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CASE REPORT

Neuroleptic Malignant Syndrome in an Elderly Patient with Bipolar Disorder

WOON LSC[1], NAZIRAH A[1], MOHD MUHAIMIN MH[1], HATTA S[1], WAN ASYRAF WZ[2]

[1]Department of Psychiatry, [2]Neurology Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

ABSTRAK

Neuroleptic malignant syndrome (NMS) atau sindrom neuroleptik malignan adalah sindrom perubatan yang diketahui umum boleh menyebabkan komplikasi kematian dalam kalangan para pesakit yang mengambil ubat-ubatan antipsikotik. Golongan pesakit warga emas dengan pelbagai faktor risiko adalah yang paling terdedah kepada bahaya sindrom ini. Kami membentangkan kes kajian, seorang lelaki yang berumur 80 tahun yang mengalami penyakit kecelaruan dwi-kutub dan sedang dirawat dengan ubat-ubatan sodium valproate 'extended-release', aripiprazole dan suntikan palliparidone yang bertindak secara lama. Beliau disahkan mengalami NMS, dicirikan dengan kekejangan otot menyeluruh, demam, tekanan darah yang turun naik dan kenaikan paras 'creatinine kinase' semasa beliau dimasukkan ke hospital disebabkan oleh episod mania. Faktor penyumbang termasuklah umur yang semakin meningkat, masalah disfungsi Parkinonism jenis vaskular, ketidakseimbangan elektrolit, jangkitan pada paru-paru dengan diperparahkan dengan penyakit obstruktif pulmonari yang kronik, delirium hiperaktif dan penggunaan antipsikotik tipikal secara parenteral. Penggunaan antipsikotik diberhentikan sementara waktu dan pesakit dirawat dengan dantrolene, bromocriptine dan amantadine. Gejala yang dialami beliau beransur baik selepas seminggu. Seterusnya, beliau menjadi semakin sihat dengan rawatan sodium valproate 'extended-release'. Beberapa petunjuk klinikal dibincangkan. Kewaspadaan klinikal, kerjasama inter-disiplinari yang rapat dan intervensi segera adalah kunci kejayaan rawatan NMS dalam kalangan pesakit warga emas.

Kata-kunci: antipsikotik, delirium, haloperidol, neuroleptic malignant syndrome, Parkinsonism jenis vaskular , warga emas

Address for correspondence and reprint requests: Luke Sy-Cherng Woon. Department of Psychiatry, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-9145 6142 Email: lukewoon@ukm.edu.my

ABSTRACT

Neuroleptic malignant syndrome (NMS) is a well-known and potentially fatal complication of antipsychotic use. The elderly population, with multiple risk factors, are more vulnerable to this condition. We described a case of an 80-year-old man with bipolar disorder, previously on oral extended-release sodium valproate, aripiprazole and long-acting injectable paliperidone, who developed NMS. He presented with generalised muscle rigidity, fever, fluctuating blood pressure and elevated creatinine kinase during his hospitalisation for a manic episode. Contributing factors included old age, underlying vascular Parkinsonism, electrolyte imbalance, intercurrent lung infection with acute exacerbation of chronic obstructive pulmonary disease, hyperactive delirium, and repeated administration of parenteral typical antipsychotic. Antipsychotics were withheld promptly, and the patient was treated with dantrolene, bromocriptine and amantadine. His symptoms resolved after a week. He subsequently remained well with oral extended-release sodium valproate alone. Relevant clinical points are discussed. Clinical vigilance, close interdisciplinary cooperation, and prompt interventions are keys to successful to management of NMS in elderly patients.

Keywords: antipsychotic, delirium, elderly, haloperidol, neuroleptic malignant syndrome, vascular Parkinsonism

INTRODUCTION

Antipsychotics are used in the elderly for psychotic and mood disorders, as well as behavioural and psychological symptoms in dementia (Behrman et al. 2018). Among the less frequent but more serious adverse effects of antipsychotics is neuroleptic malignant syndrome (NMS). It was first described in 1960s during early studies on haloperidol (Delay et al. 1960), and is characterised by hyperthermia, rigidity, changes in mental status, and dysautonomia.

Although our knowledge on NMS has increased over the years, relatively little is known about NMS in the elderly. Given the multiple risk factors commonly present in aging patients, such as medical comorbidities, organic brain syndrome, dehydration, malnutrition, and polypharmacy, they should be considered as a high-risk group for NMS (Hall et al. 2006).

Early case reports highlighted the role of typical antipsychotics, especially haloperidol as the causative agent for NMS in the elderly (Addonizio 1987). As the usage of atypical antipsychotics among aging patients increased, more reports of NMS implicating these agents have appeared (Feng et al. 2013; Isik & Soysal 2015; Langley-DeGroot 2016; Dua & Grover 2017). Here we describe a case of NMS in an elderly man with underlying mood disorder and brain pathology involving

the use of both atypical and typical antipsychotics.

CASE REPORT

An 80-year-old male with bipolar disorder presented with a manic relapse. His medical comorbidities included hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), and benign prostate hypertrophy. He also had a history of stroke six years earlier.

For two months, he displayed increased irritability, reduced need for sleep, and talkativeness. There were increased goal-directed activities such as holding a grand birthday feast and planning to marry a second wife, incurring large amount of spending. He also showed grandiosity by proclaiming his close ties to top leaders of the country.

The patient stopped taking his medications three months earlier, complaining of over-sedation and hypersalivation. He was previously on tablet extended-release sodium valproate 1.5 g ON, tablet aripiprazole 20 mg ON, tablet zolpidem 10 mg ON, tablet benzhexol 2 mg BD, and long-acting injectable (LAI) paliperidone 100 mg monthly.

Upon admission, his full blood count, renal, liver and thyroid function tests, and urine analysis were normal. Serum sodium valproate level was within the therapeutic range. Aripiprazole was restarted and increased up to 20 mg OD over two weeks. IM Paliperidone 100 mg was also given on D15 of admission. However, his symptoms did not improve. Aripiprazole was switched to olanzapine on day 22, given his previous record of good response to olanzapine.

In view of observed Parkinsonism features, including shuffling gait and reduced arm swing despite not receiving antipsychotics, he was referred to the neurologist. Computed Tomography (CT) brain revealed an old left lentiform nucleus infarct with age-related generalised cerebral atrophy and small vessel disease (Figure 1). He was treated as vascular Parkinsonism and was continued on tablet aspirin.

Two weeks after his admission,

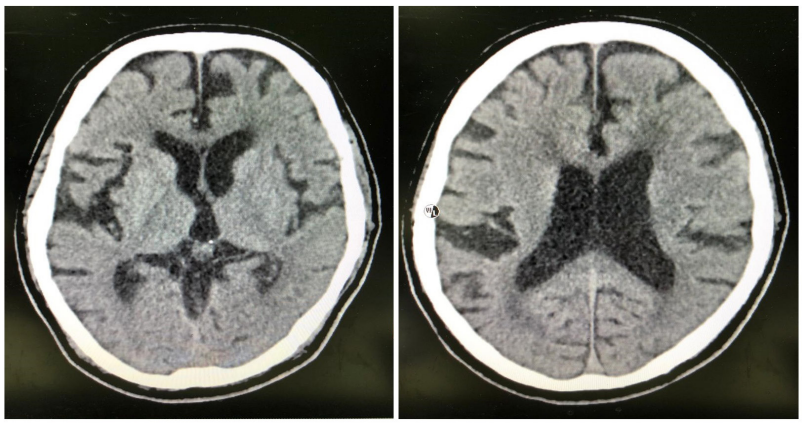

Figure 1: Plain CT brain image of the patient

the patient developed persistent cough, wheezing, shortness of breath, desaturation, and fever. He was treated for acute exacerbation of COPD secondary to hospital-acquired pneumonia, and was started on intravenous antibiotics. He was also found to have hyponatremia, which was subsequently corrected with intravenous hydration.

The patient soon developed hyperactive delirium with fluctuating consciousness, disorientation, and agitation. He experienced fleeting auditory and visual hallucinations as well as paranoid delusions. He was given intramuscular haloperidol 5 mg stat on D28 and had to be physically restrained. He also rejected his oral medication. In the following three days, another two doses of intramuscular haloperidol 5 mg and one dose of intramuscular midazolam 5 mg were given.

On day 35 of admission, the patient developed a temperature spike (37.8°C), fluctuating blood pressure, and generalised rigidity. Creatinine kinase (CK) level was raised at 1,437 IU/L; white cell count was normal (8.3 x 10^9/L). His Glasgow Coma Scale scores were between 12-13/15. A diagnosis of NMS was made. All antipsychotics were withheld. He was transferred to the high dependency unit for close monitoring and was started on intravenous dantrolene 40 mg BD, tablet bromocriptine 2.5 mg TDS, and tablet amantadine 100 mg BD. Hydration and ventilation support were also provided.

The patient's condition improved over the following week. Muscle rigidity resolved early, and CK levels declined progressively. His fever subsided, and he was weaned off oxygen support. His confusion resolved and he no longer manifested manic symptoms since regaining full consciousness. On D44, tablet extended-release sodium valproate was restarted. By D50, it was optimised to 1 g ON. He was not started on any antipsychotic. He was eventually discharged home on D53 of admission.

The patient came for clinic appointment two weeks after discharge. He was manageable at home and could ambulate independently. Except for the pre-existing Parkinsonian symptoms, there were no other residual neurological symptoms. No mood symptoms were elicited. He was adherent to his medications and tolerated them well.

DISCUSSION

NMS is uncommon. Estimations of its incidence vary widely depending on the diagnostic criteria used, prescribing practices, and other local factors. Earlier estimates of NMS incidence associated with typical antipsychotics were about 0.2% (Caroff & Mann, 1993), but more recent studies estimated the incidence to be approximately 0.02% (Spivak et al. 2000; Stübner et al. 2004).

The mortality rate can be as high as 10% to 20% when NMS is not recognised (Caroff et al. 2007). The main complications include cardiopulmonary failure, pneumonia, and myoglobinuric acute renal failure secondary to rhabdomyolysis. As older patients frequently have pre-

existing medical illnesses involving these systems, they are more likely to experience serious complications.

Although NMS is thought to be more common among young, male patients, age and gender are not useful predictors (Caroff et al. 2007). Contrarily, agitation, exhaustion, dehydration, electrolyte abnormalities, and infections are known to predispose to NMS (Kulikowski & Parthasarathi 2019; Keck et al. 1989; Berardi et al. 1998; Bodani et al. 2009). As illustrated in this case, concurrent pneumonia, hypoxaemia secondary to acute exacerbation of COPD, agitation due to hyperactive delirium, and hyponatraemia contributed to the condition.

Moreover, patients with dysfunction of basal ganglia structures (Caroff et al. 2007; Feng et al. 2013; Isik & Soysal 2015) are at higher risk, as with our patient who had vascular Parkinsonism. Since acute reduction in dopamine activity in the brain is thought to be the triggering mechanism of NMS (Caroff 2003; Mann et al. 2000), pre-existing central dopamine hypoactivity in the nigrostriatal pathway could have increased the patient's vulnerability to NMS.

Practically all antipsychotics have been linked to NMS, including LAI paliperidone (Langley-DeGroot 2016). Between LAI paliperidone and parenteral haloperidol, the latter was the more likely causative agent of NMS in our case. The occurrence of NMS is not dose-dependent and can also develop after long-term use of antipsychotic at the same dose (Caroff & Mann 1993). However, high-potency antipsychotics administered parenterally within a short period may carry a greater risk (Keck et al. 1989; Berardi et al. 1998). Quick resolution of symptoms within a week of treatment also suggested that the shorter-acting haloperidol injections were associated with the symptoms.

In hindsight, the repeated usage of parenteral haloperidol could have been avoided if more intensive nursing and medical care were provided for the patient's delirium and underlying medical conditions, while reducing risk factors such as exhaustion and dehydration. There is a need to equip healthcare workers in general medical wards to manage patients with delirium. Staff's stigma towards mental patients with medical conditions is another obstacle to overcome.

The diagnosis of NMS in this patient was fairly straightforward. He fulfilled all three major Levenson's criteria (Levenson 1985) and scored more than 74 for the International Expert Consensus Diagnostic Criteria (Gurrera et al. 2017). It is important to note the variability in severity and presentations in the clinical features, laboratory or imaging findings of NMS (Caroff et al. 2007). CK is typically more than 1,000 IU/L, as seen in this case, and can be as high as 100,000 IU/L, but can also be normal (Feng et al. 2013; Dua & Grover 2017). Conversely, CK can also be elevated in agitated or restrained patients, or caused by intramuscular medications.

Early recognition allowed prompt therapeutic interventions in this case, which was among the essential measures in preventing NMS-related

complications or mortality (Shafti et al. 2019). Besides supportive care, specific treatments, including bromocriptine, amantadine, and dantrolene were also promptly given. While it is difficult to evaluate treatment efficacy in trials due to its uncommon and unpredictable nature, some recent case reports of NMS in elderly patients indicate that bromocriptine, in particular, can be effective (Langley-DeGroot, 2016; Dua & Grover, 2017).

Once diagnosed and antipsychotics discontinued, NMS is usually self-limited. The mean recovery time after drug discontinuation is seven to 10 days, and nearly all within 30 days (Caroff et al. 2007). In a recent review, in comparison to patients with schizophrenia, patients with affective disorders tend to have a later age of onset (mean 43 years versus 32 years) and shorter duration of illness (mean: 11 days versus 23 days) (Srinivasan 2019); our case appeared to match this pattern.

CONCLUSION

NMS is rare but potentially fatal. Its diagnosis is often challenging, as its symptoms may mimic other medical conditions. This is especially true among the elderly. Measures for risk reduction, early recognition, and prompt treatment can be life-saving. Close inter-disciplinary collaboration is required to achieve successful treatment outcomes.

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