NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

CASE REPORT

Arch Neuropsychiatry 2021;58:166–168
https://doi.org/10.29399/npa.27421

Atypical Neuroleptic Malignant Syndrome Induced by Low Dose Quetiapine in a Patient Treated with Donepezil

Elçin ÖZÇELİK EROĞLU, M. İrem YILDIZ, M. Kâzım YAZICI

Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey

ABSTRACT

Neuroleptic malignant syndrome is a rare idiosyncratic drug reaction that causes morbidity and mortality. Although muscle rigidity and fever are accepted as major symptoms, there is no consensus on the diagnostic criteria. This flexibility in diagnostic criteria allows for the diagnosis of atypical cases. Keeping in mind that neuroleptic malignant syndrome may also occur with the use of low doses of atypical antipsychotics is important for making the diagnosis quickly and reducing the risk of morbidity and mortality. In this report, we aim to present a case with atypical neuroleptic malignant syndrome associated with the use of very low dose quetiapine and discuss the risk factors that facilitate its emergence.

Keywords: Quetiapine, antipsychotic agents, donepezil, cholinesterase inhibitors, neuroleptic malignant syndrome

Cite this article as: Özçelik Eroğlu E, Yıldız Mİ, Yazıcı MK. Atypical Neuroleptic Malignant Syndrome Induced by Low Dose Quetiapine in a Patient Treated with Donepezil. Arch Neuropsychiatry 2021;58:166-168.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction to antipsychotic drugs that causes morbidity and mortality (1). In NMS, the neuroleptic drugs block dopamine, which causes hyperthermia, rigidity, altered mental status, elevated creatine kinase (CK) levels, and autonomic dysfunction (2). Symptoms of NMS usually develop within two weeks of antipsychotic therapy or dose changes; however, they may also occur at any stage of treatment and without any dose changes (3,4).

The neuroleptic malignant syndrome was first described in 1960 as a complication associated with the use of haloperidol (5), after which the number of NMS cases increased rapidly in the following years (6). Although NMS is more common with typical antipsychotic drugs, a significant number of cases have also been reported with many atypical antipsychotics, including quetiapine (1,7). However, due to different mechanisms of action of atypical antipsychotics, it has been reported that NMS associated with atypical antipsychotic use may have different clinical features in terms of quantity and quality compared with NMS associated with typical antipsychotic use (7). Although muscle rigidity and fever are considered essential features of diagnosis, different guidelines use different diagnostic criteria. This flexibility in diagnostic criteria allows the diagnosis of atypical cases (1). The present case report discussed an atypical presentation of NMS induced by low-dose quetiapine and risk factors associated with its development.

CASE REPORT

An 84-year-old man was brought to the emergency department of our hospital by his relatives with complaints of drowsiness, appetite loss, low fluid intake, weakness, and urinary incontinence for the past two to three days. After being evaluated by departments of infectious diseases, neurology, internal medicine, and cardiology, the consulting psychiatrist saw the patient in the emergency department upon request. The patient had a medical history of type 2 diabetes mellitus, hypertension, coronary artery disease, and previous cerebrovascular events. The patient had been regularly taking metformin 2000 mg/day, repaglinide 2 mg/day, insulin glargine 11 units/day, acetylsalicylic acid 100 mg/day, clopidogrel 75 mg/day, pentoxifylline 600 mg/day, amlodipine 10 mg/day and pantoprazole 40 mg/day for more than 1 year. The patient's psychiatric history revealed that he had attended our outpatient clinic with complaints of forgetfulness and decreased instrumental activities two years ago, for which donepezil at 10 mg/day was prescribed with the diagnosis of dementia. In addition to this, quetiapine at 12.5 mg/day was started three months ago at another clinic due to complaints of insomnia and irritability.

Physical examination of the head, neck, heart, and abdomen was unremarkable. Chest examination revealed widespread bilateral rales in the emergency department. Confusion, disorientation to time and place, problems with naming and repetition, and mild rigidity in the flexor muscles of the arm and forearm were revealed in the neurological examination. His mental status examination revealed a lack of cooperation, impaired orientation in time and place, distracted attention, and perseverative thought process.

The vital signs of the patient at the time of admission to the emergency department were as follows: body temperature, 37.7°C; pulse, 77 beats/min; respiratory rate, 24 breaths/min and arterial blood pressure, 148/74 mm Hg. The Glasgow Coma Score of the patient was 14. Complete blood

Correspondence Address: Elçin Özçelik Eroğlu, Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey • **E-mail:** elcin.ozcelik@hacettepe.edu.tr
Received: 08.09.2020, **Accepted:** 23.12.2020, **Available Online Date:** 03.06.2021

count (CBC) results showed a leukocyte count of 11.2×10^3/μL, erythrocyte count of 4.36×10^6/μL, hematocrit of 35.7%, and platelet count of 141×10^3μL. His blood biochemistry revealed fasting glucose (blood) level of 316 mg/dL, creatinine of 1.45mg/dL; blood urea nitrogen of 30.59 mg/dL, glomerular filtration rate of 43.91 ml/min/1.73m^2; CK of 585 μg/L and myoglobin of 810.1 μg/L. His serum electrolyte levels, cardiac enzyme levels, and liver function test results were within the normal range. Routine urinalysis revealed no abnormality except for proteinuria and glycosuria. The chest X-ray revealed no infiltration. Normal sinus rhythm was seen in the electrocardiogram. No ischemic or hemorrhagic lesion was detected on brain computed tomography and brain magnetic resonance imaging. His left ventricular ejection fraction was 55%, and left ventricular systolic function was normal on an echocardiogram. With these results, the patient was re-evaluated by the relevant departments. Conditions that could explain the current clinical picture, such as lung infection, acute cerebrovascular event, acute coronary syndrome, and diabetic ketoacidosis, were excluded. Acute kidney injury due to low oral fluid intake was diagnosed.

The neuroleptic malignant syndrome was diagnosed because of the symptoms of muscle rigidity, fever, changes in mental status, increased blood pressure, increased respiratory rate, urinary incontinence, and increased leukocytosis, total CK, and myoglobin levels. Quetiapine was discontinued, and hydration of the patient was planned. A follow-up examination after two days revealed decreased CK, myoglobin, and leukocyte values, which were in the normal range. Symptoms such as rigidity and clouded consciousness improved after one week.

DISCUSSION

In this article, we have presented a case of atypical NMS associated with the use of low-dose quetiapine. Although there is no single set of diagnostic criteria for NMS, at least 10 different diagnostic criteria have been proposed (7, 8). While muscle rigidity, body temperature above 37.5°C, changes in mental status, autonomic dysfunctions, leukocytosis, increased CK were accepted as common diagnostic criteria in many guidelines, some other guidelines suggest that dysphagia, catatonia, mutism, incontinence, metabolic acidosis, and exclusion of other internal diseases should also be considered diagnostic criteria of NMS (7, 8). In the present case, accompanying mild rigidity, body temperature above 37.5°C, mental status changes, leukocytosis, increased CK, and signs of autonomic dysfunction, such as high blood pressure and respiratory rate in the absence of other possible NMS causes have supported the diagnosis of atypical NMS. Following the diagnosis of NMS, quetiapine treatment was discontinued. Although refusal to eat or drink and perseverations suggest catatonia, it should be kept in mind that catatonic symptoms are considered among the diagnostic criteria of NMS by some authors (9). Autonomic dysfunction and changes in mental status seen in patients using quetiapine may also be associated with anticholinergic or serotonergic effects of quetiapine. Thus, anticholinergic syndrome or serotonergic syndrome (SS) should also be considered in the differential diagnosis (10, 11). The anticholinergic syndrome was excluded since our patient did not use any other drug with anticholinergic properties, and peripheral anticholinergic effects were not present. Although there have been reports that quetiapine-induced SS mainly occurs with the use of concomitant serotonergic drugs, single-use of quetiapine may also induce SS (12). In the presented patient, SS was excluded because of the absence of increased bowel sounds, diarrhea, tremor, mydriasis, hyperreflexia, clonus, and myoclonus. Drug interactions should also be considered when NMS is suspected. Several case reports of NMS are associated with cholinesterase inhibitors, especially donepezil alone or in combination with antipsychotics (13, 14). It has been suggested that the imbalance between dopamine and acetylcholine may facilitate NMS in vulnerable patients (14). After discontinuation of quetiapine in the present patient who had been using donepezil for dementia for two years, symptoms of NMS improved, although other drugs, including donepezil, were continued. It was thought that donepezil was one of the facilitating factors for NMS development, but the main factor responsible for NMS occurrence was low-dose quetiapine use.

Although the pathophysiology of NMS remains unclear, dopamine receptor blockade is believed to play a triggering role (11,15). It is argued that dopamine blockade in the nigrostriatal system leads to rigidity, hypothalamic dopamine blockade leads to hyperthermia, and mesocortical dopamine blockade leads to changes in the level of consciousness (15). Moreover, weaker symptoms in patients with atypical NMS may be associated with a lower binding affinity of atypical antipsychotics to D2 receptors in the basal ganglia and hypothalamus (7).

The neuroleptic malignant syndrome is an idiosyncratic drug reaction, which may occur at any treatment stage (4). In some cases reported in the literature, quetiapine-induced NMS has been associated with the use of quetiapine in extremely high doses, indicating a possible dose-dependent relationship (16,17). However, another study reviewing quetiapine-induced NMS cases has shown quetiapine use in doses ranging between 50 and 400 mg/day and different usage periods between seven days and five months (6). In the present case, NMS occurred during the administration of 12.5 mg/day of quetiapine for three months. This was the first NMS case reported with such a low dose of quetiapine.

Although NMS is considered to be an idiosyncratic reaction, there are several factors that increase the likelihood of developing the syndrome. These factors include male sex, being under the age of 40, presence of neurological and medical disorders, use of antipsychotics in the postpartum period, extrapyramidal syndromes, mental retardation, agitation, dehydration, physical restraints, iron deficiency anemia, depot antipsychotic use, rapid escalation of antipsychotic dose, high ambient temperature and history of NMS (1,4). The present case had several factors (such as male sex and concomitant neurological and medical disorders) that increased the risk of NMS and facilitated its emergence after low-dose quetiapine. Although NMS cases associated with atypical antipsychotics are clinically milder and associated with less mortality, attention must be paid to this condition because it results in higher mortality in elderly patients (11).

While prescribing antipsychotics in combination with cholinesterase inhibitors, one has to keep in mind that NMS may be associated with very low doses of atypical antipsychotics in the presence of additional risk factors such as neurological and medical disorders, dehydration, or concomitant use of cholinesterase inhibitors. This would allow early diagnosis and treatment of the syndrome and reduce the risk of morbidity and mortality.

Peer-review: Externally peer-reviewed.

Informed Consent: Verbal consent was obtained from the patient and her relatives.

Author Contributions: Concept - EÖE, MKY; Design - (-); Supervision - (-); Resource - (-); Materials - (-); Data Collection and/ or Processing - EÖE, MİY; Analysis and/or Interpretation - EÖE, MİY, MKY; Literature Search - EÖE, MİY, MKY; Writing - EÖE, MİY; Critical Reviews - MKY.

Conflict of Interest: There is no conflict of interest.

Financial Disclosure: None.

REFERENCES

1. Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS Drugs 2009;23:477–492. [CrossRef]

2. Gurrera RJ, Caroff SN, ohen A, Carroll BT, DeRoos F, Francis A, Frucht S, Gupta S, Levenson JL, Mahmood A, Mann SC, Policastro MA, Rosebush PI, Rosenberg H, Sachdev PS, Trollor JN, Velamoor VR, Watson CB, Wilkinson JR. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 2011;72:1222–1228. [CrossRef]
3. Velamoor, R. Neuroleptic malignant syndrome: A neuro-psychiatric emergency: Recognition, prevention, and management. Asian J Psychiatr 2017;29:106–109. [CrossRef]
4. Schneider M, Regente J, Greiner T, Lensky S, Bleich S, Toto S, Grohmann R, Stübner S, Heinze M. Neuroleptic malignant syndrome: evaluation of drug safety data from the AMSP program during 1993–2015. Eur Arch Psychiatry Clin Neurosci 2020;270:23–33. [CrossRef]
5. Delay J, Pichot P, Lempiere T, Elissalde B, Peigne F. A non-phenothiazine and non-reserpine major neuroleptic, haloperidol, in the treatment of psychoses. Ann Med Psychol (Paris) 1960;118:145–152. https://pubmed.ncbi.nlm.nih.gov/13815606/
6. Gortney JS, Fagan A, Kissack JC. Neuroleptic malignant syndrome secondary to quetiapine. Ann Pharmacother 2009;43:785–791. [CrossRef]
7. Detweiler MB, Sullivan K, Sharma TR, Kim KY, Detweiler JG. Case reports of neuroleptic malignant syndrome in context of quetiapine use. Psychiatr Q 2013;84:523–541. [CrossRef]
8. Singhai K, Kuppili PP, Nebhinani N. Atypical neuroleptic malignant syndrome: A systematic review of case reports. Gen Hosp Psychiatry 2019;60:12–19. [CrossRef]
9. Sachdev P, Kruk J, Kneebone M, Kissane D. Clozapine-induced neuroleptic malignant syndrome: review and report of new cases. J Clin Psychopharmacol 1995;15:365–371. [CrossRef]
10. Almeida F, Albuquerque E, Murta I. Delirium Induced by Quetiapine and the Potential Role of Norquetiapine. Front Neurosci 2019;20:886–889. [CrossRef]
11. Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G, Innamorati M, Pompili M, Amore M. Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. Drugs RD 2015;15:45–62. [CrossRef]
12. El-Gaaly S, St John P, Dunsmore S, Bolton JM. Atypical neuroleptic malignant syndrome with quetiapine: a case report and review of the literature. J Clin Psychopharmacol 2009;29:497–499. [CrossRef]
13. Matsumoto T, Kawanishi C, Isojima D, Iseki E, Kishida I, Kosaka K. Neuroleptic malignant syndrome induced by donepezil. Int J Neuropsychopharmacol 2004;7:101–103. [CrossRef]
14. Mican LM, Schlunberg S. In the Balance: A Case of Neuroleptic Malignant Syndrome When Donepezil Is Added to Maintenance Haloperidol Decanoate. J Pharm Tech 2014;30:235–239. [CrossRef]
15. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;164:870–876. [CrossRef]
16. Khan KH, Tham TCK. Neuroleptic malignant syndrome induced by quetiapine overdose. Br J Hosp Med (Lond) 2008;69:171. https://pubmed.ncbi.nlm.nih.gov/18426017/
17. Teo DCL, Wong HK, Tan SN. Atypical Neuroleptic Malignant Syndrome Precipitated by Clozapine and Quetiapine Overdose: A Diagnostic Challenge. Innov Clin Neurosci 2018;1:15:20–22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145603/