

Weight Loss Associated with Clozapine: A Case Report



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SUMMARY

Clozapine is one of the second generation antipsychotics most commonly associated with serious metabolic side effects including weight gain. Unexpectedly, weight loss can also be seen as a rare side effect of clozapine. The mechanism underlying clozapine induced weight loss is not clearly understood. Several factors including certain brain areas, neurotransmitters, neuropeptides and genetic variants were identified to play a role in weight loss associated with clozapine. In some patients who were reported to have a significant weight loss (13.5-50% of body weight) with clozapine, weight loss might not be associated with any underlying physical disorder. Weight loss may be due to the patients' engagement in diet and exercise after clinical improvement, pharmacodynamic effects of clozapine, or other medical problems such as gastrointestinal tract hypomotility caused by clozapine. Some case reports suggested that clozapine-associated weight loss might be a sign of poor response to clozapine. Clinicians should keep in mind the fact that a specific group of patients may lose weight during clozapine treatment. In this case report, possible causes of weight loss due to clozapine use is discussed. We also discussed the possible relationship between clozapine dose and weight loss which has not drawn attention in previous case reports.

Keywords: Schizophrenia, clozapine, weight loss, treatment resistance

INTRODUCTION

Clozapine is the most effective treatment for treatment-refractory schizophrenia (TRS) (Chakos et al. 2001). Weight gain, metabolic problems, and life-threatening side effects such as agranulocytosis and myocarditis limit the use of clozapine. It has been reported that clozapine produces more weight gain than do other antipsychotics; the weight gain is rapid in the initial weeks and reaches a plateau between 42 and 46 months (Rummel-Kluge et al. 2010). Weight loss associated with clozapine, in contrast, is rarely reported; the literature contains only 15 reported cases of weight loss associated with clozapine. Possible causes are discussed in case reports (Thomas et al. 2009, Hanwella et al. 2010, Osman and Devadas 2016, Das et al. 2018); however, a possible relationship between clozapine dose and weight loss has not been recorded in these reports.

In this report, the case of a patient with schizophrenia whose weight loss resulting from clozapine treatment was alleviated by dose reduction is discussed.

CASE

A 53-year-old male was admitted to our outpatient clinic with the delusions that he was being followed and that a device had been placed in his body. He also thought that he was being talked about on television. He was not able to leave his home on his own and had tremor in his hands. It was learned that his complaints had started at the age of 25 with avolition, anhedonia, suicidal ideation and an incident of suicidal attempt by hanging. He had been put on various antidepressants and had been observed in the follow up period to display irritability, hypermobility and insomnia. He was put on lithium with the diagnosis of bipolar affective disorder. In the later stages of his disorder, he had begun experiencing persecutory and referential delusions

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when he had to be hospitalized four times and diagnosed variously with bipolar affective disorder, schizoaffective disorder and schizophrenia in different healthcare centers. Despite treatments with appropriate dosage and duration using various antipsychotics including olanzapine, quetiapine and zuclopenthixol decanoate, his psychotic symptoms had not improved. He had been on lithium since his complaints had begun and, while maintaining lithium, was also started on clozapine 1 year before admission to our clinic.

It was observed during mental status examination that his associations were loose, his thought contents were pervaded with referential and persecutory delusions. It was learned that he was unable to leave his home on his own because of his fears, had been unemployed for a long time and had difficulty accomplishing everyday tasks.

At the time of his admission, he had been on clozapine (200 mg/day) and lithium (900 mg/day), he weighed 75 kg, his height was 168 cm, and his body mass index (BMI) was 26.6 kg/m². It was planned to titrate the clozapine dose to 500 mg/day within a month, and lithium treatment continued at 900 mg/day because he had been taking this dose for a long time. After 3 months, while on clozapine (500 mg/day) and lithium, the patient's symptoms had not improved, his weight had dropped to 66.9 kg (BMI: 23.7 kg/m²) and the patient reported that his appetite had decreased during this period and that he had vomited once or twice a month. It was learned that he did not follow a low-calorie diet. The serum clozapine level was 720 µg/L (norclozapine: 499 µg/L), and the serum lithium level was 0.83 mEq/L.

In his clinical examination, no clozapine-associated side effects were detected except for hypersalivation and constipation. He did not have abdominal pain, dysphagia or the sensation of food sticking when swallowing. Weight loss could not be explained on the basis of psychotic or affective symptoms. The endocrinology department was consulted for evaluation of weight loss. The results of laboratory investigations including kidney, liver and thyroid function tests, electrolyte levels, sedimentation rate, lipid profile, serum fasting glucose level, serum C-reactive protein level and hemogram were within normal limits. The test for human immunodeficiency virus (HIV) showed nonreactivity. Pathological findings were not detected in posteroanterior chest and abdominal radiography, abdominal ultrasonography or upper gastrointestinal endoscopy.

Sudden weight loss was not considered to be related to lithium and the treatment was continued with the same dose (900 mg/day) because the patient had been on for twenty years. Clozapine dose was reduced to 400 mg/day; and it was observed 2½ months later that weight loss had stopped at 66.5 kg, his appetite had improved, the nausea and vomiting had resolved. It was learned that his TV related suspicions

had ceased and he had begun to go out alone. Treatment with clozapine (400 mg/day) and lithium (900 mg/day) was continued.

DISCUSSION

In this report, a case was presented with longstanding symptoms of schizophrenia not responding to appropriately dosed and timed treatment with various antipsychotic agents and presenting with weight loss after switching to clozapine therapy with dose increase, which was reversed by clozapine dose reduction. Although clozapine is the most effective treatment option for TRS, next to its common side effects, such as constipation, hypersalivation, sedation, and weight gain, rarely observed weight loss is known. Thomas et al. (2009) argued that weight loss in five patients not improving by clozapine treatment may have been a sign of poor response to clozapine. On the other hand, in a review of 12 published cases, Tungaraza (2016) stated that weight loss with clozapine might have been associated with good treatment response resulting in increased physical activity or as a direct effect of clozapine itself. More recently, the case of a patient who could not maintain clozapine treatment at the dosage of 150 mg/day because of nausea and weight loss was reported to be improved after switching to olanzapine treatment (Singh and Bhaumik 2018). Weight loss next to improvement of psychiatric symptoms observed in our patient do not agree with the previous arguments of weight loss being due to bad response to clozapine. Reducing clozapine dose to 400 mg/day stopped weight loss while maintaining the improvement of psychiatric symptoms.

It has also been proposed that improved psychiatric symptoms after clozapine use facilitated weight loss by increased physical activity and dietary compliance (Lally and McDonald 2011, Appriani et al. 2011, Webster and Ingram 2013, Das et al. 2018). In the case presented here, increased physical activity or changes in dietary habits were not observed in as short a period as 3 months.

Hanwella et al. (2010) discussed the possibility of weight loss observed in 3 patients to result from genetic variations in receptors acted upon by clozapine without giving backup data on genetic testing. In our patient, weight loss may have been due to genetic variations in receptors, but further comment cannot be made since genetic testing was not performed.

Dysphagia developed through clozapine use may also cause weight loss. In a case report published in 2016, gastrointestinal hypomotility caused by clozapine was regarded as one of the possible reasons for dysphagia (Osman and Devadas 2016). In our patient, there was not any evidence of swallowing difficulty or intestinal hypomotility.

Although it is unclear whether metabolic side effects of clozapine are dose related or not (Simon et al. 2009), Subramanian et al. (2017) reported that very low dosages of clozapine (<150 mg/day) caused less weight gain than did the standard dosage (301 to 600 mg/day). Weight gain is common in the majority of patients using clozapine, but the weight loss in our patient and in previously reported cases could have resulted from a reverse metabolic process caused by a different pharmacological effect in these patients. The relationship between weight loss and drug dosage was not been reported in previous cases published. To our knowledge, our patient is the first case in which weight loss was improved by clozapine dose reduction.

Clozapine is a second-generation antipsychotic that has effects on dopaminergic (D), serotonergic, (5-HT), muscarinic (M), histaminergic (H), glutamatergic, and adrenergic receptors. This effectivity on multiple receptors is thought to play a role in the mechanism of action specific to clozapine and its side effects (Wenthur and Lindsley 2013). It is known that the antipsychotic drugs that have strong antagonistic effects on dopamine D2, 5-HT2C, muscarinic M3, and histamine H1 receptors cause weight gain, and the antipsychotics that have low affinity to these receptors or have agonistic effects (e.g., aripiprazole and ziprasidone) cause lesser weight gain. Antagonistic effects of clozapine on the 5-HT2C, muscarinic M3, and histamine H1 receptors play a part in weight gain (Volpato et al. 2013). Some investigators have reported that polymorphisms in the 5-HT2C receptor, which is a target of clozapine, have a role in BMI changes caused by clozapine use (Vasudev et al. 2017, Zhang et al. 2016). Individual variations in the effects of clozapine at the receptor level may be taken a reason why weight gain is not observed in a group of patients using clozapine.

Apart from the neurotransmitter systems, the hypothalamus has also been implicated in weight gain due to impairment of its control on body weight resulting from leptin insensitivity induced by clozapine and other antipsychotic agents (Reynolds and Kirk 2010). It was emphasized that the observed BMI increase in patients started on clozapine was associated with the LEP-2548A/G polymorphism of the leptin gene (Kang et al. 2014). It was also reported that the LEPR c.668A>G polymorphism next to that of the LEP-2548A/G was a genetic predictor of the BMI change due to clozapine use (Vasudev et al. 2017). Since genetic investigations were not carried out on the patient discussed here, a genetic link of the observed weight loss cannot be confirmed.

In conclusion, although clozapine is known to be one of the antipsychotic agents most frequently associated with weight gain, it should be kept in mind that some patients

lose weight after starting on clozapine treatment. Weight loss may be secondary to gastrointestinal side effects of clozapine or caused by genetic variations as well as arising from the response to clozapine. To clarify the involvement of genetic variation, additional genetic analyses may be recommended on the subgroup of patients who lose weight with clozapine treatment. Dosage reduction may be effective in alleviating weight loss with clozapine use.

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