need for heightened diagnostic awareness within both the adult and pediatric populations.¹² We present the first published case of CIM in a pediatric patient with DGS.

Case Report

History of Present Illness

A 17-year-old male with a history significant for DGS, hypothyroidism, and bipolar disorder was admitted for his initial inpatient psychiatric hospitalization in the context of worsening psychosis characterized by auditory hallucinations, paranoia, social isolation, and inability to complete activities of daily living. Home medications included delayed-release divalproex 500 mg twice daily, lithium 300 mg twice daily, levothyroxine 75 mCg daily, and quetiapine 500 mg nightly. A 5-day history of medication refusal was reported at admission. Notable historical medication trials per family report include lurasidone, olanzapine, and an unknown antidepressant agent.

Hospital Course

The patient's presenting symptoms and evaluation supported a diagnosis consistent with schizophrenia or schizoaffective disorder. Upon admission to the inpatient adolescent psychiatric unit, quetiapine and lithium were discontinued, and haloperidol was initiated. Haloperidol was titrated to 20 mg daily over 19 days with limited response; therefore, cariprazine was initiated with titration to 12 mg daily. In the context of only slight, transient improvement on cariprazine over a 1-month period and failure of multiple other antipsychotic trials, the patient and family consented to a clozapine trial with the intention of tapering cariprazine to discontinuation.

Clozapine 12.5 mg nightly was initiated on day 1, which was titrated according to prescribing recommendations. Because of somatic complaints of cough and mild chest pain without fever, an electrocardiogram (ECG) was obtained on day 4. Minor ECG changes were identified and attributed to his DGS diagnosis rather than to clozapine. On day 7, thyroid stimulating hormone, creatine kinase-MB, creatine kinase, and troponin were within normal limits.

On day 11, he became febrile to 101.6°F and developed mild diarrhea. Persistent sinus tachycardia and fever prompted transfer to the emergency department. A chest x-ray demonstrated right-sided atelectasis with no pneumonia, and lab findings were remarkable for a platelet

count of 55 k/mL (reference range [RR]: 150 k/mL to 450 k/mL). Divalproex (serum concentration: 81 µg/mL) was subsequently discontinued. Complete metabolic panel, viral panel, and strep throat screen were unremarkable. Following administration of intravenous fluids and mental status improvement, he was transferred back to the inpatient psychiatric unit carrying a diagnosis of viral illness.

On day 15, the temperature remained elevated at 103.2°F for the fifth consecutive day with no identifiable source. Creatine kinase, creatine kinase-MB, and troponin remained within normal limits; C-reactive protein was elevated at 12.5mg/dL (RR: ≤0.5 mg/dL). The initial diarrhea worsened and was accompanied by neck stiffness, right lower quadrant pain, cough, and mild sore throat. Given the wide differential including myocarditis, infectious etiology, and neuroleptic malignant syndrome, the patient was transferred again to the emergency department. His brain natriuretic peptide was elevated at 1800 pg/mL (RR: <125 pg/mL) with a mildly decreased ejection fraction to ~45% on transthoracic echocardiogram (ECHO), warranting transfer to a pediatric intensive care unit (PICU) of a large academic medical center for further management. Scheduled medications at the time of this transfer included cariprazine 6 mg nightly, levothyroxine 100 mCg every morning, and clozapine 75 mg every morning and 100 mg nightly.

Upon PICU admission, the eosinophil count was 0.49 kcells/mL (RR: ≤0.54 kcells/mL). Oxygen was initiated, and troponins and urine toxicology were repeated and remained negative. An ECG showed sinus tachycardia to a maximum rate of 130 beats per minute with overall normal voltages. Deep but narrow Q waves were noted in the lateral leads with no ST elevations. Psychiatry consultation recommended discontinuation of clozapine during the first day of admission. Cariprazine was continued for management of the patient's psychiatric symptomatology. Pediatric cardiology was consulted and diagnosed the patient with CIM based upon clinical presentation.

On day 2 following discontinuation of clozapine, transthoracic ECHO showed ejection fraction improvement to 54.4%, mild aortic root dilation, and lower end of normal left ventricular systolic function. At this time, the patient's psychiatric needs were managed with benzodiazepines, bextropine (added following cogwheeling and fine tremor of the upper left extremity on day 2 of PICU admission), and cariprazine augmented with olanzapine. A repeat ECHO on day 5 of admission was unchanged from previous with resolution of tachycardia. On the sixth day of PICU admission, the patient was medically cleared for transfer to the general psychiatric unit. The CIM was considered resolved 3 weeks later by the cardiology

consult team with no additional management required. He was discharged from the psychiatry service stabilized on olanzapine monotherapy (20 mg nightly) after treatment failure with cariprazine.

Discussion

This case of CIM is notable for its nonspecific presentation in a pediatric patient with DGS. While acute PICU management ultimately circumvented the development of life-threatening sequelae of CIM, this patient's symptomatology was consistent with hallmark subjective and objective markers of CIM including fever, ECG changes, and reduced ejection fraction. To date, no specific ECG abnormality has been identified as a diagnostic marker for CIM. While tachypnea and other respiratory symptoms are most prevalent initially, gastrointestinal and cardiac symptoms may also arise with or without fever.¹⁷ Tachycardia and fever may also be typical of an initial clozapine titration; therefore, clinicians may not place myocarditis high on the differential for patients presenting solely with these symptoms. Electrocardiogram changes secondary to cardiac defects are possible in DGS patients; however, the patient did not present with acute cardiac issues prior to clozapine initiation.¹⁷ This patient's acute stabilization followed recommendations for the treatment of CIM, which include discontinuation of clozapine and symptomatic management with serial monitoring of chest x-ray, ECG, and ECHO.¹⁸

In order to assess causality of CIM, the authors independently completed the Naranjo Scale.¹⁹ Each author calculated a score of 7, which deemed clozapine a "probable cause" of myocarditis. Despite its adverse effect burden, clozapine remains an evidence-based therapeutic option for treatment-resistant schizophrenia. Clozapine-induced myocarditis remains one of the most severe adverse effects of clozapine use despite its low incidence. A 2012 Australian-based case-control study²⁰ suggests that concomitant sodium valproate administration (odds ratio: 2.59) and rapid dose escalation (odds ratio: 1.26) may be significant risk factors for CIM development.

Limited literature describes clozapine use in the DGS population. In a 2015 evaluation of atypical antipsychotic effectiveness in 28 DGS patients with treatment-resistant psychosis, the safety and efficacy of clozapine was successfully demonstrated in 8 patients.³ One report²¹ of a 32-year-old man with DGS described positive psychiatric benefit; however, he experienced adverse effects including seizures. Another report²² described development of a grand-mal seizure at 150 mg of clozapine following a reasonable titration schedule. However, given the highly variable degree of impact of the DGS phenotype on

neuropsychiatric systems, it is unclear if this patient population is truly more susceptible to clozapine adverse effects. A 2017 retrospective chart review²³ reported lower rates of adverse effects from atypical antipsychotics in patients with DGS compared to those without.

Even fewer cases of CIM have been reported in pediatric patients. Aboueid and Toteja¹¹ report the case of a 17-year-old patient who developed significant left ventricular hypertrophy and ST segment elevation requiring admission to an intensive care unit. Although this presentation differed from our case because of the presence of ST elevation, both cases resolved with appropriate supportive care. Myocardial damage is typically reversible with prompt discontinuation of clozapine.²¹

Conclusion

Clozapine-induced myocarditis is a complication of clozapine therapy with a reported mortality rate approaching 50%. Clinicians should remain cognizant of the nonspecific presentations of CIM and maintain a low threshold for early evaluation to mitigate cardiac damage. This case of CIM in an adolescent male with DGS, characterized by a subtle, nonspecific clinical presentation and concomitant divalproex use, underscores the need for heightened clinical awareness. Further research to determine optimal diagnostic and treatment strategies for CIM in the pediatric population is merited. Until additional studies are conducted to elucidate the safety and tolerability of clozapine and other psychotropics in this patient population, cautious prescribing is warranted.

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