7-1-2021

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Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-021-05174-7

LETTER TO THE EDITOR

Case Report: Clozapine-Induced Myocarditis in a Patient with Autism Spectrum Disorder and Schizophrenia

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Accepted: 25 June 2021

Case Report

A 21-year-old man with a history of autism spectrum disorder (ASD), which was diagnosed in the 1st grade, presented to the psychiatric emergency department with signs and symptoms concerning for catatonia. Physical examinations revealed mutism, posturing, catalepsy, immobility, stupor, staring, negativism, withdrawal, impulsivity, mitgehen, ambitendency, and autonomic abnormality of tachycardia; Bush-Francis catatonia rating scale was 18. He was admitted to the general unit where extensive medical workup was completed which was unremarkable, and he was discharged with a prescription for lorazepam 1 mg three times per day.

Over the following months, the patient developed auditory hallucinations, delusions, disorganized speech and thought, internal preoccupation, and intermittent aggressive outbursts; he was eventually diagnosed with catatonic schizophrenia. Since his first hospitalization, his lorazepam was never discontinued and the dose was titrated up to 9 mg three times daily. Once catatonia was adequately treated with lorazepam, he was prescribed multiple antipsychotics with minimal to modest benefit and with intolerable side effects (Table 1, Online Supplementary Information). The patient and his family agreed to a trial of clozapine, which was titrated to 150 mg nightly over 15 days while the catatonia was controlled with lorazepam 3 mg three times daily.

While on clozapine 150 mg nightly monotherapy, the patient showed a 50%-60% improvement by his mother's subjective report: He was engaged with family members, able to have conversations, was less disorganized, and had decreased hallucinations and delusions. Clozapine serum level was not obtained as clozapine was still being titrated. After four days of taking clozapine 150 mg, he developed mild chest pain, tachycardia, mild fever, and flu-like symptoms. Prompt workup revealed C-reactive protein was 1.8 mg/dL (reference range < 0.5 mg/dL) and troponin-I was 50 ng/L (reference range < 19 ng/L). Chest x-ray was normal. Due to concern for clozapine-induced myocarditis, clozapine was discontinued as a precautionary measure and he was advised to go to the emergency department. Workup in the emergency department revealed D-dimer elevated at 1.69 µg/mL, high sensitivity troponin I elevated at 43 ng/L, and non-specific T wave abnormalities on electrocardiogram. Computed tomography of the chest with intravenous contrast was normal and negative for pulmonary embolism. Transthoracic echocardiogram was unremarkable which showed ejection fraction estimated at 65% in the range of 60%–65% and normal left ventricular ejection fraction. His left ventricular cavity size was normal and left ventricular wall thickness was mildly increased. Right ventricular size was normal and he had normal global right ventricular systolic function. Other unremarkable workup included complete blood count with differential which showed no evidence of leukocytosis or eosinophilia. He was given ketorolac tromethamine 15 mg and aspirin 324 mg and was observed in the cardiology unit for telemetry monitoring. Within two days of discontinuing clozapine, his symptoms resolved, and his labs returned to the normal range. The differential diagnosis for etiology of the myocarditis included viral illness, clozapine-induced, or idiopathic. Given the clinical findings, cardiac marker, inflammatory marker, association of symptoms presentation and lab abnormalities with initiation of clozapine, resolution of symptoms and normalization of lab values with discontinuation of clozapine; the cardiologist, internist, and psychiatrist believed his myocarditis was best explained by clozapine. The patient was diagnosed with clozapine-induced myocarditis and discharged home. After his clozapine was discontinued, he had a trial of quetiapine fumarate titrated up to 200 mg in the morning and 600 mg at night. However, he continued to have prominent auditory hallucinations and delusions, so

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Published online: 01 July 2021

the patient was re-trialed on olanzapine and titrated up to treatment-resistant dose of 40 mg daily. After four months of stability, the patient and his family requested to use the lowest effective dose of all medications, so the dosage of his medications were gradually reduced to olanzapine 30 mg daily and lorazepam 3 mg three times daily. On this regimen, the patient's symptoms of psychosis and catatonia were well controlled as evidenced by clinical examination and subjective report of the patient and his family.

Discussion

Clozapine is approved by the United States Food and Drug Administration for patients with treatment-resistant schizophrenia and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. It is also sometimes used off label for irritability in children and adolescents with ASD after other treatments have failed. One of the major side effects of clozapine is myocarditis, which often presents with nonspecific symptoms such as tachycardia, shortness of breath, fever, flu-like symptoms, nausea, and dizziness. This can be an elusive diagnosis, especially in patients with communication deficits such as those with ASD. Myocarditis typically occurs in the first 6 weeks of clozapine titration, and the incidence of early myocarditis ($\leq$2 months from initiation of treatment) ranges from < 0.1 to 1.0% (Curto et al., 2016). The mortality rate is 10%–46% (Knoph et al., 2018). Known factors which increase risk of clozapine-induced myocarditis are age $\geq$ 50 years old, rapid clozapine titration, and use of valproate (Ronaldson et al., 2012). Currently, it is not known whether patients with ASD have a higher risk of developing clozapine-induced myocarditis.

Recent research has shown some neurobiological overlap between ASD and schizophrenia as they both present with atypicality in social cognition, sensory processing, and information processing (Lanillos et al., 2020). One study of first episode psychosis in children with ASD found this population is more likely to have multiple antipsychotic treatment failures (Downs et al., 2017). Psychiatric comorbidities are common and frequently multiple in children with ASD: In one study of ASD, 70% of participants had at least one comorbid disorder, and 41% had two or more (Simonoff et al., 2008). Children with ASD are frequently prescribed off-label psychotropic medications: One study showed up to 48.5% of children with ASD are prescribed at least one psychotropic medication (Madden et al., 2017). Finally, children with ASD are psychiatrically hospitalized at a higher rate than those without ASD (Croen et al., 2006). All of this could increase the likelihood of the ASD population being prescribed clozapine, however, due to the lack of studies done in patients with ASD, clinical guidelines for treatment of schizophrenia in people with ASD are extrapolated from data on non-ASD patients.

Our focused literature search showed a lack of data on the incidence of clozapine-induced myocarditis in patients with ASD: none of the publications we reviewed reported it, but all mentioned the risk in their discussions (Table 2, Online Supplementary Information); the true incidence of myocarditis is likely higher than what is routinely diagnosed. Clinicians should be aware that because patients with ASD are at high risk of developing side effects from psychotropic medications, they may also have different risk factors regarding clozapine-induced myocarditis. A high index of clinical suspicion should be maintained when prescribing clozapine to this population who may have significant communication deficits, as myocarditis is nonspecific and therefore may be mistaken for other intolerances. Following a slower titration rate and conducting more frequent laboratory monitoring in this population may also be prudent until more data are available. A recent systematic review found 87% of reported clozapine-induced myocarditis displayed symptoms within 30 days or less of treatment, and all but four cases developed symptoms within 12 weeks (Bellissima et al., 2018). In another study which analyzed only confirmed cases of clozapine-induced myocarditis using pre-specified criteria, all cases occurred within 6 weeks (Segev et al., 2021). Therefore, a reasonable practice would be to obtain weekly C-reactive protein and troponin levels for the first 6 weeks after initiating clozapine, which could conveniently be done when patients have weekly complete blood counts. While there is a risk of false positive from the C-reactive protein test, utilizing the troponin test will minimize any false positives, therefore, we believe the benefits of this systematic approach outweigh the risks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10803-021-05174-7.

Acknowledgments The authors thank Karla D. Passalacqua, PhD, at Henry Ford Hospital for assistance with editing.

Author contribution MS identified the case as unique and worthy of adding to the scientific literature, GB and MS conceived and structured the presentation. GB aquired the data for the systematic review, and lead the team. GB, NF, and NB performed the analysis and interpretation of data. All authors drafted the manuscript and revised it critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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