

Neuroleptic malignant syndrome with abnormally elevated cardiac troponin I: a case report

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Abstract

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological emergency that is primarily characterized by altered consciousness, hyperpyrexia, muscular rigidity, and autonomic instability. Here, we describe a unique case of NMS. A 54-year-old woman with major depressive disorder (MDD) was admitted to our hospital to relieve painful emotions; her laboratory tests and physical examinations were unremarkable. Her medication regime was as follows: day 1, quetiapine (200 mg), clonazepam (2 mg), and zopiclone (7.5 mg); day 2, olanzapine (5 mg) and sertraline (100 mg); day 3, olanzapine (15 mg), sertraline (100 mg), zopiclone (7.5 mg), and clonazepam (2 mg); day 4, olanzapine (15 mg) and haloperidol (5 mg); and day 5, sertraline (50 mg) and olanzapine (5 mg). The patient then developed NMS, and a series of tests showed further abnormalities. Unusually, her cardiac troponin I (TNI) was abnormally elevated as her NMS symptoms worsened, but gradually decreased after she was transferred to the cardiology department for treatment. The increased TNI was suspected to be related to the NMS. Here, we provide several potential explanations for the relationship between TNI and NMS. Based on the present case, it may be important to measure and monitor TNI concentrations in NMS patients.

Keywords

Neuroleptic malignant syndrome, myocardial infarction, creatine kinase, cardiac troponin I, case report, major depressive disorder

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Introduction

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening neurological condition. It primarily arises as an idiosyncratic reaction to the use of antipsychotic agents. The primary symptoms of NMS are the classical tetrad of altered consciousness, hyperpyrexia, muscular rigidity, and autonomic instability.¹⁻³ In addition, patients exhibit elevated serum creatine kinase (CK) and leukocytosis, among other symptoms.^{3,4} In contrast, abnormally elevated cardiac troponin I (TNI) levels are rare in this syndrome.

Here, we describe a unique case of NMS that we encountered in clinical practice. Specifically, this patient showed abnormally elevated TNI levels at the same time as she exhibited symptoms of NMS, which occurred after being treated with antipsychotic drugs. We consulted the literature and numerous textbooks for descriptions of the symptoms and diagnostic markers of NMS.^{3,5,6} However, although variations among the different criteria for NMS were noted, we were unable to find any previous description of excessive TNI concentrations in patients with NMS.

Case presentation

The 54-year-old female patient, a retired nurse, was admitted to our hospital on 26 November 2018 because of “recurrent depressed mood and irritability for 35 years, with symptoms reoccurring 3 months ago”. Her initial presentation, 35 years earlier, was for depressive syndrome and disorganized speech. At that time, she was taken to the local hospital and treated with clozapine (12.5 mg/day), and obtained remission. Over the subsequent 34 years, her occupational and interpersonal functions remained acceptable and she was able to continue working as a nurse in a hospital. However, 1 year ago, she was

hospitalized for depressive syndrome, verbal auditory hallucinations, and referential delusions. She was diagnosed with psychotic depression and was discharged from the hospital with quetiapine (200 mg/day) and sertraline (100 mg/day) treatment. In September 2018, the patient again developed depressive syndrome, and auditory hallucinations and persecutory delusions appeared 2 months later (20 November 2018). On 26 November (about 1 week later), she was again admitted to hospital.

After admission to our psychiatric ward, a series of laboratory tests were performed. Examination of sex hormones showed pituitary prolactin at 586.1 mIU/L, which may have been related to the use of sertraline; the results of other tests (including tumor markers, liver function, blood lipid analysis, immune function and autoantibodies, thyroid function, lipoprotein-associated phospholipase A2, biochemical tests, and routine bloods) and an electrocardiogram (ECG) were unremarkable. Quetiapine (200 mg/night) and sertraline (100 mg/day) were continued, and the patient commenced treatment with oral clonazepam (2 mg/day) for anxiety and zopiclone (7.5 mg/night) for insomnia.

On day 2 of admission, the patient’s persecutory delusions worsened and she developed grossly disorganized behavior. She refused food and water and would not cooperate with medical treatment. As a result, quetiapine was discontinued and olanzapine oral disintegrating tablets (5 mg/day) were given to control her psychotic symptoms. At that time, she continued sertraline treatment at 100 mg/day, but zopiclone and clonazepam were suspended.

On day 3 of admission, the patient remained nervous and irritable and developed slightly assaultive behavior and a speech disorder, making it difficult to communicate with her. She also refused to eat or drink. As a result, olanzapine was titrated up to 15 mg/day. In addition, the patient

received sertraline (100 mg), zopiclone (7.5 mg), and clonazepam (2 mg) treatment. On day 4, the patient's symptoms and physical nutritional status worsened. Sertraline was not successfully administered, and both zopiclone and clonazepam were withdrawn that night; only olanzapine (15 mg/day) was continued. In addition, on day 4, the patient was intramuscularly injected with 5 mg of haloperidol to ensure her cooperation with a chest computed tomography (CT) examination.

On the morning of day 5 of admission, 50 mg of sertraline (we had started to reduce the antidepressant dose because of the patient's poor physical condition) and 5 mg of olanzapine oral disintegrating tablets were administered. At approximately 08:00, the patient's temperature reached 38.3°C. She developed excessive sweating, muscle rigidity, and mutism, and exhibited active negativism when her eyelids were checked. The patient's condition alerted the doctor and all psychiatric drugs were immediately stopped, including the olanzapine that should have been taken at noon and in the evening. A series of routine urgent examinations for critically ill patients were performed. It should be noted that we also performed a cardiac function test, including measuring TNI and CK isozyme, for the following two reasons. First, the patient had been taking psychotropic drugs for an extended period, which can have an impact on the heart, and the patient's vital signs were unstable. Second, a previous study reported a relationship between insomnia, depression, and subsequent myocardial infarction, and suggested that doctors should pay attention to cardiac function to reduce the incidence of myocardial infarction;⁷ the patient met the aforementioned characteristics.

By 11:33 of day 5, the patient had developed hyperthermia (38.9°C), diaphoresis, autonomic hyperactivity, and drowsiness. Laboratory tests showed elevated

concentrations of TNI (2.66 ng/mL), CK isozyme (32.8 ng/mL), myoglobin (>1000 ng/mL), high-sensitivity C-reactive protein (>5.0 mg/L), alanine aminotransferase (121 U/L), aspartate aminotransferase (339 U/L), and neutrophils (93.2%). Her ECG showed sinus tachycardia (heart rate 133 bpm), and V1 showed QS-type waves.

At 14:50, the patient's TNI reached 4.91 ng/mL, CK isozyme 37.9 ng/mL, myoglobin >1000.0 ng/mL, and brain natriuretic peptide (BNP) 406 pg/mL (this test was performed because TNI had been abnormally high, indicating that the patient may have heart failure). The patient was worsening, and exhibited confusion, disorganized speech, sweating, and muscular rigidity (although this was less severe than earlier in the day). Her body temperature decreased to 37.6°C.

The consulting psychiatrist considered the patient to be a case of NMS; at this time, all psychiatric medications had been withdrawn and supportive treatment was given. However, the patient's TNI levels continued to rise, so we decided to first deal with the acute myocardial infarction. After consultation with a cardiologist, the patient was diagnosed with acute non-ST-segment elevation myocardial infarction. Because of its severity and the associated high mortality, the patient was transferred to the cardiology department at 21:00 that night. In the cardiology department, the doctors immediately treated the patient's acute myocardial infarction, including anticoagulation, antiplatelet, lipid-lowering, and other treatments. They also performed dynamic checks of cardiac function, including ECG, TNI, CK isozyme, BNP, biochemical tests, and routine blood examinations. From this point on, the patient's myocardial infarction gradually improved. The treatment of NMS was also effective and her NMS symptoms improved 1 week later.

After being transferred to the cardiology department, the patient's TNI gradually decreased. It took 8 days for her TNI to reach normal concentrations (Table 1 shows the trends in her serum TNI and CK levels).

Discussion

NMS is a rare but life-threatening neurological emergency. An international multi-specialty panel reached a consensus regarding the characteristics of NMS^{3,5}; the four main symptoms of NMS are hyperthermia, rigidity, mental status changes, and autonomic dysfunction. In addition to these four principal symptoms, a considerable amount of literature has described various other symptoms, including elevated heart rate, labile blood pressure, mutism, elevated respiration rate, excessive sweating, difficulty swallowing, elevated white blood cell count, tremor, incontinence, metabolic acidosis, myoglobinuria, and dystonic reactions.⁴ Of these symptoms, the heart-related indicators are elevated CK concentrations, heart rate, and blood pressure. Elevated TNI or troponin T (TNT) have not been previously reported in NMS patients.

In relation to the elevated TNI observed in the current patient, there was no history of heart disease, and she had no heart-related abnormalities when she was admitted to hospital. Thus, we propose the following two suppositions. The first possibility is that the increasing TNI was a direct result of the NMS. It is possible that

NMS may cause myocardial damage.² Specifically, NMS is often accompanied by increased CK, also known as creatine phosphokinase. CK is an enzyme expressed by various tissue and cell types, including the myocardium. Clinically, it is assayed in blood tests as a marker of damage to CK-rich tissue, such as that which occurs in myocardial infarction. Serum CK is used clinically for the diagnosis of acute myocardial injury (AMI) and estimation of myocardial infarction size. The second possibility is that our patient developed acute non-ST-segment elevation myocardial infarction at the same time as NMS, and the increasing TNI was thus directly caused by the myocardial infarction, and not the NMS.

It should be noted that in simple myocardial infarction, CK increases within 4 hours of onset, peaks within 16 to 24 hours, and returns to normal in 3 to 4 days.^{8,9} Furthermore, TNI increases within 3 to 4 hours of onset, peaks within 11 to 24 hours, and returns to normal in 7 to 10 days.^{8,9} On day 5 of admission, our patient's TNI concentration was found to be high at approximately 08:00 and reached its highest value around 13:00 (these two time points were the time of blood drawing, rather than the reporting time that is shown in Table 1). It therefore took 5 hours to reach its highest concentration, which is shorter than that observed with AMI. Our patient's TNI concentration then took 8 days to return to normal values, on day 12. Meanwhile, on day 12 (8 days after the onset of NMS), her malignant syndrome

Table 1. Trends in cardiac troponin I and serum creatine kinase.

	Day 5 11:27	Day 5 14:50	Day 5 22:57	Day 6	Day 7	Day 8 09:55	Day 8 19:34	Day 9	Day 10	Day 12	Day 15	Day 18
TNI (ng/mL)	2.66	4.91	1.92	1.14	0.36	0.21	0.23	0.15	0.13	0.04	0.03	<0.02
CK (ng/mL)	32.8	37.9	39.3	38.5	14.5	1.3	9	10.5	8.9	4.7	4	1

TNI: cardiac troponin I; CK: creatine kinase; Day: day since the patient's admission.

also began to markedly improve, which is consistent with the course of NMS (the average recovery time after withdrawal of psychiatric drugs is 7–10 days, according to the DSM-5).³ However, it took much longer for the patient's CK concentration to return to normal. The patient's CK concentration generally exhibited a downward trend, and returned to normal 9 days later. These time characteristics of the patient's TNI and CK changes led us to suspect that these alterations were the result of NMS. However, there were still the following situations to consider. In the present case, the TNI peak time was calculated from the first measurement. Although physical discomfort had not been observed over the 6 hours (11 minus 5) before the first measurement, it remains possible that the patient's TNI had already increased before the first measurement was taken. Another possibility is that the relatively short peak time of TNI may have been caused by the joint action of AMI and NMS.

The patient had no previous heart-related medical history, no history of angina pectoris, and no history of heavy smoking or drinking. She was not obese and had no remarkable abnormalities in her blood lipids or ECG upon admission. Given the timing of myocardial infarction onset in this patient, we believe that the myocardial infarction was likely caused by NMS.¹ Becker² proposed that, when NMS occurs, the increased metabolic demands caused by hyperthermia produce relative ischemia, which might affect the myocardium, and protracted muscular contraction may produce the diversion of oxygen away from the myocardium to the skeletal muscle. Regardless of whether the increase in TNI was directly caused by NMS or concurrent AMI, there is likely a potential relationship between NMS and myocardial injury, which requires the attention of clinicians.

The purpose of this manuscript is to present the clinical phenomenon of a case of NMS accompanied by abnormally elevated TNI concentrations, which has not yet been reported. In the future, patients with NMS should be monitored for acute myocardial damage to prevent the occurrence of serious medical complications or death. As such, we make the bold conjecture that, although not specific to NMS, it may be important to detect and monitor TNI concentrations during the course of NMS. As such, TNI concentrations should be routinely checked and recorded in patients who present with features of NMS.

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Author contributions

Qiang Wang: conceptualization, data curation, and writing the original draft. Jiabo Shi: conceptualization and writing the original draft. Peng Zhao, Qiuyun Cao, and Zhijian Yao: conceptualization.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

Written informed consent was obtained from the patient. This study was approved by the Research Ethics Review Board of the Affiliated Brain Hospital of Nanjing Medical University.

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