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Neuroleptic malignant syndrome after overdose of haloperidol – A case report

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ABSTRACT

Introduction: The Neuroleptic Malignant Syndrome (NMS), alternatively referred to as the Antipsychotic Malignant Syndrome, is a potentially fatal condition that is infrequently observed and is linked to the administration of antipsychotic medications. This syndrome is characterized by a disturbance in consciousness, autonomic instability manifesting as hyperthermia, and muscular rigidity. The onset of this syndrome is typically within the initial month of treatment or following an escalation in the dosage of an antipsychotic medication. This case report delineates a case where NMS was precipitated by an excessive intake of haloperidol, a typical antipsychotic drug.

Case description: In the Emergency Department (ED), a 23-year-old male was admitted following an overdose of haloperidol, a typical antipsychotic drug. The patient exhibited symptoms of tachypnea and tachycardia, and initially presented with hypotension. His level of consciousness was variable, but maximal upon stimulation. Notably, there was a significant increase in muscle tension, characterized by cogwheel rigidity. His body temperature rose to 38.6 degrees Celsius. Laboratory findings revealed a substantial high anion gap metabolic acidosis, with a lactate level of 21.2 mmol/L. Additionally, his creatine kinase level was elevated, measuring 1347 U/L. The therapeutic approach encompassed the intravenous administration of midazolam (2.5 mg), lorazepam (2.5 mg), and biperiden (5 mg), in conjunction with resuscitation involving 2 liters of 0.9% NaCl. The patient demonstrated a positive response to this regimen, leading to his admission to the ward. Following a full recovery, he was discharged from the hospital the subsequent day.

Discussion: The patient in our case fulfilled all the diagnostic criteria for NMS as stipulated in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). NMS is not contingent on the dosage, although an increased dosage does elevate the risk. A thorough review of existing literature did not yield any cases mirroring ours.

Conclusion: In conclusion, we present a case where NMS developed after an overdose of haloperidol.

1. Introduction

The Neuroleptic Malignant Syndrome (NMS), alternatively termed the Antipsychotic Malignant Syndrome, is a seldom observed and potentially fatal condition associated with the utilization of antipsychotic medications [1,2]. This syndrome is characterized by a disturbance in consciousness, autonomic instability (including hyperthermia), and muscular rigidity [2]. The manifestation of symptoms typically occurs over a span of one to three days [1]. The syndrome is most likely to occur within the initial month of treatment or following an increase in the dosage of an antipsychotic. However, it may also emerge after extended usage or upon discontinuation of dopamine-agonists, which are employed in the treatment of Parkinson's disease [1,3].

In this case report, we describe a case where Neuroleptic Malignant Syndrome (NMS) was precipitated following an excessive intake of haloperidol, a typical antipsychotic.

2. Case description

A 23-year-old male was brought to our Emergency Department (ED) around 10:00 am. He was discovered sitting on a bench outdoors by passersby (in July, with an average temperature of 18.8 degrees Celsius that day) who subsequently dialed the emergency number. Upon the ambulance's arrival, the paramedic observed a man in a state of

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obtundation, profusely sweating and exhibiting extraordinary muscle tension. His vital signs were recorded: a respiratory rate of 55 breaths per minute, an oxygen saturation of 97% with 4 liters of oxygen administered via a nasal cannula, a heart rate of 140 beats per minute, and a low blood pressure of 90/60 mmHg. His body temperature was 35.6 degrees Celsius and his glucose level was 7.0 mmol/L. Thus, he was tachypneic, tachycardic, and hypotensive. There were no indications of traumatic injury. The patient disclosed that he had ingested three to five tablets of haloperidol, each presumably 10 mg, the previous evening. He had a history of alcohol abuse and benzodiazepine misuse and had recently become homeless. He was not on any other medication and had not been taking antipsychotics previously. Unable to procure benzodiazepines, he had received haloperidol tablets from another individual at the homeless shelter. The patient had the blister pack in his back pocket, which labeled the medication as haloperidol, but did not specify the dosage. The paramedic inserted an intravenous catheter and administered 2.5 mg of midazolam (a benzodiazepine) intravenously, after which the patient was transported to the ED.

Upon arrival at the ED, we saw a man with a respiratory rate of 32 breaths per minute, maintaining an oxygen saturation of 97% with 4 liters of oxygen delivered via a nasal cannula. There was no evidence of a (lateral) tongue bite. His lung sounds were normal upon auscultation, and he exhibited sinus tachycardia with a heart rate of 130 beats per minute and a blood pressure of 127/65 mmHg. He was sweating excessively. His heart sounds were normal and his abdomen was soft and non-tender upon palpation. His level of consciousness was variable; he was lethargic but achieved a maximum Glasgow Coma Scale score (E4M6V5) upon stimulation. His pupils were three millimeters in diameter, equal in size, and exhibited normal light reflexes. He demonstrated an extremely elevated muscle tone, characterized by cogwheel rigidity. Additionally, he exhibited tremors in both arms and hands. No clonus could be elicited. His body temperature increased to 38.6 degrees Celsius.

The patient's electrocardiogram (ECG) exhibited sinus tachycardia with a rate of 127 beats per minute (shown in Fig. 1). The venous blood gas analysis revealed a pH of 7.15, a CO2 level of 3.2 kPa, a bicarbonate level of 8 mmol/L, and a lactate level of 21.2 mmol/L. This translates into a substantial metabolic acidosis, with an elevated lactate level. The anion gap was calculated to be 42.0 mEq/L, indicating a high anion gap metabolic acidosis (HAGMA). The delta gap was 30.0 mEq/L with a delta ratio of 1.9, suggesting a pure anion gap acidosis. His osmolality was 314 mOsmol/kg. The calculated serum osmolality was 282 mOsmol/kg, resulting in a significant osmol gap of 32 mOsmol/kg. This osmolgap could be entirely attributed to the ethanol level of 0.9 g/L (90 mg/dL). Thus, the high anion gap metabolic acidosis with increased serum osmol gap was completely explained by the elevated lactate and ethanol levels [4].

Additional laboratory results indicated mild renal insufficiency, with a creatinine level of 122 umol/L, mild liver function abnormalities, and an elevated creatine kinase (CK) level of 1347 U/L. There were no indications of inflammation. All laboratory results are presented in Table 1.

Upon arrival at the ED, the patient was initially treated with 5 mg of biperiden administered intravenously to address his dystonia. He was also given a total of 2 liters of 0.9% NaCl over a period of 2 hours. Lorazepam 2.5 mg was administered intravenously. Additionally, he received 50 ml of 8.4% sodium bicarbonate intravenously to treat his metabolic acidosis. To prevent or treat a potential Wernicke's syndrome, he was administered 250 mg of Thiamine intramuscularly.

Following this treatment, the patient's vital signs improved, his lactate levels decreased to 10.7 mmol/L in just over an hour, and his muscle rigidity significantly reduced. Subsequently, the intensive care consultant did not find a need to admit the patient to the Intensive Care Unit (ICU), and the patient was admitted to a regular ward with continued intravenous fluids and lorazepam. The patient made a full recovery shortly thereafter and was discharged from the hospital the following day.

3. Discussion

The Diagnostic and Statistical Manual of Mental Disorders (DSM V) and the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome by Gurrera et al. in 2011 provide established criteria for the diagnosis of Neuroleptic Malignant Syndrome (NMS) [5–7]. The case we discuss herein fulfills all the diagnostic criteria for NMS as per both the DSM V and Gurrera et al., following the consumption of an estimated thirty to fifty milligrams of haloperidol over a span of several hours. These criteria are delineated in Tables 2 and 3 [6,

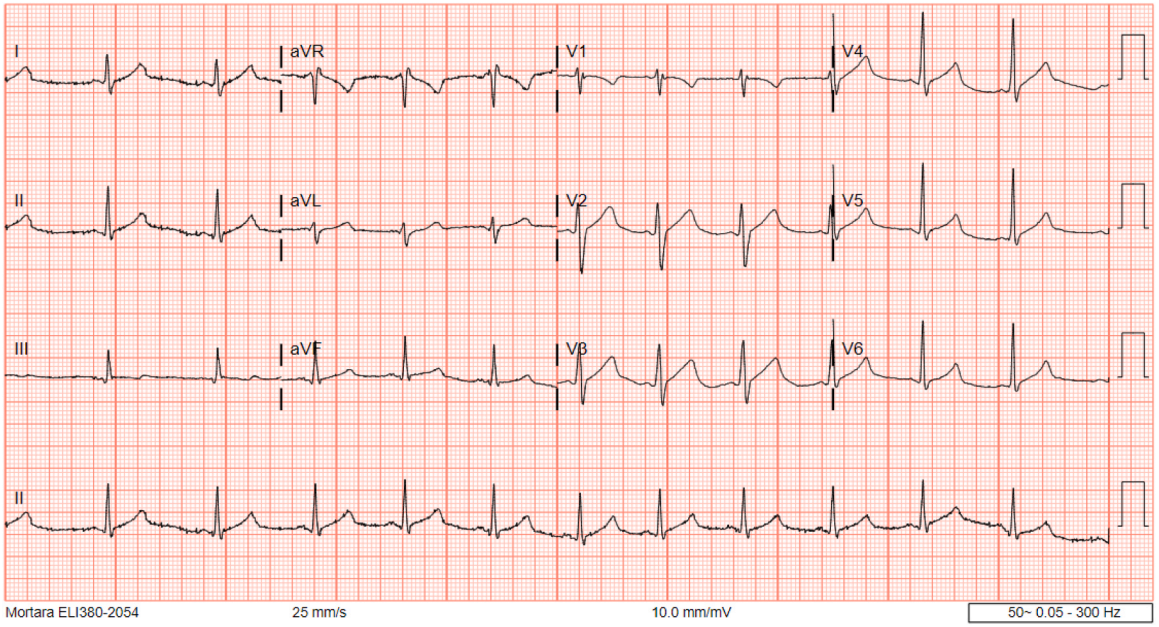

Fig. 1. ECG. ECG description: sinus rhythm with a rate of 73 beats per minute, normal heart axis, a shortened PQ interval of 115 ms, a QRS complex duration of 110 ms, a QT interval of 423 ms, no ST-segment elevation, no pathological Q-waves.

Table 1
Laboratory results.

Hematology	Value in patient	Reference values	
BSE	6	0-15	mm/h
Hemoglobin	9.0	8.5-11.0	mmol/L
Hematocrit	0.446	0.400-0.500	L/L
Erytrocytes	4.53	4.50-5.50	10*12/L
Trombocytes	310	150-400	10*9/L
Leukocytes	15.76	4.00-10.00	10*9/L
Neutrofiles	12.85	1.50-7.50	10*9/L
Lymfocytes	1.65	1.00-3.50	10*9/L
Chemistry			
Sodium	136	136-145	mmol/L
Potassium	3.6	3.8-5.2	mmol/L
Chloride	86	97-108	mmol/L
Bicarbonate	8	22-29	mmol/L
Osmolality	314	275-300	mOsmol/kg
Creatinine	122	64-104	umol/L
eGFR	71	>60	ml/min(1.73_m2)
Ureum	3.7	2.5-7.5	mmol/L
LDH	427	<248	U/L
ASAT	418	<35	U/L
ALAT	201	<45	U/L
Alkaline phosphatase	158	<115	U/L
Gamma GT	125	<55	U/L
Bilirubin total	12	<17	umol/L
C-Reactive protein	4.0	<5.0	mg/L
Creatine Kinase	1347	<171	U/L
Glucose	6.6	3.9-7.7	mmol/L
Ethanol	0.9	<0.1	g/L
Venous blood gas			
pH	7.15	7.32-7.43	[pH]
pO2	12.1		kPa
pCO2	3.2		kPa
Bicarbonate	8		mmol/L
Base excess	-19		mmol/L
Carboxy-Hemoglobin	<1.0	<5.0	%
Met-Hemoglobin	<1.0	<1.5	%
Lactate	21.2	0.5-2.2	mmol/L

Laboratory results

Values indicated in blue are beneath the standard range, while those denoted in red exceed the normative threshold.

7]. To our knowledge, such a case has not been documented in existing literature.

The etiology of Neuroleptic Malignant Syndrome (NMS) remains elusive. It is predominantly associated with older, typical antipsychotics such as haloperidol, but instances with atypical antipsychotics have also been reported. Central to most theories regarding its pathogenesis is the blockade of the D2-dopamine receptor, leading to diminished central dopaminergic activity, although this does not account for all clinical manifestations [8,9]. NMS is not absolutely dose dependent, still higher or rapid escalating antipsychotic doses have been reported as risk factors [8–10]. Certain studies propose a genetic predisposition for its onset [11,12]. Additionally, males have approximately a fifty percent higher likelihood of developing NMS compared to females, and NMS is most frequently diagnosed in young adulthood, peaking at ages 20–25 years. This could however be attributed to the higher prevalence of certain psychiatric disorders among young males for which antipsychotics are prescribed, potentially contributing to the unequal sex distribution of NMS [13].

The incidence of NMS is low, currently estimated at 0.01–0.03% among patients treated with antipsychotics [14,15]. This incidence has decreased over time, possibly due to the transition from typical to atypical antipsychotics, more conservative prescribing practices, and

Table 2
Criteria for neuroleptic malignant syndrome (NMS) as established in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) [6].

Major symptoms	1. Rigidity 2. Hyperthermia (> 38 degrees Celsius, measured minimum 2 times orally) 3. Diaphoresis 4. Exposure to dopamine antagonist within 72 hours prior to the beginning of symptoms
Minor symptoms	*Autonomic nervous system*: tachycardia (rate >25% above baseline), hypertonia (>25% above baseline or with fluctuation), sialorrhea, urinary incontinence, pallor, tachypnoea (>50% above baseline), dyspnea *Mental status:* Altered consciousness: qualitative (delirium), quantitative (stupor to coma) *Motor symptoms*: Tremor, akinesia, dystonia, myoclonia, trismus, dysarthria, dysphagia *Laboratory findings:* ↑Leukocytes, ↑CK, ↑Myoglobin, ↑Catecholamines, ↑Creatinine, ↓Fe, metabolic acidosis, hypoxia
Exclusion criteria	The above-named symptoms are not due to another substance or a neurological or other general medical condition

Table 3
Criteria for neuroleptic malignant syndrome (NMS) as established in the International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome by Gurrera et al [7]. Copyright 2024, Physicians Postgraduate Press. Reprinted by permission.

Diagnostic Criterion	Priority Score
Exposure to dopamine antagonist, or dopamine antagonist withdrawal, within past 72 hours	20
Hyperthermia (>100.4 degrees Fahrenheit or > 38.0 degrees Celsius on at least 2 occasions, measure orally)	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least 4 times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least 2 of the following: 1. Blood pressure elevation (systolic or diastolic ≥ 25% above baseline) 2. Blood pressure fluctuation (≥ 20 mmHg diastolic change or ≥ 25 mmHg systolic change within 24 hours) 3. Diaphoresis 4. Urinary incontinence	10
Hypermetabolism, defined as heart-rate increase (≥25% above baseline) AND respiratory-rate increase (≥50% above baseline)	5
Negative work-up for infectious, toxic, metabolic, or neurologic causes	7
Total	**100**

heightened awareness of side effects [14]. Nevertheless, the identification of this syndrome remains crucial due to its high acute mortality rate, ranging from 5% to 15% [15,16].

NMS is a diagnosis of exclusion, necessitating the ruling out of other diagnoses [1,15]. The differential diagnosis for NMS encompasses several other conditions, including serotonin syndrome, malignant catatonia, malignant hyperthermia, anticholinergic toxidrome, recreational drug use, and medical and neurological disorders such as sepsis and central nervous system infections [9,15].

Serotonin syndrome, which is often confused with NMS, requires exposure to a serotonin-increasing agent for its development, which was not the case in our patient [17,18]. Furthermore, our patient did not exhibit clonus, thereby not fulfilling the Hunter Serotonin Toxicity criteria for diagnosing serotonin syndrome [19]. Malignant catatonia, another differential diagnosis, typically includes a prodromal phase of several weeks with psychosis and agitation. The movement disorders characteristic of each diagnosis differ slightly, with NMS presenting with a coarse tremor and catatonia with more choreiform stereotypy. [20,21] Laboratory values are usually normal with catatonia. However, there is overlap between NMS and malignant catatonia, and these syndromes are sometimes indistinguishable. [10,20] In conclusion, due to the limited information available regarding the patient's symptoms in the weeks preceding his presentation at the ED, and the absence of a comprehensive neuropsychiatric examination at that time, the possibility of malignant catatonia cannot be entirely dismissed at this stage, although our patient's rapid and positive response to therapy makes this diagnosis less likely. Malignant hyperthermia, another medication-induced syndrome to consider, is caused by a rare genetic disorder and presents with severe hyperthermia, muscle rigidity, and autonomic disorder. However, it occurs with the use of halogenated inhalational anesthetic agents and succinylcholine, to which our patient was not exposed, thereby excluding malignant hyperthermia. An anticholinergic syndrome, which can be induced by haloperidol due to its anticholinergic effects, could also be part of the differential diagnosis. Anticholinergic symptoms can include confusion and elevated temperature, but do not encompass diaphoresis, muscle rigidity, and elevated CK levels. The consumption of stimulant recreational drugs, such as cocaine or 3,4-methylenedioxymethamphetamine (MDMA), can also result in symptoms such as elevated temperature, agitation, and confusion. While rigidity is not a typical symptom in these cases, MDMA can induce serotonin toxicity, which may include increased muscle tension [9]. Additionally, withdrawal from certain substances, such as baclofen or gamma-aminobutyric acid (GHB), can induce a syndrome resembling NMS. However, our patient denied any use of recreational drugs. It is also crucial to consider alternative medical and neurological disorders in a patient presenting with confusion and fever, including central nervous system infections (such as meningitis or encephalitis), systemic infections (sepsis), seizures, or a post-ictal state [15]. The patient's laboratory results did not indicate inflammation, with a low C-reactive protein (CRP) level of 4.0 mg/L. Although the patient did not have a tongue bite, we cannot entirely rule out the possibility of a pre-existing seizure.

One could argue that our patient simply suffered from an overdose of haloperidol, exhibiting extrapyramidal and anticholinergic side effects. The patient presented with a clear history of ingesting an excessive amount of haloperidol, as evidenced by the empty blister package found in his back pocket. Haloperidol, a high-potency first-generation (typical) antipsychotic, is widely used globally [22]. Its antipsychotic effects are primarily due to the antagonism of the D2-dopamine receptor within mesolimbic and mesocortical brain regions. Haloperidol is prescribed for psychotic disorders such as acute psychosis, schizophrenia, and acute delirium [23]. Despite its efficacy in managing psychosis, haloperidol's side effects include several unpleasant movement disorders, such as dystonia, akathisia, parkinsonism, and tardive dyskinesia. Moreover, haloperidol blocks several other receptors, including cholinergic and histaminergic receptors, leading to additional side effects such as sedation, hypotension, and weight gain. Due to these side effects, first-generation antipsychotics have largely been replaced by second- and third-generation (atypical) antipsychotics, such as olanzapine and quetiapine. However, haloperidol remains in frequent use, primarily due to its high affinity and strong antagonistic effect on the D2-dopamine receptor [24]. A typical dose for an adult patient would be half to two milligrams two or three times a day for moderate symptoms and three to five milligrams two or three times a day for severe symptoms. The combination with alcohol may potentiate central nervous system depressant effects and hypotension. Consequently, our patient presented with reduced consciousness, transient hypotension, and elevated muscle tension, which could be classified as generalized dystonia in the context of extrapyramidal features. These effects can all be observed following an overdose of haloperidol.

However, we believe the additional symptoms our patient presented with are convincing enough to diagnose him with NMS. Our patient exhibited an altered and fluctuating level of consciousness, ranging from obtunded to a maximal Glasgow Coma Scale score. He demonstrated signs of autonomic dysfunction, and exhibited generalized and extreme muscle rigidity, including typical cogwheel rigidity. His laboratory

results showed an elevated creatine kinase (CK) level of 1347 U/L. While mild to moderately elevated CK levels are not specific to NMS, CK levels greater than 1000 U/L are more specific, and the degree of elevation appears to correlate with disease severity [9,15]. At the outset, the patient's lactate level was recorded at 21.2 mmol/L, a value that signifies a substantial elevation. It is noteworthy that milder increments in lactate levels are frequently observed in cases of NMS [9]. Furthermore, there were no indications of the patient having ingested any substances other than haloperidol and alcohol. Owing to the patient's swift recovery in response to the treatment, further diagnostic procedures such as toxicology screening tests, cranial computed tomography (CT), and lumbar puncture were deemed unnecessary and hence, were not performed.

4. Conclusion

In summary, this report delineates the case of a 23-year-old male patient who manifested Neuroleptic Malignant Syndrome (NMS) subsequent to an excessive intake of 30–50 milligrams of haloperidol within a span of several hours.

CRediT authorship contribution statement

Tim Mieloo: Writing – review & editing, Conceptualization. **Nicole Kraaijvanger:** Writing – original draft, Investigation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Microsoft 365 Copilot and Google Grammarly for Chrome, in order to improve English language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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