The Journal of Medical Research

Case Report

JMR 2017; 3(5): 214-216
September- October
ISSN: 2395-7565

www.medicinearticle.com
Received: 09-10-2017
Accepted: 28-10-2017

Recurrent episodes of sinus arrest in neuroleptic malignant syndrome: A management challenge for physicians

Kashif Bin Naeem[*1], Vinod Choondal[2], Najiba Abdulrazzaq[3]*

1 *Specialist in Cardiology, MRCP (UK), Dip National Board of Echo, Raleigh, North Carolina, USA*
2 *Specialist in Neurology, Al Baraha hospital, Dubai, Ministry of Health and Prevention, UAE*
3 *Consultant Internist, Head of Department, Al Baraha hospital, Dubai, Ministry of Health and Prevention, UAE*

Abstract

Neuroleptic malignant syndrome (NMS) is a rare, potentially lethal, idiosyncratic disorder related to the use of neuroleptic agents that produce dopaminergic blockade. The disorder is characterised by several cardinal features, including autonomic dysfunction, altered mental status, muscular rigidity and hyperthermia. The common cardiac feature mentioned in various diagnostic criteria for NMS is tachycardia. We report a 27 year old lady who presented with cardinal features of NMS. Soon after presentation, she developed severe bradycardia (lowest 35/min) followed by documented episodes of sinus arrest lasting up to 9 seconds. She was managed in intensive care unit with temporary pacemaker and recovered after 2 weeks of intensive management. We conclude that although NMS is usually associated with tachycardia, one might face transient episodes of prolonged sinus arrest that pose a significant management challenge for physicians.

Keywords: Sinus arrest, Neuroleptic malignant syndrome, Pacemaker.

INTRODUCTION

Neuroleptic malignant syndrome is a rare but life-threatening, idiosyncratic reaction to neuroleptic/antipsychotic medication. It is characterized by fever, muscular rigidity, altered mental status,autonomic dysfunction and elevated creatine phosphokinase [1]. It was first described in association with the use of neuroleptic haloperidol in 1960 by Delay *et al* [2]. Incidence rates for NMS range from 0.02% to 3% among patients taking neuroleptic drugs [3]. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for diagnosis of NMS includes cardiac features like high/labile blood pressure and tachycardia, However, we report a rare case of severe sinus bradycardia and episodes of sinus arrest associated with NMS.

CASE Report

A 27 year old female, a graphic designer, from Vietnam, was transferred to our center from the mental health hospital with complaints of sudden onset fever and generalized rigidity. She initially presented to the mental health hospital with an acute psychotic episode. She had been using anti-psychotic medications in the past. While in the mental health hospital, she received high doses of anti-psychotic and sedative medications. She was given intravenous haloperidol injections at a total dose of 110 mg in five days. She also received 300 mg total dose of promethazine and 100 mg of olanzapine. Seven days later, suddenly she developed high grade persistent fever, generalized muscle rigidity, increased irritability and confusion. A provisional diagnosis of neuroleptic malignant syndrome was considered and all the anti-psychotic medications were held. The patient was then transferred to our center for further management.

She was admitted directly to the intensive care unit under close monitoring. Her blood pressure (BP) was 178/90 mmHg, heart rate 139/min. Her initial laboratory tests showed normal complete blood count, high creatinine (111 IU/L), normal liver function tests and normal electrolytes. However, serum creatine kinase (CK) was markedly raised at 4218 IU/L. Initial electrocardiography (ECG) showed sinus tachycardia with increased corrected QT interval (QTc) 518 ms (upper limit for women 460 ms) (Image 1). All neuroleptics

***Corresponding author:**
Dr. Kashif Bin Naeem
Specialist in Cardiology, MRCP (UK), Dip National Board of Echo, Raleigh, North Carolina, USA
Email:
kbncardiology[at]yahoo.co.uk

were already withdrawn. She was commenced on intravenous labetalol to control her BP.

In view of her persistent agitated behaviour, she was electively intubated and ventilated next day after discussion between medical and intensive care physicians. She was treated by the neurologist with pramipexole (D2 receptor agonist, 180 mcg 8 hourly), levodopa/carbidopa (DA agonist, 110 mg 8 hourly), baclofen (GABA agonist, 5 mg 8 hourly) and midazolam infusion. After 1 week of admission, she developed recurrent episodes of severe sinus bradycardia, lowest 35/min, without any hypotension. As BP was normal, she was initially given intravenous injections of atropine as needed with temporary improvement.However, she began to manifest episodes of sinus arrest, longest up to 9 seconds at day 7 (Image 2). She was commenced on intravenous isoproterenol infusion but developed severe hypertension and hence the infusion was stopped. An external transcutaneous pacemaker was then placed on demand rate of 60/min.

Gradually, the duration of sinus pauses reduced as her general condition improved (Image 3). Her follow up laboratory tests showed gradual improvement in serum CKlevels(Table 1). Magnetic resonance imaging (MRI) brain was performed that was reported normal. After 2 weeks of stay, she was gradually weaned off sedation and extubated successfully. The episodes of bradycardias resolved and the pacemaker was turned off. She was commenced on quetiapine 100 mg 12 hourly after 2 weeks with clonazepam 0.25 mg 8 hourly that was tolerated well.A follow up ECG showed normal corrected QT interval. After 5 weeks of intensive care, she was transferred back to the mental health hospital for further care.

Table 1: Serial serum creatine kinase measurements.

Days after admission	Serum creatine kinase (IU/L)
Day 1 (day of admission)	4218
Day 2	3210
Day 3	1224
Day 4	919
Day 5	778
Day 10	471
Day 13	228
Day 19	92
Day 34 (day of discharge)	72

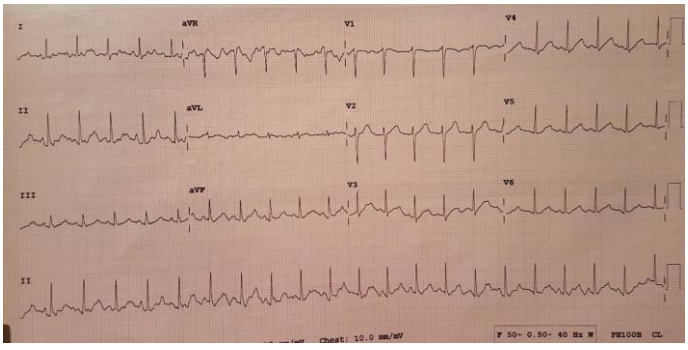

Figure 1

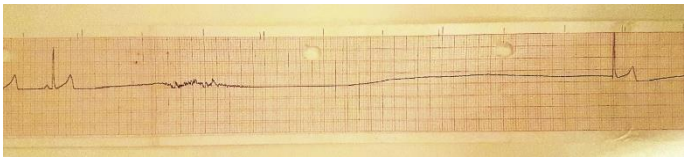

Figure 2

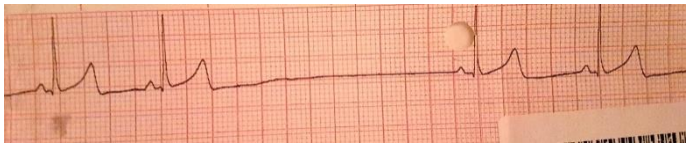

Figure 3

DISCUSSION

Neuroleptic malignant syndrome (NMS) is a rare, but life-threatening idiosyncratic reaction to neuroleptic/anti-psychotic medications. It is characterised by fever, muscular rigidity, altered mental status, autonomic dysfunction and elevated creatine phosphokinase [1]. The pathophysiology involves reduced dopamine (DA) activity in the central nervous system either from blockade of dopamine type 2 receptors or decreased availability of DA itself. Central DA blockade at the hypothalamus level results in hyperthermia and autonomic instability resulting in arrhythmias, labile blood pressure and breathing problems. At the corpus striatum level, this results in rigidity and tremors. Other features result from sympathetic overactivity and direct peripheral muscle effect (rhabdomyolysis). It is most often associated with typical high-potency neuroleptics (e.g. haloperidol, fluphenazine) [4].However every class of neuroleptic has been implicated, including the low-potency neuroleptics (e.g. chlorpromazine) and newer atypical antipsychotics (e.g. clozapine, risperidone, olanzapine) as well as antiemetic drugs (e.g. metoclopramide, promethazine) [5]. Risk factors for developing NMS include psychomotor agitation, higher doses of neuroleptics (mean and maximum dose), greater neuroleptic dose increments over a short period of time (increased dose within 5 days and parental administration of drugs especially depot intramuscular (IM) preparations [6]. Our patient received high cumulative doses of haloperidol, promethazine and olanzapine rendering her at high risk to develop NMS.

The diagnosis of NMS is essentially clinical and no pathognomonic tests exist. Levenson in 1985 had proposed a set of diagnostic criteria, incorporating physical signs and routine laboratory tests which are being used routinely to diagnose NMS [7]. Major criteria include fever, rigidity and elevated creatinine phosphokinase concentration. Minor criteria include tachycardia, abnormal arterial pressure, altered consciousness, diaphoresis and leukocytosis. All the three major or two major and four minor, criteria suggest a high probability of NMS, if supported by clinical history. Further guide to diagnosing NMS is provided by the Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-5, 2013) criteria for diagnosing NMS. Our patient fulfilled all the criteria for the diagnosis of NMS and hence managed accordingly.

It is worth noting that all the criteria include tachycardia and do not mention possibility of bradycardia in NMS. However, our patient developed severe sinus bradycardia followed by episodes of sinus arrest. Although she maintained her blood pressure, she needed temporary supportive treatment and close monitoring. Parry *et al* (1994) reported a case of recurrent sinus arrest in association with neuroleptic malignant syndrome that required insertion of temporary pacing wire [8]. To our knowledge, this is the only other reported case.

The hallmark laboratory finding is raised creatine kinase (CK). It is typically more than 1,000 IU/L and can be as high as 100,000 IU/L. This reflects rhabdomyolysis due to muscular rigidity. The degree of CK elevation seems to correlate directly with disease severity and higher levels are consistent with a worse prognosis [7]. Other laboratory abnormalities include leukocytosis, renal and liver dysfunction, and electrolytes disturbances. Our patient had very high CK values (as shown in Table 1) consistent with the diagnosis of NMS.

NMS is known for its diverse clinical presentation, where clinical features may be easily missed causing delay in diagnosis. Features like muscle rigidity, hyperthermia and mental changes are quite similar to

those of malignant hyperthermia (MH), central cholinergic syndrome and serotonin syndrome. Severe central nervous system infection, tetanus, and drug interactions with monoamine oxidase inhibitors can also mimic this picture [9]. We considered all the differentials in our patient and excluded each clinically.

NMS is a medical emergency that needs immediate recognition and prompt treatment. The patient is best monitored in intensive care unit where treatment is largely supportive. The principles of management include withdrawal of neuroleptics/anti-psychotics, maintain cardio-respiratory stability, that may include mechanical ventilation, antiarrhythmic agents or pacemakers [8] and maintain euvolemic status with intravenous (IV) fluids accounting for fever and diaphoresis. In case CK is very high, high volume IV fluids and urine alkalinization with IV sodium bicarbonate [$Na(HCO_3)$] may help to prevent renal failure from rhabdomyolysis [10]. Specific pharmacotherapy is controversial as randomized controlled trails are lacking and recommendations are based on consensus and expert opinion only. Major options include bromocriptine (central DA agonist), levodopa/carbidopa (DA agonist), amantadine (release DA from dopaminergic terminals and other central sites) and dantrolene (skeletal muscle relaxant via inhibition of calcium release from sarcoplasmic reticulum). Treatment must continue for several days after the resolution of symptoms and gradually tapered off. Sudden withdrawal of treatment inspite of recovery is discouraged [11]. Most episodes of NMS resolve within 2 weeks and reported mean recovery times are 7–11 days [5]. Reported mortality rates for NMS are 5–20%. Patients can be resumed on neuroleptics. However, certain precautions need to be taken [3]. Wait for at least 2 weeks, use low-potency drugs, gradually build up doses, avoid concomitant lithium, avoid dehydration and carefully monitor for symptoms of NMS.

Our patient fulfilled all the criteria for the diagnosis of NMS as per Levenson and DSM-5 criteria. She was immediately recognised and promptly treated. However, she developed episodes of sinus arrest that was treated supportively and resolved as the general condition improved.

CONCLUSION

NMS is a rare potentially lethal disorder secondary to neuroleptics that needs early recognition and prompt intervention. Treatment is largely supportive with careful monitoring for complications. Although tachycardia is traditionally described, clinicians should be aware that patients may develop recurrent episodes of sinus arrest that resolves as the overall condition improves.

Conflicts of interest

None to declare.

Authors' contributions

Case management: KBN, VC, NA; literature review: KBN; writing; KBN, VC; proofreading: VC, NA.

REFERENCES

1. Strawn JR, Keck PE, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007; 164(6):870-6.
2. Delay J, Pichot P, Lemperiere T, *et al*. A non-phenothiazine and non-reserpine major neuroleptic, haloperidol, in the treatment of psychoses. Ann Med Psychol (Paris) 1960; 118(1):145-52.
3. Velamoor VR. Neuroleptic malignant syndrome. Recognition, prevention and management. Drug Saf 1998; 19(1):73-82.
4. Seitz DP, Gill SS. Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. Psychosomatics 2009; 50(1):8-15.
5. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome—a case review. Hum Psychopharmacol 2003; 18(4):301-9.
6. Berardi D, Amore M, Keck PE, *et al*. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case-control study. Biol Psychiatry. 1998; 44(8):748-54.
7. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142(10):1137-45.
8. Parry AK, Ormerod LP, Hamlin GW, *et al*. Recurrent sinus arrest in association with neuroleptic malignant syndrome. Br J Psychiatry 1994; 164(5):689-91.
9. Ambulkar RP, Patil VP, Moiyadi AV. Neuroleptic malignant syndrome: A diagnostic challenge. J Anaesthesiol Clin Pharmacol 2012; 28(4):517-519.
10. Lappa A, Podestà M, Capelli O, *et al*. Successful treatment of a complicated case of neuroleptic malignant syndrome. Intensive Care Med 2002; 28(7):976-7.
11. Caroff SN, Mann SC, Keck PE. Specific treatment of the neuroleptic malignant syndrome. Biol Psychiatry 1998; 44(6):378-81.