**CASE REPORT**

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# Clozapine-Induced Myocarditis in Huntington's Disease: Case Report

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**ABSTRACT**

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease. Its clinical presentation is primarily characterized by motor dysfunction, cognitive decline, and a broad spectrum of neuropsychiatric symptoms. Common psychiatric manifestations of HD include mood and anxiety disorders as well as behavioral and personality changes. Psychosis is relatively rare. Clozapine may be used for HD with psychosis because of its low extrapyramidal side effect profile. However, clozapine administration has been associated with rare but potentially fatal adverse effects, such as agranulocytosis and myocarditis. Clozapine-induced myocarditis is a severe complication that typically emerges within the first weeks of treatment and can lead to cardiovascular collapse if not recognized early. Although cardiac autonomic dysregulation and basal cardiac stress induced by mutant huntingtin (mHTT) protein accumulation are recognized in patients with Huntington's disease (HD), data regarding clozapine toxicity within this specific context remain limited. This case report presents a 51-year-old male patient who developed acute myocarditis during clozapine treatment initiated for psychotic symptoms arising in the context of HD. Following the discontinuation of clozapine, the patient was referred for cardiological monitoring. Throughout this paper, we will discuss the diagnostic process of myocarditis—a rare but potentially life-threatening complication of clozapine—and potential contributing factors. This case highlights the vital importance of early cardiac monitoring during clozapine use, particularly in psychiatric conditions accompanied by neurodegenerative processes.

**Keywords:** Case report, chorea, clozapine, Huntington's disease, myocarditis, psychosis

## INTRODUCTION

Huntington's disease (HD) is a progressive neurodegenerative pathology with autosomal dominant inheritance that may present with various types such as chorea, dystonia, coordination disorder, impairments in cognitive performance and attitude problems (Walker 2007). Huntington's disease is caused by a CAG tripartite nucleotide (trinucleotide) increase (expansion) in exon 1 of the Huntingtin (HTT) gene (MacDonald et al. 1993). Huntington's disease is a rare disease and its worldwide prevalence has been reported to be between 6–14 per 100,000 people (Baig et al. 2016). In most cases with Huntington's disease, the age of onset is between 30 and 50 (Roos 2010). The primary manifestations of Huntington's disease are movement disorders, cognitive impairment and psychiatric manifestations (Anderson and Marder 2001). Psychiatric disorders are very common in Huntington's disease. Irritability, impulsivity, apathy, sleep disorders, sexual dysfunctions, affective disorders, anxiety and psychotic symptoms may be observed (Leroi and Michalon 1998).

The prevalence of psychosis in Huntington's disease is reported to be 3–11% (van Duijn et al. 2008). In the presence of psychotic symptoms in Huntington's disease, second-generation antipsychotics should be prioritized in treatment due to fewer extrapyramidal system side effects (Unti et al. 2017). Clozapine can be safely preferred in terms of extrapyramidal side effects in cases resistant to other 2nd generation antipsychotics. However, clozapine should be used with caution in terms of two potentially fatal side effects, agranulocytosis and myocarditis. In this case, acute myocarditis that developed during clozapine treatment in a

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patient with psychotic symptoms due to HD in a Mental Health Hospital will be presented and the follow-up will be discussed.

## CASE REPORT

A 51-year-old male patient with HD diagnosis was admitted to our outpatient clinic accompanied by his sibling with complaints of suspiciousness and self-talk. The patient was admitted to the ward for treatment arrangement. According to the story obtained from the patient's brother, it was learned that choreiform movements and loss of balance started three years ago, the patient was admitted to the neurology clinic of another hospital with these complaints and the patient and his sister were diagnosed with HD as a result of genetic tests. However, it was stated that the patient's follow-up was interrupted due to social reasons and no therapy was initiated by neurology. It was learned that the paranoid thoughts of "being watched and followed on the phone", which had been present in the patient for the last 1 year, intensified recently and they applied to our hospital. No additional medical disease was found in his medical history. There was no history of substance abuse. Physical examination revealed stature 179 cm, weight 101 kg and body mass index (BMI) 31.5 kg/m². Smoking was one package/day. In the patient's family history, it was learned that her father and mother had involuntary movements similar to him and they died around the age of 50. In addition, in the family interview with the patient's healthy older brother and sister-in-law, it was stated that choreiform movements were more severe in the sister who was diagnosed with HD at the same time as the patient, but not accompanied by psychotic symptoms at the moment; on the other hand, it was stated that choreiform movements were accompanied by paranoid thought content in his mother who died around the age of 50 and mother's father, and that the immediate family experienced social isolation for this reason.

Neurologic examination revealed dysarthric speech, gait disturbance due to involuntary movements, and choreiform movements in the hands and feet. Mental status examination revealed that he was conscious and cooperative. Time, place and person orientation was complete. Memory examination was normal. Self-care was decreased. The amount of speech was small and dysarthric. His affect was depressed and persecution delusions were present in his thought content. He had a visual hallucination that his ex-girlfriend was sitting on his left shoulder and an auditory hallucination of a male voice swearing at him and giving orders. His judgment was partially impaired and his abstraction skills were preserved. He had no insight into the disease. The total positive and negative syndrome scale (PANSS) score was 103. The patient was first consulted to the neurology department. Tetrabenazine 25 mg 2×1 was started for involuntary movements. Olanzapine 2.5 mg/day was started for psychotic symptoms. Olanzapine dose was gradually increased to 10 mg/day. As the patient's psychotic symptoms did not regress and choreiform movements increased, olanzapine treatment was terminated and clozapine treatment, which was thought to be safer in terms of extrapyramidal system side effects, was started. Hemogram parameters before clozapine was started were examined and determined as; leukocyte: 9.6 K/uL (N: 4–10.6), eosinophil: 0.3 K/uL (N: 0–0.4), C-reactive protein (CRP): 1.52 mg/L (N: 0–5) and neutrophil: 5.8 K/uL (N: 2–7.1). Electrocardiography (ECG) was in sinus rhythm. Clozapine treatment was started at a dose of 12.5 mg/day and titrated up to 200 mg/day on day 16 based on the Maudsley Prescribing Guidelines (Taylor et al. 2022). The patient's positive psychotic symptoms started to regress. Positive and negative syndrome scale total score was measured as 85. No increase in the patient's choreiform movements was observed. On the day the clozapine dose was 200 mg/day (16th day of clozapine initiation), the patient developed tachycardia (Pulse: 130 beats/min). Sinus tachycardia was accompanied by increased CRP and elevated leukocytes (Figure 1). Tests revealed; creatine kinase-MB (CK-MB): 2.7 µg/L (N: 0.6–6.3), troponin I: 15.4 ng/L (N: 12.6–20.7), leukocytes: 14.0 K/µL, eosinophils: 0.2 K/µL, CRP: 15 mg/L and neutrophils: 10.8 K/µL. No pathology was detected in the infection source investigation. On the 18th day of clozapine treatment, complaints of shortness of breath and weakness were added to sinus tachycardia. In control tests; troponin I: 825.2 ng/L, CRP: 82.75 mg/L, Leukocyte: 13.5 K/µL and Neutrophil: 10.8 K/µL, levels had elevated, while CK-MB and eosinophil levels were within normal values (Figure 1) (Figure 2). Clozapine treatment was discontinued due to general condition deterioration and marked increase in cardiac markers (troponin I); Cardiology and Pulmonology departments were consulted. Echocardiography (ECHO) performed by Cardiology showed normal findings, but daily follow-up was recommended due to elevated troponin I. D-dimer and Thorax CT Angiography were ordered by Pulmonology to rule out pulmonary embolism; acute embolism was ruled out as the results were normal.

The patient was followed up in the ward without medication. Despite a troponin I level of 500 ng/L the following day, the patient's general condition deteriorated in the evening, with troponin I rising again to 900 ng/L and CRP reaching 93.2 mg/L. The patient was referred back to the Cardiology Department with a preliminary diagnosis of "clozapine-induced myocarditis." On cardiologic evaluation, ECG was compatible with sinus tachycardia. Echocardiography showed an ejection fraction (EF) of 65%, free wall motion abnormality and no effusion; pulmonary artery pressure

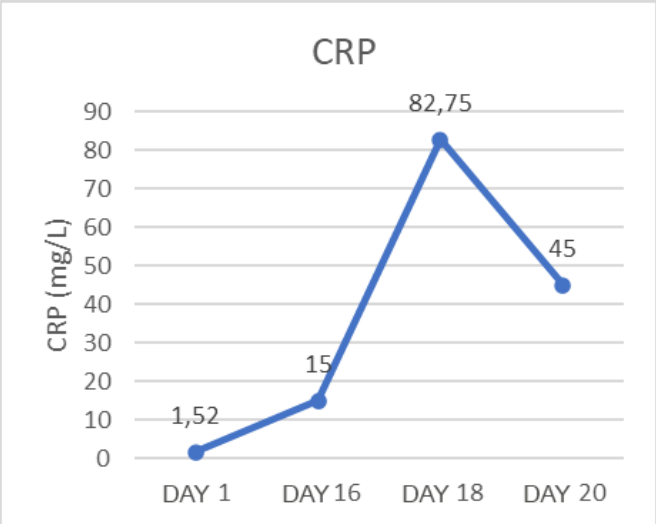


**Figure 1.** CRP course during clozapine treatment.

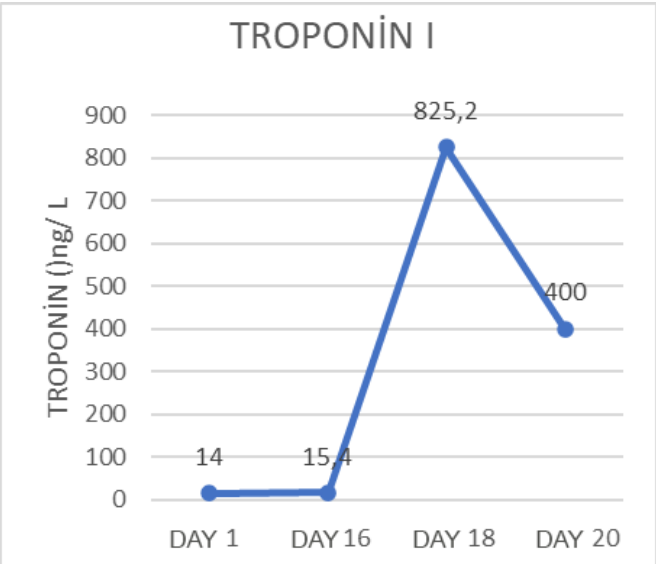


**Figure 2.** Troponin I course during clozapine treatment.

was 27 mmHg and grade 1–2 tricuspid regurgitation was observed. The patient was transferred to the Cardiology ward with the diagnosis of myocarditis and ibuprofen 400 mg 2×1, metoprolol 50 mg 1×1, colchicine 0.5 mg 1×1, enoxaparin sodium 0.6 ml 1×1 subcutaneous injection treatment was started and the patient was discharged 3 days later after the general condition improved, troponin I decreased to 400 ng/L and CRP decreased to 45 mg/L (Figure 1) (Figure 2). On the 2nd day of inpatient treatment in the cardiology service, our department was consulted with the complaint of insomnia. The patient was started on 100 mg/day of quetiapine. The psychiatric follow-up of the patient after discharge from the cardiology service was transferred to the university hospital in the same province due to the lack of relevant branch medical doctors in our hospital.

## DISCUSSION

Psychotic symptoms are rarely observed in Huntington's disease, however, psychotic symptoms show clustering in some families (Tsuang et al. 2000). The presence of similar paranoid delusions in the mother and father of the present case supports the literature in this respect. In Huntington's disease, the age of onset is earlier when the trinucleotide repeat number is high (Duyao et al. 1993). Although there is no genetic repeat number data for the patient and his sister, it is striking that his sister, who is 8 years younger than the patient, did not have psychotic symptoms although choreiform movements started at an earlier age and were more severe. This supports studies showing that the presence of psychiatric symptoms is independent of trinucleotide repeat number (Vassos et al. 2008) and suggests that psychotic symptoms may be an endophenotype with a separate genetic basis in HD (Connors et al. 2020).

Clozapine's effect upon Huntington's chorea is controversial. While Bonucelli et al. (1994) reported a decrease in chorea, van Vugt et al. (1997) reported a limited effect. In the present case, choreiform movements, which increased with olanzapine, did not increase during clozapine treatment and even benefited to some extent. In the literature, dose ranges for the use of clozapine in Huntington's psychosis are variable; there are cases with responses at doses below 300 mg (Majothi et al. 2020), as well as cases with doses up to 450 mg (Bampton et al. 2022). In the present case, PANSS scores improved at a dose of 200 mg/day, but treatment was terminated early due to myocarditis.

Clozapine-associated myocarditis usually occurs within the initial 2 months of therapy and its incidence is between 0.1% and 1.0% (Curto et al. 2016). The mortality rate varies between 10–30% (van der Horst et al. 2020). In the present case, myocarditis developed on the 18th day of therapy. Symptoms are usually non-specific; fever, tachycardia, shortness of breath are the most common symptoms (Bellissima et al. 2018). In the present case, weakness, tachycardia and shortness of breath were at the forefront. When myocarditis develops, elevated cardiac markers such as CRP, troponin and CK-MB can be detected (Bellissima et al. 2018). In the presented case, CRP was 82.75 mg/L, troponin I: 825 ng/L, leukocyte: 13.5 K/uL, which were well above the normal value ranges. CK-MB was within the normal value range.

In suspected clozapine-induced myocarditis, the medication should be discontinued promptly; steroids, diuretics, beta blockers and angiotensin converting enzyme inhibitors should be added to the treatment (Curto et al. 2016). In the case presented, the medication was discontinued upon suspicion and pertinent cardiac treatment was initiated.

Even though screening tests are controversial due to cost concerns, it is known that monitoring during the titration period increases the detection of myocarditis (Anıl Yağcıoğlu et al. 2019).

It is recommended that hemogram, CRP and troponin should be monitored weekly for the initial month, notably in asymptomatic patients started on clozapine, and cardiology consultation should be requested in risky patients (Balaban et al. 2021).

There is no data in the literature on predisposition to myocarditis in Huntington's disease patients, so it is not known whether the risk of side effects of clozapine use is distinct in this patient group. Nevertheless, recent studies suggest that the occurrence of clozapine-induced myocarditis may not be coincidental. In one study, it was suggested that the HLA-C*07:01 allele may increase the risk of clozapine-associated myocarditis, and variations in GNA15, known to be a gene associated with heart failure, may also pose a risk (Lacaze et al. 2020).

In addition, although HD is a neurodegenerative process, mutant Huntingtin protein (mHTT) is known to accumulate in cardiomyocytes, leading to loss of cardiac function at the cellular level (Park et al. 2021). Clozapine myocarditis is usually a "hypersensitivity" reaction. However, it can be suggested that this core cardiac stress caused by mHTT accumulation in HD, combined with the acute inflammatory response triggered by clozapine in the early period, may have made myocardial cells more susceptible to damage.

In addition, it has been shown that sympathetic/parasympathetic balance is disrupted and cardiac autonomic regulation is impaired even in the early periods of HD (Mehanna and Jankovic 2024). Therefore, although no definite inference can be made, it should be considered that there may be sensitivity to cardiac side effects in HD.

Another risk factor in this patient was thought to be obesity. Clozapine is a highly lipophilic molecule and it has been reported in the literature that obesity increases the distribution volume of this medication and decreases its systemic clearance (Diaz et al. 2018). The increase in adipose tissue accompanying obesity may have prolonged the elimination half-life of the medication, leading to the slow metabolism picture we observed in our patient and thus increased exposure to side effects (Hiemke et al. 2018).

As a concluding observation, in the presented case, the development of myocarditis may be considered a cumulative manifestation of various pathophysiological processes, such as autonomic dysregulation observed in HD, potential cardiac vulnerability associated with mHTT accumulation, and the early-phase inflammatory cardiotoxicity of clozapine. Furthermore, considering the patient's history of obesity, it is hypothesized that potential alterations in clozapine metabolism may have also influenced the clinical presentation. In the context of such complex clinical scenarios and potential risks, the routine implementation of weekly troponin I, Complete Blood Count (CBC), ECG, and CRP monitoring during clozapine titration, along with gradual dose escalation, are among the fundamental strategies emphasized in the literature for the early detection and risk management of myocarditis (Taylor et al., 2022). Strict adherence to this monitoring protocol is recommended during clozapine use for psychotic disorders arising in the context of HD.

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