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CASE REPORT

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Neuroleptic malignant syndrome in a patient with moderate intellectual disability treated with olanzapine: A case report

Francesco Piacenza[1] | **Suet Kee Ong**[1] | **Patrick O'Brien**[2] | **Maurice Clancy**[1]

[1]Department of Liaison Psychiatry, University Hospital Waterford, Waterford, Ireland

[2]Brothers of Charity Services, Waterford, Ireland

Correspondence
Francesco Piacenza, Department of Liaison Psychiatry, University Hospital Waterford, Waterford, Ireland.
Email: piacenza.f87@gmail.com

Abstract

This case demonstrates the challenges encountered in a case of Neuroleptic Malignant Syndrome in a young woman with moderate Intellectual Disability.

KEYWORDS

bipolar disorder, intellectual disability, neuroleptic malignant syndrome, olanzapine, psychiatry

1 | INTRODUCTION

We report the case of a 31-year-old woman with moderate intellectual disability (ID) and bipolar affective disorder who developed neuroleptic malignant syndrome (NMS) after being treated with olanzapine. Following discontinuation of the olanzapine, she made a rapid and full recovery.

Neuroleptic malignant syndrome (NMS) is a rare but has potentially fatal adverse side effect more often associated with the use of first-generation antipsychotic medications.[1] However, NMS is also associated with the use of second-generation antipsychotic and antiemetic drugs.[2,3]

Cases of NMS have been reported in patients treated for parkinsonism after dopamine agonist therapy withdrawal or dose reduction.[4]

Typical clinical manifestations include:

- Mental status changes including alteration of the level of the consciousness. Often these symptoms may be underestimated if the patient has a concomitant psychiatric condition.[5]
- Muscular rigidity often characterized by "lead-pipe rigidity" and cogwheel phenomenon.[6]
- Hyperthermia with not unusual spikes over 38°C. However, lower temperatures are more often associated with second-generation antipsychotics.[7]
- Autonomic instability usually presenting with tachycardia, labile blood pressure, and tachypnea.[6]

Relevant laboratory findings include raised serum creatine kinase (CK). The more the muscular rigidity is marked, the more creatine kinase is elevated. CK levels higher than 1000 international units/L are more specific for NMS, and they are linked with a more severe presentation and prognosis.[6]

Leucocytosis and electrolytes abnormalities are common but nonspecific.[6-8]

The incidence of NMS is relatively infrequent, ranging between 0.2% and 3%.[4-6] NMS is a life-threatening condition, and its mortality is estimated between 5% and 20% according to older literature. Mortality is increased in patients with rhabdomyolysis, myoglobinuria, and renal failure.[9] A case report of a patient taking olanzapine 10 mg developed NMS and subsequent rhabdomyolysis-induced acute renal failure that was successfully treated with hemodialysis.[10]

Initial management includes stopping any potential possible causative medications such as antipsychotics or restarting anti-parkinsonian agents.

Benzodiazepines (especially lorazepam and diazepam) are used for the treatment of mental state disturbances such as agitation. Lorazepam can be given also as first line to reduce rigidity. Dantrolene can be used for the same purpose as well.[11]

Fundamental is the supportive treatment with oxygen and measures to reduce temperature and IV fluids. IV sodium bicarbonate is given to prevent renal failure secondary to rhabdomyolysis.[12,13]

Finally, although cases of NMS secondary to olanzapine are not rare,[2] as our patient has a diagnosis of moderate ID, in the literature review, we have analyzed whether people with intellectual disabilities are more prone to develop NMS because of any particular vulnerabilities.

2 | CASE REPORT

In January 2020, a 31-year-old Caucasian woman, with an underlying diagnosis of moderate intellectual disability and a recent diagnosis of bipolar affective disorder in November 2019, was referred to her local emergency department (ED) by her GP requesting medical workup to investigate the cause of new onset impaired mobility.

In the emergency department, she had blood investigations which showed an increase in WBC and neutrophils (respectively, 14.4 mmol/L and 10.53 mmol/L). Chest radiography was unremarkable. Urine dipstick revealed increased leukocytes, and a urinary tract infection (UTI) was diagnosed.

She presented with a history of new physical symptoms for around 1 week:

- Slurring of speech (usually her family are able to fully comprehend her).
- Not able to follow commands (usually compliant).
- Not able to use her hands (usually independent and able, for example, to feed herself).
- Tremor in upper and lower limbs.

She was referred back to ED staff for further organic workup, and she was admitted to a medical ward.

One day following admission, she was referred to the Liaison Psychiatry team, and a full collateral history was obtained from her treating intellectual disability consultant in the community and her mother who is her next of kin. On the same day, a CT brain was performed and nothing abnormal was detected.

2.1 | Collateral history from mother/GP/ID consultant

The patient had been living at home with her parents until 2016 until the age of 27. She was attending the local intellectual disability day services. She was first reviewed by an ID consultant psychiatrist in 2010 when she was diagnosed with generalized anxiety symptoms and prescribed citalopram 20 mg once daily. Subsequently, she made a full recovery and she remained on the same dose of citalopram.

She was seen in a surgical ward in the hospital following a fall by the ID consultant in February and March 2016. At her first review, patient's mood was objectively anxious with separation anxiety in relation to mother in particular. There was no evidence of psychotic symptoms. On March, citalopram 20 mg once daily was stopped and sertraline 50 mg once daily and diazepam 1 mg twice daily were started.

In October 2017, her father died and her grandmother who she was very close to also died after 2 months. Following this, she was initially admitted to a respite unit due to the requirement of enhanced level of care.

In April 2018, sertraline was increased to 100 mg once daily because of anxiety. For the same reason, in July 2018 alprazolam 0.25 mg twice daily + 0.25 mg twice daily PRN were started.

In August 2019, she started presenting with an increased level of anxiety manifesting in repetitive questioning, sometimes irritability, repeated requests for food, frequent requests to go to toilet, and periods of urinary incontinence. This was very much out of character for her.

At this time, she started attending another intellectual disability consultant psychiatrist linked with the community home. In August 2019, alprazolam was discontinued and she was commenced on lorazepam 1mg twice daily PRN. In September 2019, also due to anxiety, mirtazapine 15 mg nocte was commenced. In October 2019, mirtazapine was increased to 45 mg nocte and lorazepam was decreased to 0.5 mg twice daily PRN. She was still on sertraline 100 mg once daily at this time.

In November 2019, there was deterioration in her mental state. She had early morning wakening, her mood appeared elated throughout day, she demonstrated incessant and very repetitive speech with echolalia, and she could not sit still for long periods without hyperactivity. Her symptoms were consistent with an episode of hypomania, and she was diagnosed of bipolar affective disorder. Sertraline was discontinued and quetiapine was started and gradually titrated up to 50 mg mane + 75 mg nocte. Of note, delirium was ruled out as there was no evidence indicating an organic pathology.

There was a slight reduction in her hypomanic symptoms; however, she still presented with pressured speech, flight of ideas, and repetitive behaviors. Her Mirtazapine was reduced to 30 mg nocte. Olanzapine 5 mg once daily + olanzapine 5 mg twice daily PRN were commenced.

After around 5 days, her physical condition deteriorated. Her mobility deteriorated and she became more withdrawn according to her mother. At the same time, she was diagnosed with bronchitis by her GP. She was prescribed the

antibiotic doxycycline, and it was initially thought that the impairment of the mobility was a side effect of the antibiotic.

At review in January 2020, she appeared mildly elated. She was less talkative, appeared calmer, was less repetitive, and her responses appeared more rational although grandiose in manner.

It was mentioned that she had two doses of PRN olanzapine 5 mg which appeared effective to settle her mood. Olanzapine was increased to 5 mg twice daily. Quetiapine reduced to 25 mg mane + 75 mg nocte. Mirtazapine 30 mg nocte and Lorazepam 0.5 mg twice daily PRN were left unchanged.

Unfortunately, she continued experiencing low-grade fever, vomiting, and symptoms of UTI. Furthermore, she was less mobile and she started using a wheelchair and there was an increase in behavioral problems. Therefore, GP directed her to the local ED for further investigation and management. Subsequently she was admitted to the medical ward as mentioned above.

2.2 | Course in hospital in January 2020

At Liaison Psychiatry review, the morning following her medical in-patient admission, she presented with symptoms suggestive of neuroleptic malignant syndrome (NMS): fever (38.2°C), increased muscular tone bilaterally in upper and lower limbs with cogwheel phenomenon. She had a tremor in her upper and lower limbs, reduced mobility, dysphagia, slurred speech, tachycardia (130 BPM), labile blood pressure (140/102-126/80 mm Hg), increased CK (1033 mmol/L), and increased WBC (14.4 mmol/L). She did not present with myoglobinuria (rhabdomyolysis) or change in the renal function.

Collateral history was taken from her carer and her mother. They reported that patient started experiencing physical symptoms and being also more socially withdrawn compared to her usual baseline soon after olanzapine 5 mg once daily was started in December 2019. Her symptoms subsequently deteriorated in January 2020 after olanzapine was increased to 5 mg twice daily. At the time, she was also on quetiapine 25 mg once daily + 75 mg nocte and mirtazapine 30 mg nocte.

It is relevant to mention that when she was on higher doses of both quetiapine and mirtazapine there were no concerns in relation to her physical health and that the symptoms suggestive of NMS started when olanzapine was increased.

Upon Liaison Psychiatry review on the first day of her admission, her olanzapine and quetiapine were both discontinued and she was commenced on diazepam 1 mg TDS, and it was increased to 2 mg TDS the following day. She was also commenced on lorazepam 0.5 mg QDS PRN but it was not necessary to give her this medication at any stage during the course of her medical admission. The day after, mirtazapine was reduced to 15 mg nocte.

During the course of her medical admission, she was regularly reviewed by the Liaison Psychiatry team; her mental state appeared stable.

Her physical condition improved during her admission. CK and WBC decreased, respectively, to 499 mmol/L and 9.8 mmol/L after 1 week.

On discharge after a 10-day admission, patient presented with objectively euthymic mood, no evidence of distress, and no agitation. Nil psychotic symptoms were elicited. She presented brighter, appropriate in her conversation and appeared at baseline; with no pyrexia, normal blood pressure and heart rate, and normal muscle tone in all four limbs. She was discharged on diazepam 2 mg TDS and mirtazapine 15 mg nocte. Her mother reported that she was back to her usual premorbid baseline.

The patient was medically admitted again to University Hospital Waterford 12 days after her previous discharge for treatment of a UTI. Her CK level was 100 mmol/L on admission. She was regularly reviewed by the Liaison Psychiatry team, and she always presented in a stable mental state and without features suggestive of NMS on this second admission. There was no evidence of psychomotor agitation. Her speech was repetitive but comprehensible although it remained mildly slurred. Her mood was euthymic with reactive affect. Nil psychotic symptoms were elicited. She was alert and aware of her surroundings. She was discharged after 1 week on diazepam 2 mg TDS and mirtazapine 15 mg nocte. She is now being treated by the learning disability team in the community. She has remained physically well since her last discharge from hospital six (so far) months ago.

At the time this case report is written (November 2020), the patient has remained stable on a mental state view point and she is maintained on mirtazapine 15 mg nocte, Valproate Chrono 500 mg twice daily, Depo-Provera 150 mg IM every 12 weeks (long acting contraception), and clonazepam 0.5 mg PRN max twice daily.

3 | DISCUSSION

Upon review of the literature, there are only limited reports of cases of NMS, especially in the last 15 years. This could be because this condition is rare and unpredictable.

An interesting question prompted by this particular case is whether there is a correlation between NMS and intellectual disability. A retrospective case note analysis[15] failed to demonstrate a higher than expected prevalence of NMS in clients with learning disability exposed to neuroleptics. Over a 1-year period, from 2000 to 2001, a retrospective case note analysis was completed on all case notes of two Mental Health Learning Disability services in the

West Midlands in the UK, providing a total of 570 cases. There was evidence of regular neuroleptic (did not specify individual antipsychotics or differentiate between typical or atypical antipsychotics) administration in 301 cases, a rate of 47%. It was discovered only two cases in which a patient had symptoms which would give a possible diagnosis of neuroleptic malignant syndrome. This gives a lifetime prevalence of 0.33% (95% confidence interval of 0.0%-1.8%) that is not high, in comparison with other published incidence rates (eg, between 0.2% and 3%).[4-6]

On the other hand, a more recent cohort study from 2017[16] of 9013 adults with intellectual disability and 34 242 adults without intellectual disability reported that although occurring infrequently, neuroleptic malignant syndrome was three times more common in people with intellectual disability-prescribed antipsychotic drugs (incidence rate ratio 3.03, 95% CI 1.26-7.30, P =.013).

It is relevant to consider that patients with diagnoses of intellectual disability are more vulnerable. As in our case, patients with moderate/severe ID can find it difficult to communicate their needs. Furthermore, some core NMS symptoms such as changes in mental state can be interpreted as behavioral symptoms, leading to a diagnostic overshadowing that can delay the treatment of NMS. Our case was also complicated by the concomitant onset of bronchitis. In fact, infections can confound a picture of NMS by sharing symptoms such as hyperthermia, autonomic changes, and also changes in behavior such as decreased motivation and social withdrawal and lack of interest in previous enjoyable activities.

It is relevant to differentiate NMS from serotonin syndrome (SS) as many of the symptoms of both can overlap. A case report[17] described a case of dual onset of both NMS and SS following a poly-drug overdose (venlafaxine, topiramate, divalproex sodium, risperidone, and carbamazepine). However, we are confident that our patient suffered from NMS from a clinical perspective and from a medication timeline perspective. Her mirtazapine medication that may provoke SS[18] was reduced 2 months prior to the onset of her physical symptoms.

From a review of English language literature, there are cases of NMS caused by quetiapine.[19] We were unable to identify any cases of NMS caused by mirtazapine. Also with this case both quetiapine and mirtazapine doses were reduced prior to the onset of the NMS symptoms, NMS symptoms demonstrated a temporal causality with the increase specifically in olanzapine.

One study of relevance in relation to this suggested that elevation of CK is a nonspecific finding, particularly in patients who become pyrexial while on psychotropics; therefore, the inclusion of elevation of CK as a diagnostic criterion may potentially lead to overdiagnosis of NMS if this happens just in the presence of nonspecific features as pyrexia, tachycardia, tachypnea, and diaphoresis.[20]

It is relevant that our patient developed all the four main symptoms of NMS (changes in mental state, muscular rigidity, hyperthermia, and autonomic instability), and laboratory tests showed raised CK and increased WBC. All these classical symptoms highlight all the relevant aspects of NMS, and this is very important from an academic point of view.

In our case, patient was taking olanzapine 5 mg BD regularly when she developed NMS. This is not a high dose. The maximum dose is 20 mg daily.[21] Cases of NMS associated with olanzapine are not rare. In fact, a case review[2] of 26 cases on NMS probably secondary to olanzapine reported that the dose of olanzapine responsible was not always high, being 10 mg once daily in 16 cases and 7.5 mg once daily and 5 mg once daily in other two cases. It is relevant to note that in three cases, patients had intellectual disability (one mild, one severe, and one mild/moderate) and developed NMS at a dose of olanzapine of, respectively, 10 mg once daily, 10 mg QDS, and 12.5 mg once daily.

Frighi et al in their study reported that the median dose of olanzapine in patients with intellectual disabilities is 7.5 mg daily.[22]

In summary, olanzapine needs to be considered as a risk factor for potential NMS in patients with intellectual disability.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTION

FP, SKO, PO and MC were actively involved in the clinical care of the patient. FP and SKO wrote the manuscript. MC revised the manuscript. All authors have revised and reviewed manuscript and have approved the final version.

ETHICAL APPROVAL

This material is the authors' own original work, which has not been previously published elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner.

CONSENT

Consent for the case reported has been obtained from patient's mother as the patient herself was unable to consent.

AUTHOR CONTRIBUTIONS

FP, SKO, PO and MC: were actively involved in the clinical care of the patient. FP and SKO: wrote the manuscript. MC: revised the manuscript. All authors have revised and reviewed manuscript and have approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Francesco Piacenza https://orcid.org/0000-0002-0479-4499

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