

## Caso clinico

# Clozapine related Ogilvie syndrome with fatal outcome

## *Sindrome di Ogilvie correlata alla clozapina con esito fatale*

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**SUMMARY. Background.** Clozapine, an antipsychotic medication, can ordinarily cause gastrointestinal hypomotility, but clozapine-related Ogilvie Syndrome (colonic pseudo-obstruction) has been reported rarely. **Case Report.** A 29-year-old male was admitted to the emergency department (ED) with complaints of vomiting, abdominal pain, and distension lasting for a day. He was on clozapine therapy due to schizophrenia. An abdominal-CT scan revealed dilation from the cecum to the ileum and he was diagnosed with Ogilvie syndrome. During the observation period in the ED, respiratory distress, hypotension, and alteration in consciousness were observed, and the patient was intubated electively. Arterial blood gas showed primary metabolic acidosis, with a normal anion gap with full respiratory compensation. In the control CT scan there was no visible perforation but distension persisted; the cecum diameter was 93 mm and the colonic wall was thickened. After the CT scan, the patient went into cardiac arrest and died 13 hours after his admission. In this case, excessive colonic dilatation, high WBC, and lactate levels and increased thickness of the colon wall suggest sepsis due to intestinal ischemia. **Conclusions.** Clozapine-related gastrointestinal hypomotility (CRGH) is not a trivial symptom. It can cause Ogilvie syndrome, which can be fatal due to complications. In the current clozapine prescription content, information on CRGH is insufficient. Higher levels of suspicion, lower diagnostic thresholds in the case of mental and psychiatric patients may prevent delays in diagnosis and treatment and result in lower mortality.

**KEY WORDS:** clozapine, gastrointestinal hypomotility, Ogilvie syndrome, mortality.

**RIASSUNTO. Introduzione.** La clozapina, un farmaco antipsicotico, può normalmente causare ipomotilità gastrointestinale, ma la sindrome di Ogilvie (pseudo-ostruzione del colon) correlata alla clozapina è stata segnalata raramente. **Caso clinico.** Un uomo di 29 anni è stato ricoverato nel pronto soccorso (PS) con vomito, dolore addominale e distensione della durata di un giorno. Era trattato con clozapina per schizofrenia. Una TAC addominale rivelò la dilatazione dal cieco all'ileo e gli fu diagnosticata la sindrome di Ogilvie. Durante il periodo di osservazione in PS, sono stati rilevati distress respiratorio, ipotensione e alterazione della coscienza e il paziente è stato intubato elettivamente. I gas ematici arteriosi hanno mostrato acidosi metabolica primaria, con gap anionico normale con compensazione respiratoria completa. Nella TC di controllo non è stata osservata perforazione visibile ma la distensione persisteva; il diametro del cieco era 93 mm e la parete del colon era ispessita. Dopo la TAC, il paziente è andato in arresto cardiaco ed è morto 13 ore dopo il suo ricovero. In questo caso clinico, un'eccessiva dilatazione del colon, livelli elevati di globuli bianchi e lattato e un aumento dello spessore della parete del colon suggeriscono la sepsi dovuta all'ischemia intestinale. **Conclusioni.** L'ipomotilità gastrointestinale correlata alla clozapina (CRGH) non è un sintomo banale; essa può causare la sindrome di Ogilvie, che può essere fatale per le sue complicanze. Nell'attuale contenuto di prescrizione di clozapina, le informazioni su CRGH sono insufficienti. Livelli più elevati di sospetto, soglie diagnostiche più basse nel caso di pazienti con malattie mentali e psichiatriche possono prevenire ritardi nella diagnosi e nel trattamento e comportare una riduzione della mortalità.

**PAROLE CHIAVE:** clozapina, ipomotilità gastrointestinale, sindrome di Ogilvie, mortalità.

## INTRODUCTION

Clozapine, an antipsychotic medication, can ordinarily cause gastrointestinal hypomotility, but Ogilvie Syndrome (colonic pseudo-obstruction) has been reported rarely<sup>1-4</sup>.

Ogilvie Syndrome (colonic pseudo-obstruction) is the acute and massive dilation of the colon without any obvious obstruction, although clinical and radiological findings are suggestive of a mechanical obstruction<sup>5,6</sup>. Advanced age, retroperitoneal trauma, severe infections, cardiovascular, neurological and surgical diseases, electrolyte imbalance, se-

vere constipation and medications that decrease gastrointestinal motility (such as narcotics, tricyclic antidepressants, phenothiazines, antiparkinson, and anesthetic drugs) are held to be the likely etiology for Ogilvie syndrome<sup>2,5,6</sup>. Pathogenesis is generally linked to the inhibition of colonic motility by increased colonic sympathetic tonus or atony of the distal colon due to disruption of sacral innervation<sup>5,6</sup>.

Clozapine is structurally composed of a dibenzodiazepine derivative and a piperazinyl side chain. Clozapine is a cholinergic, muscarinic, histaminergic receptor antagonist as well as dopaminergic and noradrenergic effects<sup>1-4</sup>.

The main cause of ileus due to clozapine is the muscarinic anticholinergic activity of clozapine. Clozapine is associated with conditions such as constipation, bowel obstruction and paralytic ileus caused by disruption of intestinal peristalsis. Another possible factor causing constipation is sedation due to histamine receptor antagonism. The common side effect of using ondansetron, a 5-HT<sub>3</sub> antagonist, for chemotherapy-induced nausea is constipation. The gastrointestinal tract, which contains about 95% of the body's serotonin receptors, may be highly sensitive to the effects of serotonin antagonism. Antipsychotics have multiple effects on various 5-HT receptor subtypes. Clozapine can peripherally affect the 5-HT<sub>4</sub> receptors and 5-HT<sub>3</sub> receptors, which contributes to impaired motility and the severity of constipation and bowel obstruction in some patients<sup>1-5,8-12</sup>. It has been also suggested that clozapine may induce an infection or ileus due to dose related toxicity may develop<sup>1,3</sup>.

Diagnosis is reached through radiological and clinical findings. Abdominal pain and distension are seen in almost every case. Bowel sounds are decreased or absent in 60% of the patients, whereas in 40% of the patients they are normal or increased<sup>5,6</sup>. Abdominal tenderness, guarding and rebound tenderness, intestinal ischemia and perforation may be seen<sup>4,5</sup>. Plain abdominal radiography may show dilated colonic loops, colonic gas shadows without air-fluid levels or levels typical for the small intestine. An abdominal CT scan usually shows that the colonic segments are severely dilated without mechanical obstruction. The diameter of the cecum can be measured as an important finding in treatment and follow-up<sup>5,6</sup>.

Supportive treatment includes discontinuation of oral intake, IV fluids to correct volume deficit, treatment of electrolyte imbalances, mobilization of the patient if possible, nasogastric decompression, rectal enema, and rectal tube application, and cessation of medications that decrease gastrointestinal motility. The most commonly used pharmacological agent is neostigmine – a cholinesterase inhibitor. If supportive treatment fails, colonic decompression can be performed to reduce colonic gas. Surgical treatment is recommended if medical treatment fails, if the cecum has a diameter greater than 12-14 cm, or if signs of peritoneal irritation are present<sup>5,6</sup>. Prognosis in Ogilvie syndrome is related to the severity of the underlying conditions and generally is poor<sup>5,6</sup>. In cases of intestinal ischemia or perforation, mortality increases from 15% to 40%<sup>5</sup>.

In a review published by Katharine et al.<sup>4</sup> in 2009, 8 fatal cases of clozapine-related intestinal obstruction were found and 2 new cases were presented. We found 5 more cases in PubMed as of 2016<sup>7-11</sup>. However, Every-Palmer and Ellis<sup>12</sup> reviewed all reports of serious clozapine-related gastrointestinal hypomotility (CRGH) submitted to the Australian Therapeutic Goods Administration and New Zealand Pharmacovigilance Centre between 1992 and 2013, and they published the research results in 2017. A total of 43,132 people commenced clozapine over a 22-year period. One hundred and sixty were notified as having serious gastrointestinal hypomotility with clozapine the suspected cause and at least 29 patients died. They emphasized that there was insufficient information about CRGH in the current clozapine prescription prepared by regulators. This may be contributing to low awareness of CRGH spectrum and high morbidity and mortality rates.

## CASE REPORT

A 29-year-old male patient was brought to the emergency department with nausea, vomiting, abdominal pain and distension lasting for a day. He was unable to answer questions with full sentences and gave one or two word answers, thus his medical history was obtained from his mother, who stated that the patient's mental state and consciousness level was always the same as in this case. He was using clozapine 2x100 mg for schizophrenia, for which he was going to follow-ups in another hospital. The patient had no history of any other drug use. There had been no recent changes in medication and its dosage. An ulcerated lesion had been found on his tongue and a biopsy had been performed one month earlier which showed well-differentiated squamous cell carcinoma, but he had not received treatment yet.

His vitals were BP: 118/56 mmHg, pulse: 130 bpm, RR: 18 breaths per minute, temperature: 37 °C, SO<sub>2</sub>: 95%. His abdomen was fully distended. Although his abdominal examination was sub-optimal, no abdominal tenderness, guarding or rebound tenderness were detected. The rectal examination showed stool with normal consistency. ECG findings were normal. Lab results were WBC: 19100 x10<sup>3</sup> cells/UL, Na: 134mEq/L, BUN: 22.59mg/dl, Phosphorus: 4.85 mg/dl, Ca: 11.9 mg/dl. Other tests, including the urine analysis, kidney, and liver function tests, were within normal limits.

A plain abdominal X-ray showed dilated colonic loops. An abdominal CT with IV and oral contrast matter did not show any mechanical obstruction and showed dilation from the cecum to the ileal loops. The diameter of the cecum was 87 mm (Figure 1). The patient was diagnosed with Ogilvie syndrome, and his oral intake was stopped. A nasogastric tube was inserted, but there was no drainage. The patient removed the nasogastric tube and refused reinsertion. A surgical consultation was made. A physical examination made by a surgeon showed abdominal distension with no tenderness, guarding or rebound tenderness. An enema was administered and a rectal tube was inserted. Voluminous stool discharge was observed and the surgery department discontinued observing the patient but the patient remained under observation in the ED as his symptoms had not resolved completely. Neostigmine (2 mg) was administered. Colonic decompression was not considered because of the voluminous stool discharge, partial improvement of distension, and unavailability of a gastroenterologist during the night shift. The patient became tachypneic 11 hours after his arrival and was brought to the resuscitation room. Arterial blood gas showed primary metabolic acidosis, with normal anion gap with full respiratory compensation (pH: 7.35 pCO<sub>2</sub>: 37.1 pO<sub>2</sub>: 59 SO<sub>2</sub>: 90% HCO<sub>3</sub>: 20 lactate: 3.5 mmol/L.). The patient was electively intubated due to his dyspnea, changes in consciousness and hypotension (BP: 80/50). No fecaloid material was seen during intubation. With IV hydration his BP improved to 100/60 mmHg. 4.5 mg of piperacillin-tazobactam was administered for possible peritonitis and intestinal ischemia, and the CT scan was repeated since colonic perforation was suspected. The CT scan showed persistence of dilation from the rectum to ileal loops but no perforation. Colonic wall thickness was increased and the cecum diameter was 93 mm (Figure 2). After the CT, scan the patient went into cardiac arrest three times and CPR was performed each time. The patient died thirteen hours after his admission.

## DISCUSSION

Clozapine is an antipsychotic drug used for patients with resistant and prominent negative symptoms<sup>1,4,10,11</sup>. CRGH

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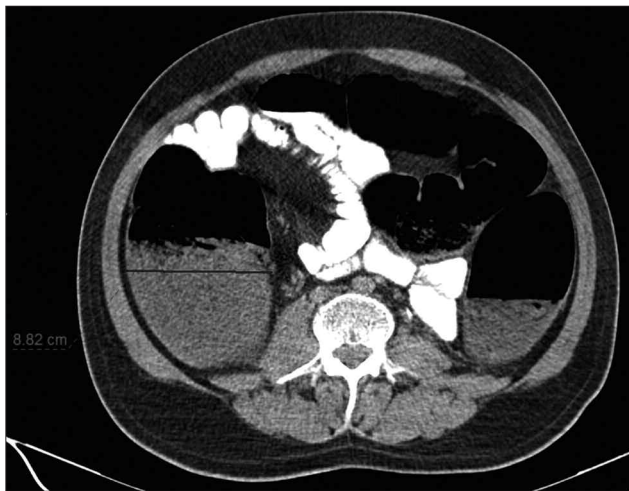


Figure 1. Ogilvie syndrome in a 29-year-old male. Axial CT image obtained after oral and intravenous contrast agent administration demonstrate dilatation of the colon mostly abundant in cecum. The diameter of the cecum is 88 mm.

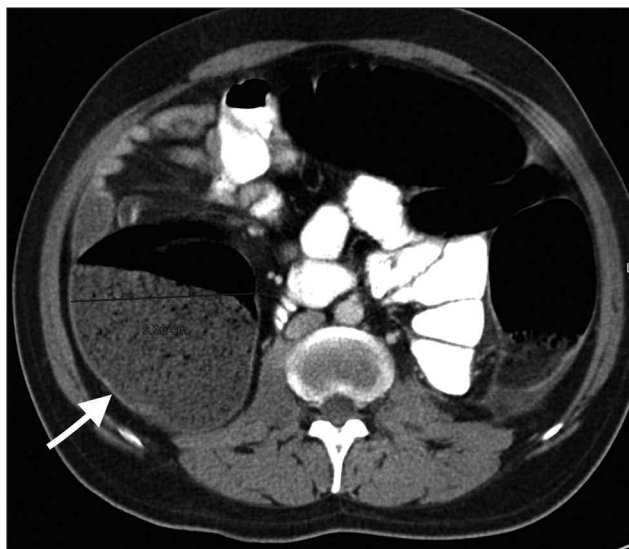


Figure 2. Axial image of CT examination performed 4-hours after initial CT scan reveal progressive dilatation of the cecum with increased diameter as 93 mm and thickening of the colonic wall.

and constipation is seen in 14% of users<sup>4</sup>. The prevalence and severity of the constipation is dose-related, although the latest data suggest a weak correlation between clozapine level and side effects in the absence of sedation, convulsion, and hypotension<sup>9</sup>. Inhibitory effects of clozapine on muscarinic and serotonergic receptors are thought to cause the constipation<sup>1-4,9,11</sup>. A low-fiber diet, lack of exercise and the usage

of other medications that inhibit gastrointestinal motility contribute to constipation in schizophrenia patients<sup>4</sup>.

Schizophrenia patients often cannot describe their symptoms adequately, and proper care might be neglected due to their psychiatric conditions. Furthermore, the pain threshold of schizophrenic patients might be overly high<sup>10</sup>. For these reasons, the level of suspicion should be high in patients with mental and psychiatric diseases.

CRGH is not an insignificant symptom. If an intestinal obstruction occurs, it can cause fecaloid aspiration, intestinal ischemia, perforation, peritonitis, sepsis, and death<sup>4,7-9</sup>. Moreover, intestinal obstruction can cause sudden cardiovascular collapse, convulsion, and ketoacidosis<sup>4</sup>. In this case, the medical course suggested septic shock in the abdominal cavity due to intestinal ischemia. Bacterial translocation can be observed in simple intestinal obstruction even in the absence of intestinal necrosis<sup>13</sup>. Intestinal ischemia caused by obstruction disrupts the mucosal barrier and increases permeability. Normal intestinal flora and bacterial products get into the bloodstream and the sepsis cascade begins<sup>14</sup>. In this case, abdominal pain, persistent distension, high WBC, phosphate and lactate levels and increased thickness of the colon wall suggest intestinal ischemia. No other infection focus was detected. However, the diagnosis is not certain as no autopsy was performed. We criticized ourselves for not being able to recognize intestinal ischemia and for not starting antibiotics soon enough. However, the partial improvement of the patient's abdominal pain and distension, the absence of fever and a cecum diameter under 12 cm had falsely reassured us. The risk of colonic perforation and intestinal ischemia is increased when the diameter of the cecum is above 12 cm and persistent symptoms continue for more than 6 days. Symptom duration is more important than cecum diameter<sup>5</sup>. In this case, as we learned from the patient's mother, symptoms had been present for one day. However, the patient might have been unable to accurately feel and express pain due to schizophrenia<sup>10</sup>. Therefore, the symptoms may have been going on for much longer.

### **CONCLUSIONS**

Gastrointestinal hypomotility related to the antipsychotic clozapine is seen frequently but rarely paid attention to. In addition to attention to the serious and potentially fatal side effects of clozapine, such as agranulocytosis, CNS depression, leukopenia, neutropenia, bone marrow suppression, cardiomyopathy and myocarditis, the possibility of CRGH should be considered that can lead to Ogilvie Syndrome, fecal aspiration, bowel ischemia, perforation, peritonitis, sepsis and death. Physicians should be dynamic at preventing and observing possible bowel obstructions along with patient education on nutrition, and the warning signs of possible bowel obstructions. Increased awareness, higher levels of suspicion, lower diagnostic thresholds in the case of mental and psychiatric patients may prevent delays in diagnosis and treatment and result in lower mortality.

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*Conflict of interests:* the authors have no conflict of interests to declare.

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