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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Atypical neuroleptic malignant syndrome associated with clozapine therapy – case report with literature review

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SUMMARY

Introduction Neuroleptic malignant syndrome (NMS) is a potentially fatal complication of neuroleptic drugs. Over the past few decades, it has been mostly considered as idiosyncratic reaction. The aim of this report is to present the case of an atypical NMS associated with clozapine treatment.

Case outline We describe a case of a young male patient treated with clozapine (400 mg), who developed NMS for the first time during the third relapse of schizoaffective disorder. The patient rapidly developed hyperthermia (40°C), tachycardia, labile blood pressure, confusion, elevated creatine phosphokinase, leukocytosis, and rhabdomyolysis, without muscle rigidity or other extrapyramidal signs. Extensive investigations excluded infectious, neurological, endocrine, and metabolic causes. Antipsychotics were discontinued, and treatment with lorazepam, intravenous hydration, and supportive care resulted in complete somatic recovery. Olanzapine was successfully reintroduced after stabilization.

Conclusion Specific pharmacodynamic profile of clozapine hampers early detection of NMS, since muscular rigidity is rare. Therefore, the presentation of NMS in this case is atypical. Atypical development of NMS during clozapine therapy imposes increased clinical attention.

Keywords: neuroleptic malignant syndrome; diagnostic criteria; clozapine; generic

INTRODUCTION

Neuroleptic malignant syndrome (NMS) was first described by Delay et al. [1] more than 50 years ago, during the treatment with first-generation antipsychotics (FGA). Since then, a growing body of literature demonstrated an incidence range from 0.01% to 3.2% of patients exposed to antipsychotics [2].

Reported mortality from NMS has declined from approximately 27% to 5.6%. This improvement in NMS outcome is due to better recognition of the syndrome and early intervention [3].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for the diagnosis of NMS consist of major criteria (which are all required) and other criteria (at least two required). Major criteria include: exposure to dopamine-blocking agent, severe muscle rigidity and fever. Other criteria are diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, elevated creatine phosphokinase (CPK) [2].

Nierenberg et al. [4] proposed hierarchical organization of symptoms, emphasizing severe muscle rigidity and elevated temperature associated with antipsychotic medication use as cardinal features of NMS, while other criteria include tachycardia, excessive sweating, fluctuating blood pressure, leukocytosis and changes in level of consciousness. However, some researchers consider that autonomic dysfunction also represents one of the key features of NMS [5]. Likewise, altered mental status has also been proposed as one of the main criteria of NMS [6]. Moreover, recent research suggests that clozapine-induced NMS may have an atypical presentation, which implies the absence of muscular rigidity with all other criteria being fulfilled [7]. Also, complicating diagnosis even further is the fact that certain signs and symptoms found in NMS could be observed in other disorders (Table 1) [8].

Several risk factors for NMS have been reported, including older age, dehydration, dementia, parenteral therapy, rapid neuroleptic loading, polypharmacy and adjunctive psychotropics (e.g. lithium) [9].

Although NMS is less common with second-generation antipsychotics (SGA), it has been reported with all antipsychotics in this group, including those with weak D2 effects such as clozapine and quetiapine [5]. To date, extensive research has reported relatively frequent occurrence of NMS during clozapine treatment [10].

The aim of the present case report is to describe atypical NMS during clozapine treatment.

CASE REPORT

A 30-year-old man, high-school graduate, employed, was admitted to our clinic due to the

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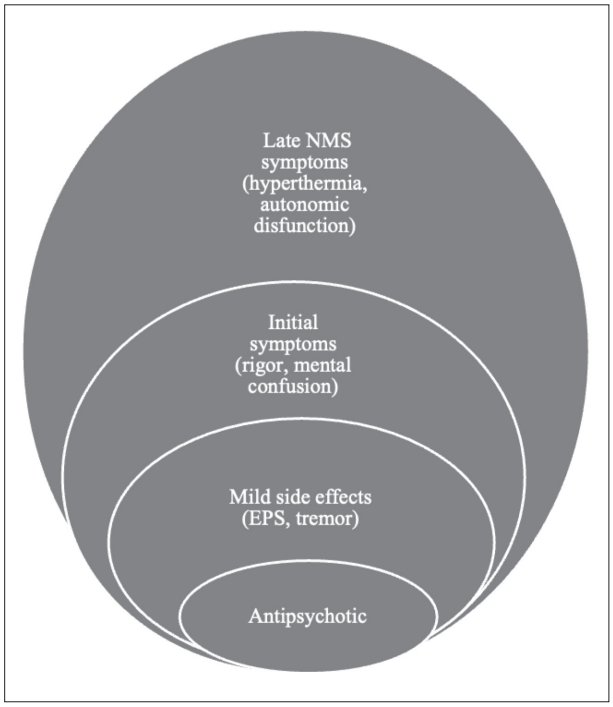

Figure 1. The continuum of neuroleptic malignant syndrome (NMS) and antipsychotic side effects (adapted from Velamoor et al. [20]); EPS – extrapyramidal symptoms

Table 1. Differential diagnosis of neuroleptic malignant syndrome (adapted from Orsolini and Volpe [8])

Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Nonconvulsive status epilepticus
Toxic or pharmacological
Anticholinergic delirium
Malignant hyperthermia
Serotonin syndrome
Substances of abuse
Endocrine
Thyrotoxicosis
Pheochromocytoma

Table 2. Criteria of the neuroleptic malignant syndrome and clinical signs of the patient

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria		Patient
Major criteria (all required)	Exposure to dopamine-blocking agent	X
	Rigidity	
	Hyperthermia	X
Two or more of the following symptoms/signs	Diaphoresis	X
	Dysphagia	
	Tremor	
	Incontinence	
	Changes in the level of consciousness	X
	Mutism	
	Tachycardia	X
	Elevated or labile arterial blood pressure	X
	Leukocytosis	X
	Laboratory evidence of muscle injury (elevated creatine phosphokinase level)	X

exacerbation of Schizoaffective psychosis – F25. The patient has been treated since the age of 19, at the following maximum daily doses:

- Haloperidol 15 mg in combination with levomepromasine 100 mg – insufficient efficacy;
- Clozapine 200 mg (original formulation) – after achieving stable remission, the patient received maintenance dose of 50 mg daily.

Due to the acute exacerbation of his primary condition – schizoaffective disorder, manic type, the patient was hospitalized at the Clinic for Psychiatry. Clozapine dosage (generic formulation) was gradually increased to 400 mg, in the combination with benzodiazepine in the dosage of 10–30 mg daily.

Owing to the further worsening of the patient's condition (high agitation with impulsivity, insomnia, delusions and hallucinatory behavior, with normal somatic and laboratory findings), the patient was treated with a first generation antipsychotic (haloperidol ≤ 5 mg for two days and chlorpromazine ≤ 200 mg for four days) during the episodes of psychomotor agitation, as augmentation therapy. Despite these measures, the patient's condition worsened, primarily due to the altered mental status.

Since the aforementioned augmentation strategies were unsuccessful, we included lithium carbonate, which was proven to be effective in the combination with clozapine in the treatment of schizoaffective disorder [11]. Two hours after receiving a single 300 mg dose of lithium-carbonate (300 mg) with clozapine (400 mg, generic compound) the patient exhibited: hyperthermia (40°C), a rise in the CPK levels (1639 U/L), neutrophilia (85.3%) and lymphopenia (7%), accompanied by increased total white blood cell count (10.2×10^9/l). Physical examination revealed tachycardia (120 beats per minute) and a labile blood pressure (ranging from 120/80 mmHg to 150/100 mmHg), without muscle rigidity and extrapyramidal symptoms. Differential diagnosis was considered according to the criteria presented in Table 1. Viral disease was dismissed after immunological analyses were negative. Computed tomography scan of the brain was normal, as well as the electroencephalography and the endocrine status (levels of thyroxine, thyroid-stimulating hormone and cortisol were within reference ranges). Although the patient did not fulfill the full DSM-5 diagnostic criteria because severe rigidity was absent, the overall presentation was highly suggestive of atypical NMS associated with clozapine therapy (Table 2). Malignant catatonia, which can also manifest by hyperthermia, was considered. Although in 20% of cases NMS and malignant catatonia cannot be distinguished [8], temporal relationship of the onset of symptoms and the use of antipsychotics is suggestive of NMS. Laboratory values are typically normal. In both cases the treatment strategy involves the discontinuation of antipsychotics and the benzodiazepine initiation.

Consequently, an antipsychotic drug was discontinued, and the patient was treated with benzodiazepine therapy (lorazepam 12.5 mg/day), accompanied by intravenous rehydration. In the following seven days the patient's temperature was between 36.5–37.5°C. We did not observe extrapyramidal symptoms, however, laboratory parameters remained elevated: CPK up to 2000 U/L, alanine aminotransferase up to 228 U/L, aspartate aminotransferase up to 160 U/L, gamma glutamyl aminotransferase up to 66 U/L, erythrocyte sedimentation up to 56 mm/hour, accompanied by mild leukocytosis.

In the following seven days, psychomotor agitation, confusion, and hallucinatory behavior remained prominent in the patient's status. The trend of somatic stabilization was observed during the second week of intensive care. On day 10, the laboratory findings were in reference ranges. Psychomotor agitation was reduced; however, confusion remained for the following few weeks (the score on the Mini Mental State Examination was 20/30 in the first week, and 23/30 in the third week). Antipsychotic therapy was reintroduced with olanzapine, administered at an initial low dose and titrated gradually to achieve clinical stabilization. The patient was discharged five weeks after the beginning of the NMS, in partial remission of primary psychiatric disorder and in stable somatic state. A year later, the patient was mostly stable, working and on continuous treatment with moderate dosages of olanzapine.

Ethics: All procedures were carried out in compliance with the institutional and/or national research committees' ethical standards (No.920/5, 08.05.2025), as well as the 1964 Helsinki Declaration and its revisions or similar ethical standards.

DISCUSSION

This case illustrates an atypical presentation of NMS, characterized by hyperthermia, rhabdomyolysis, significant autonomic dysfunction, mental confusion, and agitation, notably without extrapyramidal symptoms such as muscle rigidity.

Regarding the fulfillment of the major DSM-5 criteria, exposure to dopamine antagonists and hyperthermia were present. Severe muscle rigidity was not present in our patient. Of the additional criteria where a minimum of two are required, all were present: diaphoresis, disturbed state of consciousness, variable blood pressure, tachycardia, leukocytosis, elevated CPK up to 2000 U/L. Although one major criterion (rigidity) is absent, the combination of required exposure and fever with all additional diagnostic features and the exclusion of infectious and metabolic mimics makes the diagnosis of NMS in this patient.

Therefore, NMS should be considered as a consequence of: 1) effects of clozapine; 2) effects of lithium; and 3) effects of both clozapine and haloperidol/chlorpromazine.

In this case, clozapine is the most likely primary factor, given the titration up to 400 mg and the recognized ability of clozapine to cause atypical forms of NMS, often with mental status disturbance and autonomic dysfunction [12]. Recent reports have further demonstrated that clozapine itself may induce atypical NMS even in the absence of concomitant treatment with high-potency FGA [13]. Recent pharmacovigilance analyses additionally suggest that multiple neurochemical pathways, including dopaminergic, serotonergic and cholinergic signaling, contribute to the development and progression of NMS, supporting the atypical clinical presentation observed with clozapine therapy [14]. Therefore, early signs – particularly sudden confusion, blood pressure lability, and tachycardia – should raise the suspicion of NMS in patients on clozapine, even when rigidity is absent.

The addition of lithium to antipsychotics has occasionally been associated with the occurrence of NMS. Pope et al. [15] first described NMS associated with clozapine-lithium therapy in a man with past history of NMS with fluphenazine-lithium therapy. Tomcuk et al. [16] recently reported a case where a patient developed NMS after receiving clozapine and lithium, indicating that clozapine, though usually considered safer alternative following NMS can still lead to the syndrome when combined with lithium.

The likely temporal sequence of events in this case – the onset of severe hyperthermia and elevated CPK shortly after the first dose of lithium suggests that lithium acted as an accelerant in an already sensitive system, but does not prove singular causation; which is consistent with the recent report [16].

In polypharmacy, the use of haloperidol and chlorpromazine may contribute to cumulative dopaminergic imbalance; however, in the absence of prolonged exposure or high-dose FGA therapy, they are less likely to represent the sole trigger of NMS [5, 14]. The augmentation with moderate dose of haloperidol in short-time period, without muscle rigidity and other extrapyramidal symptoms is less likely to be the cause of NMS. We have to note that patient had already received haloperidol during the first episode of his mental illness (long-term and in a higher doses) without any complications.

The unique receptor profile of clozapine, characterized by relatively weak D2 receptor antagonism together with potent antimuscarinic and antihistaminergic activity, may explain the atypical presentation of NMS, particularly the reduced incidence of muscle rigidity [17]. The distinctive receptor pharmacology that underlies clozapine's superior efficacy in treatment-resistant schizophrenia may likewise contribute to the atypical clinical phenotype of clozapine-associated NMS [17, 18]. The atypical presentation observed in our patient may also have resulted from synergistic pharmacodynamic interactions between clozapine and chlorpromazine. Nevertheless, chlorpromazine alone has rarely been implicated in NMS, with the available literature limited to isolated case reports.

Rare studies showed that generic clozapine compared to the original formulation causes altered mental symptoms more frequently [19]. This could be the case in our patient, but the data about adverse effects of generic form of clozapine are limited and inconclusive.

In the present case, the clinical course was followed, as shown in the scheme of Velamoor et al. [20]. The patient's condition is worsening through exacerbation of schizoaffective psychosis and despite treatment, it complicated with mental confusion and agitation followed by hyperthermia, autonomic dysfunction and biochemical disorders, which all are signs of late phase of NMS. Namely, dopamine depletion in the mid-brain–cortex–limbic system pathways may be the cause of changes in mental status. Blockade of dopamine receptors in the hypothalamus causes impaired heat dissipation, resulting in hyperthermia [21]. Thus, timely recognition of NMS during the clozapine therapy is hindered by the absence of rigidity, because of clozapine receptor profile.

Our case highlights that the early emergence of changes in mental status such as mental confusion, should cause suspicion of NMS in a patient treated with clozapine, despite the absence of muscle rigidity. Thus, whenever clozapine is administered, regardless of the length of previous treatment and drug tolerability, patients should be carefully monitored in order to detect aforementioned early signs, because that is the only way to act promptly and prevent late complications.

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Атипични неуролептички малигни синдром повезан са терапијом клозапином – приказ случаја са прегледом литературе

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САЖЕТАК

Увод Неуролептички малигни синдром (НМС) јесте потенцијално фатална компликација лечења антипсихотицима која се последњих пет деценија схвата углавном као идиосинкратска реакција. Овај приказ случаја има за циљ да укаже на могућност настанка атипичног НМС-а током терапије клозапином.

Приказ болесника Описан је развој НМС-а код младића леченог клозапином (400 *mg*), који је први пут настао током треће епизоде основне болести (шизоафективна психоза). Код болесника су се брзо развили хипертермија (40° C), тахикардија, нестабилан крвни притисак, ментална конфузија, повишен ниво креатин-фосфокиназе, леукоцитоза и рабдомиолиза, без мишићне ригидности или других екстрапирамидалних знакова. Детаљна испитивања искључила су инфективне, неуролошке, ендокрине и метаболичке узроке. Примена антипсихотика је обустављена, а лечење лоразепамом, интравенском хидратацијом и супортивним мерама довело је до потпуног соматског опоравка. Након стабилизације стања, поново је успешно уведена терапија оланзапином.

Закључак Специфичан фармакодинамски профил клозапина отежава рано препознавање НМС-а, јер је појава мишићне ригидности ретка. Стога овај случај представља атипичну форму НМС-а. Атипичност развоја приликом примене клозапина налаже повишену пажњу клиничара.

Кључне речи: неуролептички малигни синдром; дијагностички критеријуми; клозапин; генерички лекови