CASE REPORT

Clozapine-induced dysphagia with secondary substantial weight loss

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SUMMARY

Dysphagia is listed as a 'rare' side effect following clozapine treatment. In this case report, we describe how significant clozapine-induced dysphagia has led to significant reduction of nutritional intake with subsequent substantial weight loss. An 18-year-old single man with an established diagnosis of treatment-resistant paranoid schizophrenia recovered well on a therapeutic dose of clozapine. However, he was noted to lose weight significantly (up to 20% of his original weight) as the dose was uptitrated. This was brought about by development of dysphagia, likely to be due to clozapine. Addition of nutritional supplementary liquids and initiation of a modified behavioural dietary/swallowing programme, while repeatedly mastering the Mendelsohn manoeuvre technique, alleviated the swallowing difficulties and restored his weight.

BACKGROUND

The prevalence of treatment-resistant schizophrenia is about 30% of all individuals with schizophrenia.¹ Clozapine is the only medication with proven effectiveness for alleviating the positive and negative symptoms of treatment-resistant schizophrenia, and also in reducing overall mortality and death by suicide.^{2 3}

At the receptor level, clozapine has a complex, yet unclear, mechanism of action. Clozapine deactivates mesocortical dopaminergic neurons via blockade of dopamine receptors D₁, D₂ and D₃; whereas the main clozapine metabolite N-desmethylozapine is a partial agonist for D₂ and D₃ receptors.^{4 5} Compared with D₂ and D₃ receptors, clozapine shows a 10-fold higher affinity for D₄ receptors.⁶ Clozapine also has strong affinity for α_1 -adrenergic receptor, 5-HT₆ and 5-HT₇ receptors,⁷ but weak affinity for the D₂ receptor.⁸ Clozapine displayed a mixed profile in terms of its effect on 5-HT_{1A} receptors;⁹ however, it blocks 5-HT₂ and 5-HT₃ receptors.¹⁰

Psychiatrists are encouraged to prescribe clozapine for patients with schizophrenia should an adequate trial of two antipsychotics fail to bring a satisfactory response; however, they should be aware of a range of common adverse effects, specifically weight gain, constipation and sedation.¹¹ Clinicians should also consider the possibility of less common but more serious side effects such as agranulocytosis, cardiomyopathy and myocarditis.^{12 13} Clozapine is also associated with gastrointestinal hypomotility which has the potential to be life-threatening.¹⁴

Dysphagias or deglutition disorders are conditions where narrowing of the oesophageal lumen results in difficulty in swallowing.¹⁵ Dysphagia is listed as a 'rare' side effect following clozapine treatment and its prevalence is unknown and it can easily be overlooked in the context of distressing psychotic symptoms.¹⁶ Dysphagia is assumed to be caused by antagonism of cholinergic receptors resulting in significant reduction in oesophageal motility.¹⁷

In this case report, we bring the theoretical possibility that significant clozapine-induced dysphagia may lead to significant reduction of nutritional intake with subsequent substantial weight loss into a real-life clinical scenario that was experienced by the authors. We also highlight how a structured dietary/behavioural approach towards clozapine-induced dysphagia may stabilise the weight loss process and alleviate such a distressing adverse effect of clozapine. To the best of our knowledge, there were no past reports of substantial weight loss on clozapine secondary to dysphagia.

CASE PRESENTATION

We report on an 18-year-old single man with an established diagnosis of paranoid schizophrenia for 2 years and comorbid Asperger's syndrome for 8 years. Partial remission was noted on oral risperidone and long-acting aripiprazole intramuscular depot injection treatment despite taking them at the maximum possible dose for over 8 weeks duration each. He was readmitted into the inpatient psychiatric unit following a relapse into persecutory delusions of 'his mother harassing him' and auditory hallucinations of 'God ordering him not to drink poisoned water'. He displayed significant hallucinatory behaviour on admission, as he was repeatedly looking over his shoulder, muttering to himself and was quite guarded, suspicious and hardly cooperative during the interview. Compliance on oral and parenteral medications was confirmed by family, his community psychiatric nurse and pharmacist. His baseline haematological and other laboratory tests were all within reference range. A decision was made to start him on clozapine. His weight was 76 kg; height was 181 cm, giving a body mass index (BMI) of 23.2 kg/m². This BMI was noted to have been stable over the year prior to recent admission.

We used the standard clozapine titration method, and the maximum dose reached over the 12-week titration period was 500 mg in two divided doses (100 mg in the morning and 400 mg at bedtime). However, a notable decline was observed in terms

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of his weight as the dose of clozapine was increased. The correlation between the dose and the weight was significantly negative (Pearson's product-moment correlation coefficient $r = -0.88$, $p < 0.001$). This started from week 1, well before a noticeable improvement was appreciated in his mental state. There was no significant change in his exercise pattern; he has always enjoyed walking, before and after the initiation of clozapine treatment. During his active psychotic phase, he was observed to be excessively walking for prolonged hours during the daytime. This pattern was lessened as he showed improvement in terms of his psychotic symptoms. He reported having significant 'difficulty swallowing' 4 weeks following initiation on clozapine treatment. There were no remarkable findings on physical examination. Ear, nose and throat specialists confirmed absence of tangible cause for his dysphagia on endoscopic and radiological examination. During the stage of up-titration of clozapine, he was on no other medication that could have explained the dysphagia. His weight continued to drop at a rate of 2 kg/week, such that by week 10 after initiation of clozapine treatment he lost 20% of his total pre-clozapine body weight.

A concern was raised as to the possibility of dryness of the mucus secretions as a cause for dysphagia. However, adding in artificial saliva did not help the situation. He did complain of nocturnal hypersalivation, which responded satisfactorily to an oral trial of hyoscine hydrobromide. Twice daily dose of the nutritional supplementary liquid Ensure Original that contains a balanced diet of 9 g of protein and 220 nutritional calories was started. An initiation of a modified behavioural dietary/swallowing programme was tried with him three times per day during breakfast, lunch and evening meal. This behavioural programme was focused on introducing thin food initially (such as mashed potatoes) then gradually increasing the thickness of food to swallow while repeatedly mastering the Mendelsohn manoeuvre technique which ameliorates the difficulty in swallowing associated specifically with the upper oesophageal sphincter malfunction.^{18 19} The patient was taught to practice the Mendelsohn manoeuvre by swallowing his saliva first followed by holding his thyroid cartilage for 2–3 s by his index and middle fingers as it elevates during swallowing to help the upper oesophageal sphincter stay open longer. This process was repeated for 7 weeks until his weight improved.

Notably, during the course of clozapine up-titration, the other more frequently reported and expected side-effects of clozapine (such as hypotension, tachycardia, dizziness and myocarditis) were evaluated regularly and a log of the daily vital signs and weekly haematological results was maintained. However, no significant adverse effects were reported apart from nocturnal hypersalivation and dysphagia.

INVESTIGATIONS

- ▶ His clozapine level was 680 $\mu\text{mol/L}$.
- ▶ Haematological and biochemical investigations were unremarkable.
- ▶ Oesophageal barium swallow was normal.
- ▶ Endoscopic examination of the upper gastrointestinal tract (GIT) was normal.

DIFFERENTIAL DIAGNOSIS

- ▶ Dysphagia secondary to antimuscarinic-related dryness of mucus secretion.
- ▶ Gastro-oesophageal reflux disease (GORD).
- ▶ Achalasia.
- ▶ Tardive dyskinesia.
- ▶ Tardive dystonia.

TREATMENT

- ▶ Artificial saliva.
- ▶ Behavioural dietary/swallowing programme.
- ▶ Mendelsohn manoeuvre technique.
- ▶ Nutritional supplementary liquids.

OUTCOME AND FOLLOW-UP

He responded and dysphagia was eased. The rate of decline in terms of BMI was noted to have improved and he started to gain weight at a rate of 0.75 kg/week. He was discharged to community psychiatric follow-up following satisfactory resolution of his symptoms. His weight continued to pick up following discharge although it did not reach the pre-clozapine level.

DISCUSSION

In this case report, we identified a patient who, contrary to the established association between clozapine and metabolic syndrome-related weight gain, lost substantial weight after initiation on clozapine treatment. A number of previous case reports of clozapine-induced weight loss have trickled over the years. Earlier reports indicated an association between clozapine and weight loss that may be related to genetic variability in neuroreceptors.²⁰ In 2011, Apian and colleagues noticed a 10 kg reduction in weight a year after a switch was made from olanzapine to clozapine. They hypothesised that improvement in negative symptoms was the main drive behind loss of weight.²¹ This line of reason was emphasised in the case reported by Lally and McDonald²² when significant improvement in motivation and engagement in regular exercise were produced about by initiation on clozapine. They noted a subsequent striking drop in BMI from 41.5 to 24.8 kg/m^2 . In our patient, we noticed the drop in weight well before significant improvement was apparent on clozapine. Unlike previous reports of clozapine-induced weight loss, the symptoms that set in our patient were largely of delusional and hallucinatory nature rather than negative symptoms. His exercise pattern remained unchanged before and after initiation on clozapine. It would be difficult to relate the weight loss simply to increased intensity of exercise in our patient following significant recovery on clozapine treatment.

Increased obsession about food and diet was reported in clozapine-treated individuals as a potential reason for weight loss.²³ Our patient has a background of Asperger's syndrome, notorious for excessive stereotypic activities. There was no identifiable preoccupation with food or dieting either on subjective report by the patient, or on objective observation throughout his inpatient treatment.

Most recent works indicate an association between baseline BMI and the potential of clozapine-induced weight loss, specifically in the genetically prepared individuals, namely those with LEP-2548A/G polymorphism GG genotype.²⁴ Our patient did have a normal baseline BMI as per the WHO classification; therefore, it was of significant distress for him to lose almost one-fifth of his original body weight by week 10 of clozapine treatment. Unfortunately, we did not have the facility to examine the genetic make-up of the patient.

One more plausible explanation for why our patient has lost weight, given his symptom of difficulty swallowing, could be the slowing effect of clozapine on the oesophagus and the GIT. Clozapine has been associated with a wide range of gastrointestinal effects. Compared with other antipsychotics, clozapine-treated patients were found to have gastrointestinal hypomotility as evidenced by a prolonged colonic transit time, which can be the basis for severe and potentially fatal complications such as bowel obstruction or ischaemia.²⁵

Arguably, two important differential diagnoses are tardive dyskinesia and tardive dystonia. Both conditions are delayed-onset involuntary movements, but tardive dyskinesia presents usually with orofacial dyskinesia, dystonia or, rarely, tremor.²⁶ However, contextualising both conditions in our patient's story makes them unlikely possibilities, for a number of reasons. First, our patient reported no abnormal movements or spasms throughout the course of his inpatient stay. Second, he was just started on the antipsychotic medication, whereas these conditions occur usually after 12–24 months of continuous treatment.²⁷ Finally, given its low D2 occupancy, clozapine is one of the least likely medication to cause tardive dyskinesia or tardive dystonia.²⁷

Another potential explanation for our patient's dysphagia could also be an increased acidity in the oesophagus. Researchers have established that patients on clozapine are twice more likely to be prescribed gastric acid-suppressive agents than other antipsychotics due to development of GORD.^{28–29} Our patient did not present with 'heart-burn' or 'excessive acidity'. Moreover, endoscopic examination failed to identify any signs of acid reflux on the oesophageal mucosa. Furthermore, impairment of swallowing was theorised by researchers to be the causative of GORD not vice versa.³⁰ This is likely to be caused by the effect of clozapine in oesophageal peristaltic movement normally regulated by the vagus nerve. Clozapine is an established selective and partial agonist at the muscarinic M2 and M4 receptors.^{31–32} All muscarinic receptors subtypes are expressed by the oesophageal smooth muscles, making it quite possible to propose that clozapine may exert a cholinergic effect on the upper oesophageal sphincter.³³ Clozapine may, therefore, be believed to exert an excitatory muscarinic effect on the upper oesophageal sphincter promoting an increased muscle tone and, thereby, difficulty swallowing.³⁴ In our patient, there was a satisfactory response to the repeated training for the patient on the so-called Mendelsohn manoeuvre. This is used at the peak of swallowing to keep the hyolaryngeal complex elevated for 2–5 s with a primary target on the upper oesophageal sphincter disorders. This provided further evidence as to the probable effect for clozapine on the oesophagus in our patient.

Notably, many other first-generation and second-generation antipsychotics were reported to cause dysphagia and difficulty swallowing. These include loxapine,³⁵ haloperidol,³⁶ quetiapine,^{37–38} risperidone³⁹ and olanzapine.⁴⁰ However, the prevalence of antipsychotic-induced dysphagia is still unknown and

further epidemiological studies are required to understand the extent of such a distressing adverse effect.

PATIENT PERSPECTIVE

I noticed the difficulty of swallowing first when I was eating sausages. I could not swallow it right. I got some water to help pass it down. I could only swallow yogurt and weetabix at the start. Then, I could hardly eat anything. My weight dropped from 11 stone to 9 stone within few weeks. I knew it was the side effect of clozapine. I did not mind the difficulty swallowing as the medication was helping me. I didn't feel it was particularly bad. By time, further on, with the help of the nursing staff, it resolved. I am gaining weight now as I am up to 10 stone.

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Learning points

- ▶ Clinicians need to be mindful of the rare adverse effects such as dysphagia in the context of clozapine treatment.
- ▶ Clozapine-induced dysphagia is likely to be caused by clozapine cholinergic effect on the upper oesophageal sphincter.
- ▶ Clozapine-induced dysphagia can be treated with addition of nutritional supplementary liquids and initiation of a modified behavioural dietary/swallowing programme and using the Mendelsohn manoeuvre.
- ▶ If not identified and treated early, clozapine-induced dysphagia can lead to undernutrition and subsequent weight loss which can add to the mental distress of the patient.

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