INTERNAL MEDICINE

□ CASE REPORT □

Catatonic Symptoms Appearing before Autonomic Symptoms Help Distinguish Neuroleptic Malignant Syndrome from Malignant Catatonia

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Abstract

A 42-year-old Japanese woman with a 10-year history of schizophrenia was admitted due to a disturbance in consciousness that met the diagnostic criteria for both neuroleptic malignant syndrome (NMS) and malignant catatonia. Despite systemic supportive treatments, the catatonic symptoms preceding autonomic symptoms persisted. The symptoms improved after lorazepam administration, leading to a retrospective diagnosis of malignant catatonia. Catatonia is thought to be caused by a dysfunction of ganmma-aminobutyric acid type A receptors in the cortico-cortical networks of the frontal lobes, which causes hypoactivity of the dopaminergic transmission in the subcortical areas. Identifying the catatonic symptoms preceding autonomic symptoms could aid in distinguishing malignant catatonia from NMS.

Key words: neuroleptic malignant syndrome, malignant catatonia, catatonic symptoms

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Introduction

A disturbance of consciousness is a common symptom in clinical settings. Although physiological disease should be excluded when diagnosing psychiatric diseases, it is difficult to make a definitive diagnosis when the patient is confused, particularly when the patient has a medical history of psychiatric disease.

Catatonia is a neuropsychiatric syndrome that is characterized by psychomotor abnormalities and it is observed in a variety of medical, neurological and psychiatric disorders (1). The prevalence of catatonia has been reported to range from 7-45% in various clinical settings (from 20-25% in psychiatric units) (1-6). Malignant catatonia is a rare but lethal variant of catatonia, and it primarily presents with the following symptoms in addition to the clinical features of catatonia: hyperthermia, tachycardia, tachypnea, hypertension or labile blood pressure, diaphoresis, and alternating excitement and stupor (1). Neuroleptic malignant syndrome (NMS) is a rare and fatal adverse reaction to neuroleptics in psychiatric patients, which shares many of the clinical features of malignant catatonia. Based on the existing diagnostic criteria (1, 7, 8), it is difficult to distinguish between malignant catatonia and NMS. Therefore, in this case report, we sought to identify the onset of catatonic symptoms prior to autonomic symptoms as a factor that could help to distinguish malignant catatonia from NMS.

Case Report

A 42-year-old Japanese woman with mild mental retardation and a 10-year history of schizophrenia, controlled by risperidone, diazepam, and sodium valproate was admitted to the emergency department due to a disturbance of consciousness.

On arrival, the patient had a Glasgow Coma Scale (GCS) score of 6 (E4 V1 M1), and was described as staring and mute, exhibiting an equal pupil size and normal pupil reactions. Although the patient was a GCS M1, her upper ex-

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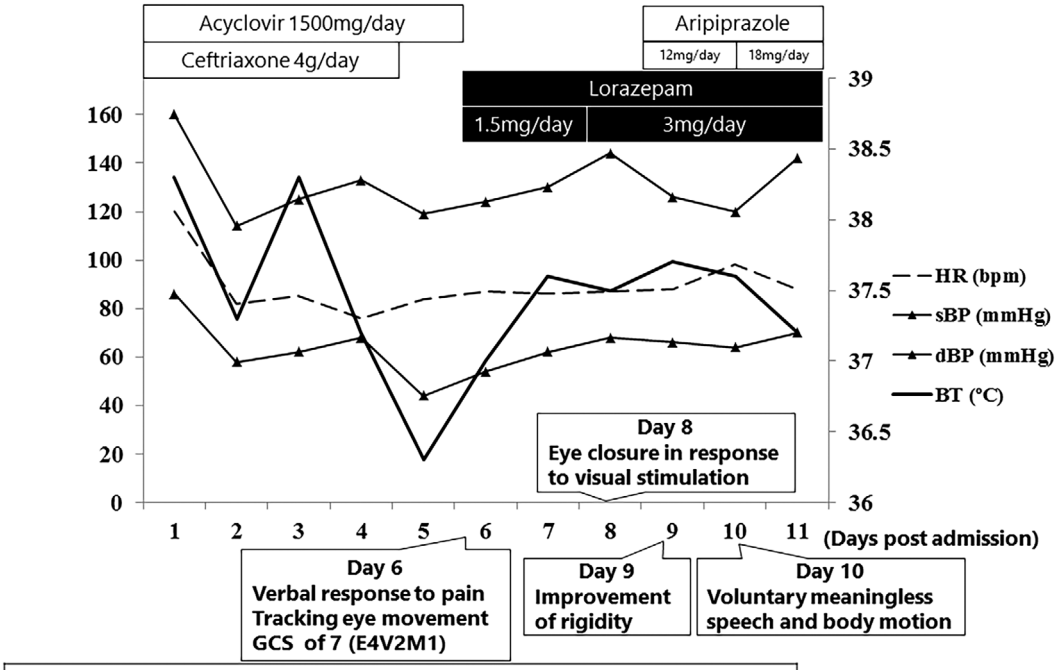
tremities were lifted passively and held in space, and this was interpreted as a sign of catalepsy and waxy flexibility. The patient also exhibited an elevated blood pressure (160/86 mmHg), tachycardia (120 beats per minute), and hyperthermia (38.3℃). Physical examination also revealed diaphoresis, neck stiffness, tremor at the extremities, and muscle rigidity throughout the body. Although most of the neurological findings were difficult to evaluate because of the consciousness disorder, the patient did not show any reflex abnormalities. Therefore, the patient fulfilled the diagnostic criteria for both NMS (muscle rigidity, fever, diaphoresis, dysphagia, tremor, altered consciousness, mutism, tachycardia, elevated blood pressure, leukocytosis and laboratory evidence of muscle injury) (7) and malignant catatonia (catalepsy, waxy flexibility, stupor, mutism, negativism, fever, tachycardia and elevated blood pressure) upon admission (1, 8). Blood tests revealed an elevated white blood cell count (16.8×10^9 cells/L), a myogenic enzyme with a creatine phosphokinase level of 1,538 IU/L, a lactate dehydrogenase level of 505 IU/L, and an aspartate aminotransferase level of 62 IU/L. The patient was diagnosed with pre-renal acute kidney injury (stage 2) based on an elevation of the creatinine level from 0.92 mg/dL at 12 days before admission to 2.44 mg/dL, and a urine sodium excretion level of less than 20 mmol/L. Extreme hypernatremia was also indicated by a serum sodium level of 183 mmol/L. Hematological examination also revealed abnormal coagulation and an elevation of fibrin/fibrinogen degradation product concentration (70.0 μg/mL). A blood gas analysis revealed a slight elevation in the lactate concentration (3.0 mmol/L) and normal ranges of pH and pCO_2. Other hematologic indices including C-reactive protein and thyroid function were normal and the anti-nuclear antibody level showed a negative finding. Triage DOA® screening (Alere Medical, Tokyo, Japan) revealed a positive result for daily benzodiazepine usage. Brain computed tomography (CT) revealed no abnormal density area or abnormal structures. Moreover, cerebrospinal fluid (CSF) examinations revealed no elevation of either the cells or the protein level with a normal glucose level. Although the patient did not exhibit tachypnea or hypoxia, an enhanced whole-body CT scan revealed bilateral pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT) from the right superficial femoral vein to the popliteal vein.

We initiated crystalloid administration for volume resuscitation and heparin for PTE and DVT. We also administered ceftriaxone and acyclovir until CSF and blood culture results were negative. Based on the patient's fulfillment of the diagnostic criteria for both NMS and malignant catatonia, we first administered dantrolene sodium hydrate to treat the NMS. Tachycardia immediately improved after volume resuscitation. Two days after admission to the intensive care unit, the abnormal blood pressure and hyperthermia also improved slightly; however, these autonomic symptoms and stupor persisted despite improvements in both dehydration and hypernatremia (see Figure) without any abnormalities on brain magnetic resonance imaging or electroencephalography. We obtained additional patient history information from the patient's mother and a local mental clinic, and discovered that catatonic symptoms had initiated prior to the appearance of autonomic symptoms (see Table). Based on the patient history, clinical presentation, and discussion with a consultation-liaison psychiatrist, we suspected malignant catatonia or NMS superimposed on catatonia, rather than solely NMS. Therefore, we halted the administration of dantrolene sodium hydrate on the next day. At six days after admission, we subsequently administered lorazepam (1.5 mg/day) via the transluminal route. A few hours after the initiation of lorazepam treatment, the eye movement tracking improved and the verbal response to pain gradually appeared. Two days after the administration of lorazepam (8 days after admission), eye closure in response to visual stimulation appeared and we elected to administer an additional dose of lorazepam (1.5 mg/day). Nine days after admission, muscle rigidity was slightly improved and we began the concomitant administration of aripiprazole (12 mg/day) as a basic treatment for the catatonic symptoms of schizophrenia. At ten days after admission, voluntary meaningless speech and body motion appeared. Hyperthermia finally resolved on day 11 after admission. Although the patient's symptoms had demonstrated a gradual improvement, consciousness disturbance remained at a GCS score of 7 (E4V2M1), and diaphoresis and slight tremor at the extremities persisted. Based on the patient's clinical courses, we made a definitive retrospective diagnosis of malignant catatonia and elected to transfer the patient to a psychiatric hospital for further treatment. The patient was finally discharged from the psychiatric hospital in a stable condition after adjusting to her schizophrenia medication.

Discussion

Because malignant catatonia has similar clinical features to NMS, it is difficult to distinguish these diseases in patients. Fabian et al. reported statistically significant symptoms in patients with NMS, including diaphoresis (with an odds ratio of 10.011), rigor (9.550), fever (7.317), tremor (4.064), laboratory evidence of muscle injury (3.542), and leukocytosis (3.081). Fabian et al. also reported symptoms observed in catatonia, such as negativism (0.262), posturing (0.241), waxy flexibility (0.223), stupor (0.158), and stereotypy (0.122) (9). However, diaphoresis and muscle rigidity also appear in malignant catatonia, and therefore an additional index is necessary for making a differential diagnosis.

The pathophysiological mechanisms of NMS and catatonia remain unclear. However, it is hypothesized that abrupt and extensive D2 dopaminergic blockade of the anterior hypothalamus, corpus stratum, and basal ganglia corresponds to the clinical features of NMS, such as high fever, muscle rigidity, and an altered mental status, respectively (10-13). Additionally, a systematic review of NMS (14) reported that non-dopaminergic receptors, including serotonergic, adrenergic, and cholinergic receptors, may play an important role in



	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day10
Na (mmol/L)	183	164	163	151	145	143	141	142	138
CPK (IU/L)	1538	1639	2065	1582	1333	1085	823	895	804

Figure. Clinical course after admission. Consciousness disturbance with a Glasgow Coma Scale (GCS) score of 6 persisted despite a resolution of dehydration and hypernatremia. After the administration of lorazepam on the sixth day of hospitalization, tracking eye movement demonstrated an improvement and the patient had a GCS score of 7 (E4V2M1). Voluntary meaningless speech and body motion appeared gradually although there was no change in the GCS score. HR: heart rate, sBP: systolic blood pressure, dBP: diastolic blood pressure, BT: body temperature

the pathophysiology of NMS in extrapyramidal motor functions (15), thermoregulation, muscle metabolism (16), and mental status (17). Alterations in the mental status can also be elicited by either "bottom-up" or subcortico-cortical dysfunction in gamma-aminobutyric acid type-A ($GABA_A$) receptor transmission in the frontal cortex secondary to any subcortical dopaminergic dysregulation (1, 16, 18). Dantrolene sodium hydrate, which inhibits calcium release from the sarcoplasmic reticulum, is therefore administered as a first-line therapy to reduce the core body temperature and peripheral muscle rigidity in NMS (13).

Conversely, catatonia may be caused by initial neurochemical abnormalities in $GABA_A$ receptors in the cortico-cortical networks of the frontal lobes (1, 18). Dysfunction in the GABAergic-mediated balance between medial and lateral orbitofrontal cortex activity may lead to alterations in the medial prefrontal cortical pathways and thus potentially account for concomitant emotional and motor symptoms in catatonia while dysfunction in the GABAergic balance between lateral orbitofrontal, dorsolateral prefrontal, and posterior parietal cortex networks may account for the behavioral symptoms of catatonia (18). Moreover, GABAergic dysfunction can cause secondary hypoactivity of dopaminergic transmission in the subcortical areas, specifically those connecting the orbitofrontal cortex with the striatum, and thus lead to autonomic symptoms similar to those observed in NMS. This process is referred to as "top-down" or cortico-subcortical dopaminergic dysfunction (1, 18). In accordance with the "top-down" theory, catatonic symptoms (e.g., changes in mental status) should precede the development of autonomic symptoms in malignant catatonia due to GABAergic dysfunction in the cortical areas of the frontal lobes. The first line therapy for catatonia is lorazepam, which is thought to suppress the $GABA_A$ receptor activity, while electroconvulsive therapy (ECT) is an alternative treatment in cases refractory to the administration of lorazepam or in cases of malignant catatonia (1, 19). In the clinical setting, the most important treatment goal for both NMS and malignant catatonia is addressing the occurrence of life-threatening medical complications such as severe dehydration, hypernatremia, PTE, and DVT. However, basic advisable treatments for each disease based on the respective pathophysiological mechanisms are also required.

In this case report, it was difficult to definitively diagnose NMS on admission because the patient also exhibited various catatonic symptoms. Firstly, we hypothesized that malignant catatonia had developed from catatonia, or that NMS had been superimposed on catatonia. In either circumstance, the autonomic symptoms could be partially treated by dantrolene sodium hydrate supplemented with systemic support, and eventually lorazepam was required as a basic treatment for persisting catatonic symptoms. However, we eventually

Table. **Time Course of Patient's Symptoms.**

	Symptoms	Changes in medication
> 39 days before admission	No abnormalities	Trihexyphenidyl hydrochloride 4mg/ day Diazepam 10mg/ day Sodium valproate 200mg/ day Risperidone 2mg/ day
30	General fatigue	No change
29	Agitation	No change
22	Weakness in the hands	No change
13	1) Whole body rigidity 2) Attendant required for walking	Risperidone increased to 3 mg/day Biperiden 6 mg/ day added
12	1) Difficulty in body motion 2) Poor reaction in conversation	Risperidone increased to 4 mg/day
11	Decrease of urinary volume	Distigumine 5 mg/ day added
4	1) Stupor 2) Insomnia	Risperidone decreased to 2 mg/day
Day of admission	1) Hyperthermia 2) Tachycardia 3) Elevated blood pressure 4) Catalepsy 5) Waxy flexibility 6) Stupor 7) Mutism 8) Negativism 9) Diaphoresis 10) Dysphasia 11) Tremor 12) Muscle rigidity	

In this patient, autonomic symptoms initiated prior to changes in the dosage of risperidone. On the day of admission, the patient had met the diagnostic criteria for both NMS and malignant catatonia, with additional leukocytosis and elevated serum creatine phosphokinase.

made a retrospective diagnosis of malignant catatonia based on the clinical course of improvement of catatonic and the remaining autonomic symptoms after the administration of lorazepam. As a result, we therefore propose the initial performance of a lorazepam test (1, 20) in patients with overlapping catatonia and NMS symptoms.

The present case report demonstrates the difficulty of correctly diagnosing malignant catatonia, and suggests the utility of detecting any preceding catatonic symptoms in order to differentiate malignant catatonia from NMS. Though Walter and Jordi reported (1) the importance of events chronology in diagnosing catatonia, to our knowledge our report is the first to describe the use of vent chronology in the differentiation of malignant catatonia from NMS in a patient. Larger clinical studies should thus be performed to confirm our findings.

Author's disclosure of potential Conflicts of Interest (COI).
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