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First onset of persistent neutropenia in patient undergoing long-term clozapine treatment after vaccination against COVID-19 and SARS-CoV-2 infection in short interval – a case report

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Summary

Clozapine is one of the most effective antipsychotic drugs, but its use is limited due to the possibility of severe side effects, such as neutropenia and agranulocytosis. The risk of these complications is the highest at the beginning of the treatment, but they can occur later, particularly when additional risk factors are present. In the described case, either COVID-19 vaccination or the infection itself led to severe neutropenia, which recurred during subsequent independent trials of other antipsychotic drugs. The paper presents the case of a 23-year-old woman diagnosed with early-onset, treatment-resistant schizophrenia who had been undergoing clozapine treatment with satisfying outcome for over 10 years. A week after the first dose of an mRNA vaccine against COVID-19, the patient developed a severe SARS-CoV-2 infection and experienced an extreme neutropenia, followed by a change of treatment. Although the patient fully recovered from the infection, the re-stabilization of her mental state remained unsatisfactory. The introduction of various newly implemented antipsychotic drugs led to partial improvement or another decline in the neutrophil count, despite discontinuing the use of clozapine.

The authors discuss a few possible pathomechanisms. Based on our current knowledge, this is the first reported case of persistent neutropenia triggered by various antipsychotic drugs following exposure to SARS-CoV-2 antigens.

Key words: clozapine, COVID-19, neutropenia

Introduction

The utilization of antipsychotic drugs marked the beginning of modern psychiatry. Their effectiveness in the treatment of a wide spectrum of psychiatric disorders has enabled millions of people around the world to recover and function in all areas of life. However, some patients present symptoms that are refractory to treatment with first-line antipsychotics. Then the drug that is characterized by the highest effectiveness among neuroleptic drugs is used – clozapine.

Clozapine is an atypical antipsychotic drug, which is used in treatment of schizophrenia due to its superior efficacy, as nearly a third of patients who did not respond to the first lines of treatment satisfactorily, reported improvement in experienced symptoms after clozapine introduction. Initially clozapine was considered to be the best therapeutic option for patients, however, when in 1977 de la Chapelle et al. [1] described first case of severe agranulocytosis as a result of clozapine and in 1975 nine deaths due to clozapine-induced agranulocytosis were reported in Finland, its safety was significantly undermined. However, further studies have proven that with careful monitoring of neutrophil count and blood morphology, clozapine proves to be an efficient and safe therapeutic option [2, 3]. It is currently considered as highly effective medication, implemented in patients who have not shown improvement in their mental state with first-line medications. However, the initiation and continuation of therapy are carried out under strict monitoring of morphology due to the possibility of serious side effects.

Neutropenia occurs when an absolute neutrophil count (ANC) is less than 1,500/μl. When the ANC is lower than 500/μl, it is classified as severe neutropenia or agranulocytosis [4]. The occurrence of neutropenia associated with clozapine treatment is reported in 3.8% of patients [5], while agranulocytosis is ten times less likely, with a presence in 0.4% of patients treated with clozapine [6]. Agranulocytosis usually occurs within the first 18 weeks of treatment and presents with fever, sore throat and mouth ulcers. The acute phase lasts around 12 days and may be shortened by the use of granulocyte colony stimulating factor. Probable risk factors are female gender, older age and Asian ethnicity. In the literature there are reports available suggesting that the risk of neutropenia and agranulocytosis consecutive to clozapine utilization has a genetic background. In this regard, several different genes are proposed, above all an intronic single nucleotide polymorphism 6672G>C of the DQB1 gene, as well as inter alia intronic polymorphisms of two hepatic transporter genes (SLCO1B3 and SLCO1B7). The pathogenesis remains unclear, but latest research on the clozapine metabolites, N-desmethylclozapine and N-oxide clozapine, found that N-desmethylclozapine was toxic to granulocyte progenitors (CFU-GM) at concentrations 3–6-fold higher than those normally achieved during treatment [7]. Another studies highlight the role of intermediate metabolite, nitronium ion, which is one of the reactive oxygen species, as being the particular factor that damages the progenitors [8].

Antipsychotic drugs are among a broad range of factors causing reduction in the white blood cells count. One of them is also SARS-CoV-2 virus. Studies conducted at the beginning of the COVID-19 pandemic indicated that leucopenia is more common than neutropenia [9]. However, with the growing body of literature a transitory drop in ANC was noticed in the population of patients undergoing stable and long-lasting clozapine treatment before the infection [10]. The reason for this occurrence is not known. In one of the studies it was suggested that clozapine may affect immune response, for example, causing a drop in immunoglobulins, and that it may be broadened to granulocytes as well [11]. Furthermore, together with the introduction of the SARS-CoV-2 vaccine, concerns about its interaction with clozapine and higher risk of post-vaccine neutropenia were raised. In Japan, where clozapine-related blood monitoring schemes are among the most thorough, one patient presented with a noticeable drop in ANC on the third day after receiving the vaccine, with gradual improvement up to starting values around the seventh day. Both doses followed the similar pattern [12]. Somewhat similar effect was noticed in a study by Veerman et al. 2022, where 20 people after the first dose and in 16 people after the second one developed blood count abnormalities. There was a significant decrease in leukocyte levels after both doses and a decrease in neutrophil count after the second dose of the vaccine. Interestingly, this phenomenon was correlated with a significant increase in serum clozapine concentration following vaccination despite no change in dosage [13].

The aim of this case study article is to is to analyse the possible causes of severe neutropenia after contact with SARS-CoV-2 virus antigens in a patient receiving long-term clozapine treatment, as well as to draw attention to the pathomechanisms of this phenomenon, its clinical presentation and possible treatment patterns in response to its occurrence.

Case study

The patient was a 23-years-old woman with treatment-resistant schizophrenia and autism spectrum disorder. She has been treated with clozapine for 10 years, after unsuccessful attempts at treatment with olanzapine, aripiprazole, haloperidol, zuclopenthixol, and risperidone. The patient was undergoing regular blood tests that always presented no deviation from the norms considering white blood cells. Prior to COVID-19 infection, she used clozapine in a daily dose of 225 mg.

In 2022, the patient was administered with the first dose of mRNA vaccination against SARS-CoV-2 virus. A week later, she was admitted to the emergency unit with severe respiratory symptoms and fever. Quick antigen test confirmed the COVID-19 infection, and CT chest scan revealed pneumonia with diffuse inflammatory changes in both lungs, corresponding to a typical clinical presentation. However, doctors were particularly concerned about the sudden decrease in granulocyte count observed in blood counts. In the test performed three weeks earlier, it was normal, while in the emergency unit a level of 200/μl was observed. Due to her somatic condition, the pa-

tient was admitted to the department of internal medicine, where she was administered granulocyte growth factor. Clozapine was discontinued, and aripiprazole was started due to deteriorating mental state.

After successful treatment of COVID-10 infection, the patient was discharged from the internal medicine department in satisfying somatic state, but insufficient improvement in her mental state, as the change of antipsychotic medication led to an exacerbation of psychotic symptoms. Due to the limited possibility of the psychiatric services provided in internal medicine ward, the patient was referred again to psychiatric outpatient care. During the consultation electroshock treatment was suggested, but the patient refused to undergo such procedure and upheld the refusal throughout the whole time of exacerbation of psychotic symptoms. As a result, decision was made to add quetiapine to aripiprazole. The blood test showed an ANC of 750/µl and a white blood cell (WBC) count of 2.62 x 109/l. The patient was consulted haematologically. A decrease in the neutrophils and white blood cells values was observed in control blood counts, so quetiapine was discontinued and risperidone was added, however, not only did it not improve the blood picture, but caused it to deteriorate further. The patient was re-consulted haematologically. The haematologist stated that "the whole picture points to the infectious neutropenia, although the influence of long-term antipsychotic treatment cannot be ruled out. Despite the neutropenia, there are no symptoms of infection, there are no indications for the administration of granulocyte growth factor – this drug should be reserved only for severe infections. Currently, the patient only requires periodic blood count control. Antipsychotic drugs with the least impact on blood counts should be utilized. Currently, there are no indications for extending haematological diagnostics".

Due to a further decrease in neutrophil levels (380/µl), risperidone was discontinued and lurasidone was initiated. After modification of treatment, blood results improved (WBC 3.03 x 109/l, ANC 1,700/ µl), however, the patient's mental state was deteriorating, so the dose of lurasidone was increased to 111 mg. Unfortunately, the patient began to present severe extrapyramidal symptoms and required introduction of biperiden with mediocre results. Further progression of side effects in the patient led to admission to a psychiatric ward outside of the place of the residence. During hospitalization, an attempt was made to reduce the doses, but the psychotic symptoms exacerbated. This led to a switch to amisulpride, which resulted in a drastic drop in ANC followed by infection. Finally, a decision was made to reintroduce lurasidone, but this time with a worse clinical effect. The patient was discharged from the hospital in a stable somatic condition and partially improved mental state in order to further stabilization in outpatient care. The information regarding diagnostic decisions is limited to those described in the discharge summary.

The last contact of the patient with the attending physician occurred in December 2022. During a telephone conversation, the patient presented moderately exacerbated psychotic symptoms and fleeting thought disorders. Since then, the further fate of the patient is unknown.

Table 1. **The timeline of the presented case**

Date	Event
2012	The beginning of the illness, unsatisfying treatment, implementation of clozapine with good effect.
2012 – 2022	Satisfying clozapine treatment, regular blood count monitoring.
02.2022	Vaccination against SARS-CoV-2.
02.2022 (a week after the vaccination)	Severe COVID-19 infection, neutropenia 200/µl, discontinuation of clozapine, implementation of aripiprazole.
03.2022	Decline of the mental state, implementation of quetiapine
04.2022	Further decline of the mental state, haematological consultation, change of treatment from quetiapine to risperidone
05.2022	Further decline of the mental state
06.2022	Haematological re-consultation
07.2022	Discontinuation of risperidone and implementation of lurasidone, improvement in white blood counts
08.2022	Persisting improvement in white blood counts, unsatisfying improvement in mental state, increase of lurasidone dose
09.2022	Appearance of severe extrapyramidal symptoms, introduction of biperiden
10.2022	Further increase in side effects of treatment, admission to the psychiatric ward
11.2022	An attempt of dose reduction in inpatient care, leading to an increase of psychotic symptoms. Switch to amisulpride, resulting in a decline in ANC, followed by infection. Reintroduction of lurasidone with unsatisfying result. Discharge from the hospital in a stable somatic condition and only partially improved mental state.
12.2022	Last contact with patient via telephone conversation.

Discussion and conclusions

Due to wide range of symptoms and length of treatment, it is often problematic to distinguish between side effect secondary to the utilized treatment and those resulting from infections or developing somatic diseases. In this case, there is no evident explanation as to what the direct cause of persistent severe neutropenia could be, so each possibility should be analysed thoroughly.

Methodological considerations should begin with an explanation of the specificity of treating this particular patient. The management of schizophrenia started with the introduction and stabilisation of treatment by a child psychiatrist specialist since the patient was a minor, but at the beginning of the events described in the case, she was

still under his care. Due to the experience gained from the patient's limited response to treatment during her adolescent years, in the described situation, the decision was made to treat clozapine intolerance similarly to its ineffectiveness (the decision was based on guidelines for clozapine-resistant schizophrenia) [14]. Therefore, it was decided to introduce a previously unused medication, namely quetiapine, and then return to the previously best-tolerated medication, risperidone. Following a similar principle, lurasidone was used when significant neutropenia occurred as a side effect of risperidone. During treatment, medications with the highest potential for causing neutropenia and agranulocytosis, such as clozapine (1.57‰) and perazine (0.52‰), were not considered useful. Monotherapy was preferred in the pharmacotherapy approach, as polypharmacotherapy is considered a risk factor for haematologic complications [15].

Subsequent steps in the patient's care, including her stay in the internal medicine ward, psychiatric hospital and current care, were managed by other specialists. Therefore, it is not possible to present the patient's treatment based on their experience.

Even though leukopenia and drop in absolute neutrophil count is usually associated with clozapine, this is not the only substance that may result in a similar outcome. Individual cases of neutropenia or agranulocytosis were described for risperidone [16], amisulpride [17], lurasidone [18], olanzapine [19], aripiprazole [20], and quetiapine [21, 22]. The pathophysiology of this side effect is currently unclear. Usually immunological causes are proposed, as in some patients with higher risk of drug-induced agranulocytosis particular human leukocyte antigens are being observed [17]. However, this explanation may not be fully applicable for the presented case, as the most unusual issue is persistent and recurring neutropenia caused by various antipsychotic drugs. It has not been reported before, as in the articles cited above, describing various medications, the drop in ANC was usually transient and mediocre [18] and in one of the described cases leukopenia appeared only when drug was used together with clozapine [16]. Differently, in the presented case, neutropenia and leukopenia were present with various severity for over six months, with periodical deterioration associated with changes in treatment, and clozapine was not re-implemented during that time. There is one potentially similar case report from 2011, where the patient developed neutropenia with independent sequential trials of quetiapine, olanzapine and aripiprazole, but said side effects appeared within first initiation of treatment. In that particular case of drug-induced neutropenia in the patient, large genetic component involving clozapine metabolites targeting predominantly peripheral blood neutrophils was suggested as a pathomechanism [23].

Nevertheless, it is important to notice that the patient' mental health and blood results had been stable on clozapine for 10 years. Health condition of the described patient declined after a particular moment – the vaccination and following COVID-19 infection, and those are the factors that should be taken into consideration while searching for possible explanations. There is no evidence of leukopenia or neutropenia during COVID-19 infection that happened in patients using other antipsychotic drugs than clozapine, so analysis is based on the studies considering clozapine only.

The process of full immunization lasts for 2 to 4 weeks after the administered dose of vaccine (WHO Q&A as for 17th May 2022). It is possible that the presented patient contracted a virus while being in serological window period and the infection led to significant drop in absolute neutrophil count. Psychiatric societies were aware of the possible impact of SARS-CoV-2 virus on morphology of clozapine-treated patients. In the described patient's case, neutropenia appeared in connection with a severe COVID-19 infection. Infection itself, especially of the respiratory tract, is a condition in which the activity of CYP450 1A2 is reduced, which increases the risk of clozapine accumulation and adverse effects associated with its use [24]. In this regard, appropriate recommendations have been proposed. Initially, as the pandemic began, the continuation of clozapine treatment was recommended, as sudden disruption in therapy could lead to relapse and have dramatic outcomes in patients with psychotic disorders. In case of infection, reduction of the dosage was suggested [25]. Three years later, in everyday practice this recommendation is mostly limited to cases where clozapine blood level or ANC start reaching abnormal values, as recent studies show that clozapine itself is not a factor responsible for a more severe course of COVID-19 infection [26]. Additionally, the incidence of COVID-19-related neutropenia is not very common, as the percentile presented in studies ranges from 5 to 10%. Severe neutropenia risk is around 0.8% and is more common in people who initially had lower ANC throughout the clozapine treatment. The dose itself did not influence the risk of severe neutropenia [27, 28]. Another risk factor was short treatment time, as drops in ANC were more serious in patients at the beginning of therapy [29] rather than in patients with long-term use of clozapine, but also some exceptions were reported – one case of severe agranulocytosis occurred in patient that had started clozapine treatment in 2007 [30]. The changes in all cell counts generally occur at the beginning of the infection, and usually get back to normal in around a fortnight [11]. Nevertheless, in cited cases neutropenia was either mild or transient and ANC improved with time, reduction of the dose or, in worst cases, after change of medication.

On the other hand, the drop in absolute neutrophil count could be caused directly by the vaccination itself. First reports of the neutropenia following the vaccination against SARS-CoV-2 virus in clozapine-treated patients described the changes in ANC after the second dose of the vaccine [31, 32], but the same effect could also be noticed after the first dose [12]. Most of the reports came from Japan, as this is the country with the strictest regulations considering clozapine treatment, with biweekly blood monitoring in long-term use patients and implementation of said drug during mandatory inpatient care [33]. Similarly, in all the reports more pronounced ANC drops occurred in patients at the beginning of the treatment. The study conducted on a bigger group of patients revealed that a slight group of patients encountered mild granulocytopenia – 3% after the first dose and 5% after the second one. The changes in treatment and monitoring scheme were not necessary. More concerning was the increase in serum blood level of clozapine without the change of the dosage, which was present in 22% of patients after the first dose and 29% of patients after the second one [13]. In one of the referred

cases, the increase was significant enough to cause toxicity symptoms, such as lethargy, excessive salivation, head drop, and sedation [34]. The observed increase may be explained by the inhibition of P450 1A2 cytochrome caused by the vaccination, as this cytochrome is also responsible for clozapine metabolism [35]. This is one of the reasons that could explain the mechanism of neutropenia.

Finally, in one of the lately published case reports the lower effectiveness of vaccination was reported in two patients using clozapine. Both of them received Johnson & Johnson one-dose vaccines without booster, and their level of IgG antibodies was unexpectedly low, suggesting the suppression of immunization caused by the antipsychotic drug [36]. However, the only available systematic review on the topic concluded that even though lower neutrophil count appears in clozapine-using patients that had contracted COVID-19, neither the vulnerability to the illness nor more serious clinical outcomes appear in this group [37].

The grounds for the persistent neutropenia in the case presented above is not known. Supposedly, in the presented case the reason for leukopenia and neutropenia were the same as suggested for other cited cases, but the changes caused by the vaccination or the infection itself were not transient for some reason, differently than in other described patients. It is also possible that the cited cases would present similarly under longer observation. The most probable explanations are synergic side effects of used medication, changes in cytochrome metabolism and the damages induced by the infection itself, that altogether led to prolonged, incorrect reaction for medications other than clozapine.

In conclusion, the presented case of severe absolute neutrophil count drop should be considered as an anomaly rather than a usual occurrence. It is possible that few of the quoted reasons might have caused a synergic reaction resulting in a more dramatic outcome. As an endpoint, it is important to continue the clozapine treatment in times of global COVID-19 pandemic, bearing in mind possible side effects and staying alert to necessary changes in treatment or monitoring scheme.

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