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CLOZAPINE-INDUCED MYOCARDITIS: AN ADOLESCENT GIRL WITH VERY EARLY-ONSET SCHIZOPHRENIA

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INTRODUCTION

The first atypical antipsychotic, clozapine, is a highly effective medication for patients with treatment-resistant schizophrenia (Kane 2019). While it rarely causes extrapyramidal side effects, the potential other side effects (e.g. agranulocytosis, myocarditis, seizures) limit its widespread use (Gurrera 2022). This report presents a case of a 13-year-old female diagnosed with treatment-resistant very early-onset schizophrenia (VEOS), who experienced clozapine-induced myocarditis (CIM), and discusses its phenomenology, prodromal signs, clinical manifestations and treatment.

CASE PRESENTATION

The case involves a 13-year-old girl, an 8th-grade student who is unable to attend school. Approximately one year ago, she started experiencing symptoms such as believing that everyone was talking about her, hearing voices that nobody else could hear, irritability, and aggressive behavior towards people. As a result, her academic and social functioning deteriorated significantly. Due to an escalation in these symptoms 6 months ago, she was hospitalized in a pediatric psychiatry inpatient unit for two months and she was discharged with partial response to treatment with risperidone 6 mg/day, lorazepam 3 mg/day, chlorpromazine 300 mg/day, and biperiden 4 mg/day. After discharge, the patient, who continued to experience psychotic symptoms (disorganized speech and behaviors, persecutory, referential, and erotomanic delusions, auditory hallucinations) presented to our outpatient unit and her treatment was adjusted to include risperidone 7 mg/day, quetiapine 600 mg/day, hydroxyzine 75 mg/day, and biperiden 6 mg/day. After two months, she was admitted to our inpatient unit because of her disorganized behaviors and homicidal thoughts. In her medical history, there is a history of occasional use of pantoprazole due to a diagnosis of GER and gastritis that has existed for many years. There is no history of smoking, alcohol, or substance use. In the family history; her mother had a history of generalized anxiety disorder diagnosis and use of psychotropic medication in the past. The 27-year-old male sibling has been diagnosed with Becker muscular dystrophy. There is no known heart disease in the family. Her body mass index was 30.8 kg/m². Vital signs were within normal limits. Pediatric and neurological examinations, imaging (cranial brain tomography and magnetic resonance) and laboratory (hematological, biochemical, and metabolic screening tests) analyses were unremarkable. An electroencephalogram (EEG) examination revealed the presence of bifrontal disrhythmia, which was evaluated as unremarkable by pediatric neurologist. Intelligence level, psychometric tests, and clinical assessment indicated normal results. After the evaluation, she was diagnosed with treatment-resistant VEOS. Clozapine treatment was started and titrated by increasing the dose every three days, starting from 25 mg. Since the addition of quetiapine did not show any effect, it was gradually discontinued. The other medications (risperidone 7 mg/day, hydroxyzine 75 mg/day, biperiden 6 mg/day) were continued unchanged. On the 10th day of clozapine treatment, at a dosage of 100 mg/day, the patient experienced symptoms of nausea, vomiting, abdominal pain, increased frequency of bowel movements, and watery stools. Since the initiation of clozapine, no other gastrointestinal symptoms such as constipation and hypersalivation have been observed. No other patients admitted to the ward have reported any complaints of gastroenteritis. The patient, who was consulted to the pediatric gastroenterology department, was diagnosed with acute gastroenteritis and received symptomatic treatment (fluid support, probiotics, and pantoprazole 40 mg/day added three days later). While under observation for gastroenteritis and also being monitored for potential cardiac pathology, troponin I and ECG were normal, but CRP level was found to be 38.3 mg/L. The patient, whose gastroenteritis symptoms were improving, experienced weakness, chest pain, and elevated fever on the 15th day of clozapine treatment (at a dosage of 125

mg/day). The patient's vital signs were as follows: temperature 37.8 degrees Celsius, pulse 118 beats per minute, blood pressure 125-75 mmHg and respiratory rate 22. Although the ECG was normal, troponin I was measured at 192.1 and CRP at 96.9. The patient was consulted to the pediatric cardiology department. The echocardiography result was unremarkable. The patient was diagnosed with CIM and the clozapine treatment was discontinued. During this process, the patient received bed rest, non-steroidal anti-inflammatory drugs, and curcumin (an antioxidant and anti-inflammatory) treatment. Daily ECG and troponin I monitoring were conducted. Throughout the follow-up period, the ECG remained normal, troponin levels showed a decreasing trend, and by the end of the second week, they returned to the normal range (Table 1). The Naranjo Adverse Drug Reaction (ADR) Scale (Naranjo & Sellers 2017) yielded a score of 5, indicating a possible adverse event.

DISCUSSION

The patient, being routinely observed in a clinical setting and experiencing a regression of gastrointestinal symptoms with supportive treatment, initially did not raise suspicion of myocarditis. The diagnosis of myocarditis was made on the 15th day of clozapine treatment when the dosage was increased to 125 mg/day. It has been reported that clozapine-induced myocarditis in children, adolescents and adults generally occurs in the first month of clozapine titration (De las Cuevas & Carlos 2022), mostly develops during the use of clozapine at standard doses and is independent of the clozapine dose (Bellissima & Brandi 2018). Our case could potentially be the third youngest case following those of 7 and 12-year-olds (De las Cuevas & Carlos 2022). The timing of myocarditis and its independent relationship with clozapine dosage are in line with the literature.

Clozapine-induced myocarditis presents itself with a wide range of often non-specific clinical manifestations. These symptoms, in order of frequency, include fever (67%), tachycardia (58%), dyspnea (42%), chest pain (37%), flu-like symptoms and fatigue (18%), hypotension (13%), cough (12%), gastrointestinal discomfort (11%), and tachypnea (8%) (De las Cuevas & Carlos 2022). Similarly, our patient exhibited symptoms including fatigue, chest pain, fever, tachycardia, increased systolic blood pressure, and tachypnea.

Due to the lack of established protocols for screening these symptoms, there might be a delay in diagnosing CIM (Aboueid & Toteja 2015). In our case, when evaluating the laboratory findings, elevated troponin I and CRP levels were observed while ECG and echocardiography were normal. Similarly, elevated CRP levels were seen in 52% of cases and elevated troponin levels in 65% of cases with CIM (Bellissima & Brandi 2018). Troponin I and troponin T are more commonly recommended as biomarkers for clozapine-induced myocarditis compared to CK-MB and CRP (Knoph & Kristen 2018). However, it is stated that none of them are sufficiently specific and sensitive (Knoph & Kristen 2018). In these conditions, especially during the first 3 months of clozapine treatment (especially the first month), it is recommended to be cautious regarding CIM and to simultaneously monitor multiple cardiac markers (e.g., CRP and troponin) when suspected clinical symptoms arise, in order to prevent false negatives (Bellissima & Brandi 2018).

According to the literature, the typical progression of clozapine-induced myocarditis is as follows: within 10-19 days after starting clozapine, an increase in heart rate by 10-20 beats per minute unrelated to myocarditis, the emergence of an infection (respiratory, gastrointestinal, or urinary tract) or CRP elevation >50 mg/L, within 1-5 days, an increase in heart rate by 20-30 beats per minute, cessation of clozapine in the presence of high troponin (>2 times the upper normal limit)/CRP (>100 mg/L)/left ventricular dysfunction, within 5 days, significant improvement in left ventricular dysfunction(Correll 2022). In line with this, according to the evidence-based 28-day clozapine-induced myocarditis monitoring algorithm developed in Australia, echocardiography, troponin I or T, and CRP should be assessed initially, routine vital measurements should be completed every other day, and troponin and CRP should be repeated on days 7, 14, 21, and 28. (Aboueid & Toteja 2015). Additionally, an initial ECG is recommended, and an ECG after titration may be useful, but routine periodic ECGs are not cost-effective (Knoph & Kristen 2018). In our patient, when weakness, fever, and chest pain occurred along with the improvement of gastrointestinal symptoms, relevant recommendations were implemented, and early detection of CIM was ensured.

Despite methodological limitations and conflicting results, possible risk factors for CIM have been reported as high starting dose, rapid titration, being older (especially 50 years and older), and the use of valproate (De las Cuevas & Carlos 2022, Bellissima & Brandi 2018). In a study conducted in children and adolescents, it was found that the severity of CIM increased by 17.6 times with the use of quetiapine (De las Cuevas & Carlos 2022). It may indicate that different factors could play a role in the development or severity of CIM in children and adolescents, especially since the risk factors mentioned are not present in our case. Proposed mechanisms of clozapine-induced cardiotoxicity are type 1

IgE-mediated acute hypersensitivity reaction, increase in plasma level of the pro-inflammatory cytokines (TNF-α, IL-10), a rise in circulating catecholamines and oxidative stress (Patel 2019).

CONCLUSION

Clozapine-induced myocarditis is a challenging complication in treatment-resistant schizophrenia, often being a rarely recognized complication. The absence of cardinal symptoms and the risk of cardiomyopathy and death highlight the importance of recognizing risk factors, prodromal signs and clinical manifestations to facilitate early diagnosis and intervention. Particularly in pediatric cases, establishing and implementing evidence-based monitoring protocols is crucial, requiring each case to be documented in the scientific literature and further research to be conducted in this area.

Ethical Considerations: Does this study include human subjects? YES
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