

Case Reports: Treatment-Resistant Schizophrenia with Severe Type 2 Diabetes Mellitus Treated with Clozapine

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Abstract

Objective: Clozapine is regarded as the most effective drug for treatment of schizophrenia but has complex adverse effects associated with hyperglycemia and diabetes mellitus. **Method:** We report that clozapine was very effective to treat positive, negative, and cognitive symptoms and well tolerated to a treatment-resistant schizophrenia patient with severe type 2 diabetes mellitus (DM) under cautious blood-sugar monitoring. **Results:** Clozapine itself and discontinuation of other psychotropic and anticholinergic agents after switching may improve cognitive function and adherence to the treatment regimens for schizophrenia and DM. **Conclusion:** Clozapine can be administered to treatment-resistant schizophrenia patients even with severe DM with caution.

Keywords

Clozapine, Treatment-Resistant Schizophrenia, Type 2 Diabetes Mellitus, Brief Assessment of Cognition in Schizophrenia Japanese Version

1. Introduction

Clozapine (CZP), one of the second-generation antipsychotics, is regarded as the most effective drug for treatment of schizophrenia [1]. In spite of the low risk of extrapyramidal adverse effects, complex adverse effects associated with hyperglycemia and diabetes mellitus (DM) have been reported [2]. Because the use of CZP is limited to severe hyperglycemia and DM, there are few reports of clozapine administration to schizophrenia patients with severe type 2 DM. We report that CZP was very effective and well tolerated to a treatment-resistant schizophrenia patient with severe type 2 DM.

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2. Case Presentation

A 17-year-old man was admitted to a psychiatric practitioner with complaints of persecutory delusion and violence toward his parents from the onset. We diagnosed as schizophrenia according to DSM-IV. Various antipsychotics were administered, but his symptoms did not improve. He was hospitalized many times before he was admitted to our hospital at 29 years old. His antipsychotic history included over 12 mg/day haloperidol for more than five years, 350 mg/day zotepine for more than four years, 20 mg/day olanzapine for a year and a half, 400 mg/day quetiapine for two months, and 8 mg/day risperidone for more than four years. We urged him to take a blood sugar test many times, but he refused out for fear. At 31 years old, he revealed severe uncontrolled type 2 DM (fasting blood sugar: 499 mg/dl, Hb_{A1c}: 13.1%), and hospitalized. Although hyperglycemia improved within a few weeks, it became exacerbated after discharge due to excessive eating.

At 32 years old, he was hospitalized for administration of CZP and treatment of DM. His psychotropic drugs at the time of hospitalization were: 30 mg/day haloperidol, 350 mg/day zotepine, and 10 mg/day risperidone, in addition to 1000 mg/day sodium valproate, 7 mg/day biperiden, 5 mg/day nitrazepam, and 0.25 mg/day brotizolam. He fulfilled the criteria of treatment-resistant schizophrenia [3]. Abnormal values were not detected in blood tests except random blood sugar (420 mg/dl) and Hb_{A1c} (11.0%). After repeated persuasion, we started insulin injection (9 units/day rapid-acting and 8 units/day long-acting), and his blood sugar level decreased. On day 9, the blood sugar was stabilized within the normal range and we tried to start CZP. However, he rejected CZP again because of the adverse effects and long hospitalization for treatment. We argued repeatedly that he could not live a normal life and get a job without treatment for DM and psychotic symptoms, and we hoped to overcome his fear of his “terrifying” neighbors. He accepted our arguments on the 21st day after hospitalization, and 12.5 mg/day CZP was added to his regimen. The dosage was gradually increased to 300 mg/day in 6 weeks. At 6 weeks, he complained sedation and nausea, and his liver enzymes were elevated. The dosage was reduced to 275 mg/day CZP as maintenance. Hallucination and delusion improved, and he exhibited no irritability, anger, or violence. The total Positive and Negative Syndrome Scale (PANSS) score decreased by 26% (from 99 to 73) and the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) z-score increased by 56% (from -1.93 to -0.80) (see [Figure 1](#)). The blood sugar level improved and oral hypoglycemic agents (described

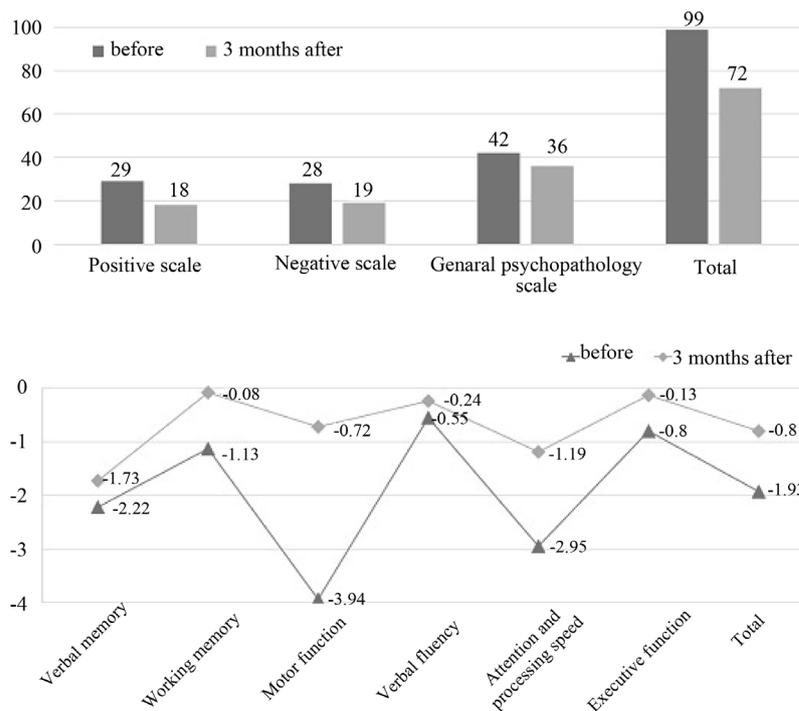


Figure 1. Positive and negative symptom scale (PANSS) (upper) and brief assessment of cognition in schizophrenia (BACS)-J (z-score) (lower) before administration of clozapine and after 3 three months treatment.

below) were administered while tapering insulin. His Hb_{A1c} decreased to 5.5% during the 3-month hospitalization and was stable after discharge. The prescriptions on discharge were 275 mg/day CZP, 5 mg/day nitrazepam, 100 mg/day vildagliptin, and 0.9 mg/day voglibose. More than one year after discharge, his psychiatric symptoms have not recurred. Though he has not worked, he is always in the good mood and sometimes enjoys finance by internet. Because he is able to continue diet and drug therapy for DM, his HbA1c is within normal range.

3. Discussion

CZP is the most effective pharmacologic treatment for positive symptoms of schizophrenia [1] and more beneficial for negative and cognitive symptoms than other antipsychotics [4]. On the other hand, it may alter glucose homeostasis by increasing peripheral insulin resistance and decreasing insulin secretion because of its affinity for muscarinic M3 receptors [5]. Several studies also reported that CZP inhibits glucose transporter expression, which hampers glucose transport through the cell membrane [6] [7]. Based on these mechanisms, the association between diabetic ketoacidosis (DKA) and CZP is strong, and the incidence of DKA with antipsychotics was most frequent in CZP [8]. A grossly elevated HbA1c level is reported in schizophrenia patients with DM presenting with DKA, and these patients are suggested to have undiagnosed DM for at least several weeks before the DKA episode [8]. Although we may discourage the administration of CZP due to the risk of noncompliance, discontinuation of DM treatment or lack of blood sugar monitoring due to severe psychiatric symptoms may subject schizophrenia patients with DM to the risk of life-threatening events such as DKA [8].

When we administrate CZP to schizophrenia patients with severe type 2 DM, two important points are suggested: cautious blood sugar monitoring and improvement of compliance. We checked the blood sugar every two weeks and HbA1c every four weeks following the Clozaril Patient Monitoring Service (CPMS) in Japan. In this case, we monitored glucose almost every day by finger sticks to identify exacerbation of DM as soon as possible. At the point of improvement of compliance, cognitive function may be the most important issue, and CZP is reported to improve cognitive function [4]. Furthermore, discontinuation of other psychotropic and anticholinergic agents improves cognitive function [9] [10]. In our case, after switching to CZP, the chlorpromazine-equivalent dose was reduced from 3030 mg to 550 mg, and anticholinergics were stopped. Subsequently, his feeling of illness may have changed to consciousness of the disease and his adherence to the treatment regimens for schizophrenia and DM may be improved.

4. Conclusion

We would recommend the administration of CZP to treatment-resistant schizophrenia patients even with severe DM, but with close observation.

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