



Case report

Reversible brain imaging findings with a severe neurological prognosis of neuroleptic malignant syndrome



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ABSTRACT

Neuroleptic malignant syndrome is a rare but life-threatening disorder associated with the use of neuroleptic drugs, and is characterized by fever, altered mental status, muscle rigidity, autonomic instability, myoclonus, elevated creatine kinase levels, rhabdomyolysis, and leukocytosis. Previous reports have shown that most patients with neuroleptic malignant syndrome recover without neurologic sequelae. Some patients with neuroleptic malignant syndrome show reversible magnetic resonance imaging (changes in the brain). The severe neurological impairments do not persist in neuroleptic malignant syndrome patients with reversible lesions. Here, we describe a 66-year-old Japanese woman who was diagnosed with septic shock secondary to obstructive pyelonephritis. She was administered haloperidol for delirium and developed neuroleptic malignant syndrome. Magnetic resonance imaging of the brain showed diffuse hyperintense signals in the cerebellar cortex, cerebellar dentate nucleus, superior cerebellar peduncle, and thalamus on T2-weighted imaging or fluid-attenuated inversion recovery, and in the bilateral substantia nigra and bilateral globus pallidus on diffusion-weighted imaging. Subsequently, the signal intensities of the cerebellar and thalamic lesions diminished and the basal ganglia lesions disappeared, but the severe neurologic sequelae remained. The cerebellum is reportedly particularly sensitive to thermal damage because Purkinje cells are believed to be vulnerable to heat. Although brain imaging studies revealed reversible changes, her disturbance of consciousness was prolonged. Therefore, brain magnetic resonance imaging findings might not reflect the neurologic prognosis in patients with neuroleptic malignant syndrome.

1. Introduction

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening disorder associated with the use of neuroleptic drugs [1]. NMS is characterized by fever, altered mental status, muscle rigidity, autonomic instability, myoclonus, elevated creatine kinase levels, rhabdomyolysis, and leukocytosis [2]. Previous reports have shown that most patients with NMS recover within 2 weeks without neurologic sequelae [2, 3]. However, only a few cases of NMS with magnetic resonance imaging (MRI) findings have been reported. Some investigators recently reported NMS cases with reversible MRI changes in the brain [1, 4].

We herein present an NMS case with severe disturbance of consciousness that persisted despite an improvement in brain MRI findings.

2. Case presentation

A 66-year-old Japanese woman with an acute onset of fever, systemic fatigue, confusion, and restlessness was transferred to our emergency department by ambulance. Her medical history included depression, rectal cancer, and osteoarthritis of the left knee. Her regular medication comprised amitriptyline, trazodone, triazolam, flunitrazepam, duloxetine, and aripiprazole. She had taken no illicit drugs and had no remarkable family history. Her physiological findings on examination were as follows: Glasgow Coma Scale, E3V4M5; blood pressure, 140/86 mmHg; heart rate, 130 beats/min; body temperature, 40.4 °C; respiratory rate, 26/min; and SpO₂, 94% (O₂, 5L/min via face mask). She had costovertebral angle tenderness, and neurological examinations were unremarkable except for confusion.

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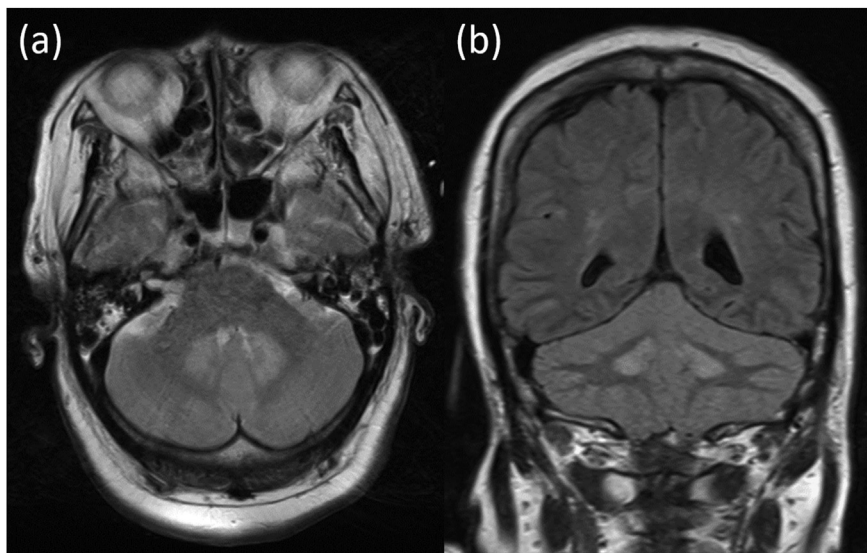


Figure 1. Magnetic resonance imaging on the 10th day of hospitalization. (a) Axial and (b) sagittal views. The examinations revealed diffuse hyperintense signal in the cerebellar cortex on T2-weighted and fluid-attenuated inversion recovery images.

Initial laboratory investigations showed marked elevations in C-reactive protein (16.22 mg/dL) and creatine kinase (852 U/L) and a mild elevation in renal function tests (blood urea nitrogen, 21 mg/dL; and serum creatinine, 1.37 mg/dL) with the complete blood count largely within the normal range. A urinary test showed pyuria, and abdominal computed tomography (CT) revealed a ureteral stone in the right urinary duct and swelling of the right kidney. Her blood pressure gradually decreased despite sufficient crystalline liquid infusion, and continuous intravenous administration of noradrenalin at 0.1 $\mu\text{g}/\text{kg}/\text{min}$ was required to maintain her hemodynamics. Septic shock secondary to obstructive pyelonephritis due to urolithiasis was diagnosed based on these findings. The broad-spectrum antibiotic meropenem was started and an intraurethral catheter was placed in the right urinary duct. She was administered 5 mg haloperidol via intravenous drip for delirium in the emergency department and in the intensive care unit because of continued restlessness. She was kept in the intensive care unit for general management.

On the second day of hospitalization, her hemodynamics improved. Noradrenaline administration was ended, and she was lucid and afebrile. However, her consciousness gradually worsened again at around noon and her Glasgow Coma Scale was finally E1VTM2 in the evening on the same day. In addition, hyperthermia, namely, a bladder temperature exceeding 40 °C, was recorded on the third day of hospitalization and continued for at least for 12 h. Head and neck examinations revealed only roving eye movement, and there was no neck stiffness or other symptoms of meningeal irritation. Motor examinations showed decreased tonus, but cogwheel rigidity appeared on the fifth day of hospitalization. Clonic spasms of the face and upper extremities were observed. Laboratory investigations showed a marked elevation in creatine kinase, from 9,613 U/L on the third day of hospitalization to a peak of 101,475 U/L on the seventh day of hospitalization. Hepatitis virus antigens, human immunodeficiency virus antigen, and autoantibodies were negative, and vitamins and trace elements were normal. Contrast-enhanced abdominal CT performed on the third day of hospitalization showed an improvement in pyelonephritis, and there were no abnormal findings on brain CT performed on the same day. Lumbar puncture was performed and cerebrospinal fluid examination showed albuminocytologic dissociation, while bacterial culture, herpes virus PCR, and cytomegalovirus antigen were negative. A total of three lumbar punctures were performed at the fourth, 18th, and 26th day of hospitalization, and the albuminocytologic dissociation was resolved with no evidence of infectious disease. Electroencephalography showed

background activity of 5–6 Hz theta rhythm without asymmetry and no electrographic seizures. Thus, the patient was diagnosed as having NMS based on diagnostic criteria involving exposure to haloperidol within the previous 72 h, hyperthermia, rigidity, altered mental status, creatine kinase elevation, unstable hemodynamics, and a negative workup for other disorders [5].

Dantrolene (160 mg/day) and bromocriptine (7.5 mg/day) were administered from the fourth day of hospitalization for 7 days. Following treatment, her muscle rigidity eased slowly. Renal replacement therapy was introduced on the fourth day of hospitalization due to anuria and renal dysfunction. Her hyperthermia and elevated creatinine kinase levels improved after the introduction of renal replacement therapy. Her vital signs and laboratory data recovered gradually, but the disturbance of consciousness, such as being unaware of her surroundings and having

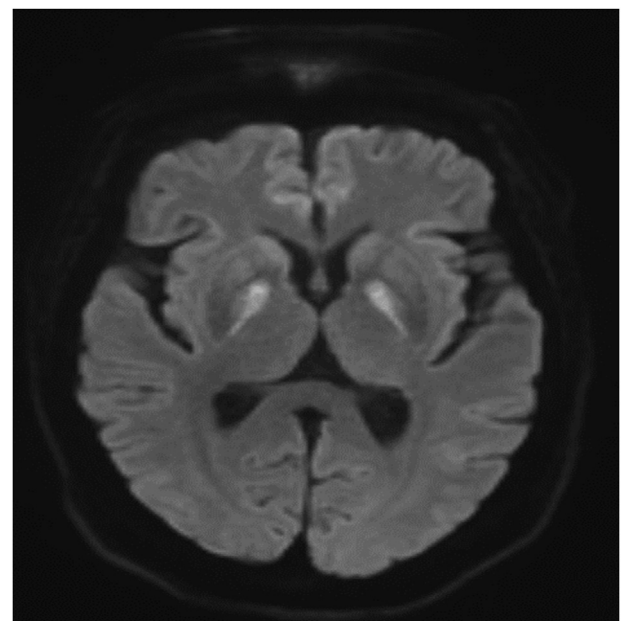


Figure 2. Axial magnetic resonance imaging on the 27th day of hospitalization. The examination revealed hyperintense signals in the bilateral substantia nigra and bilateral globus pallidus on diffusion-weighted imaging.

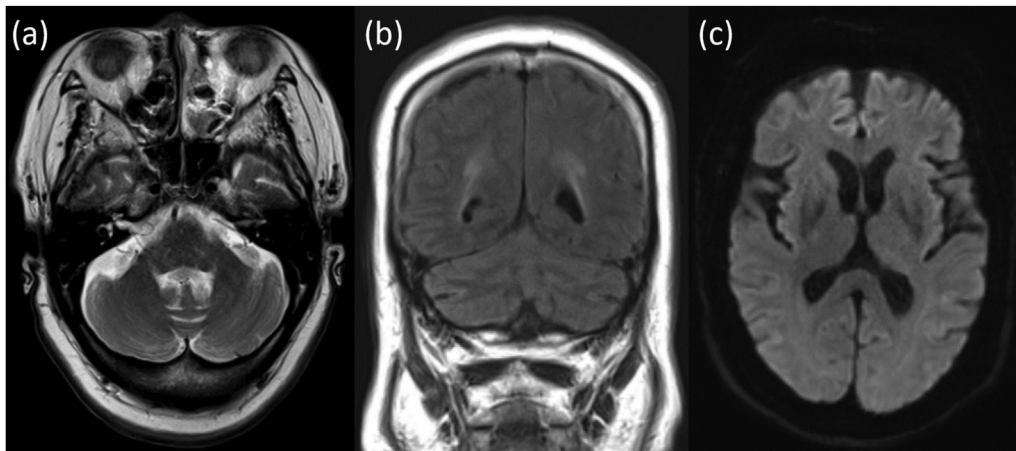


Figure 3. Magnetic resonance imaging studies 3 months later. The examinations showed reduced lesion intensity. Cerebellar (a) axial and (b) sagittal (c) views of the thalamic and basal ganglia lesions.

no interactions with the environment, remained. Tracheostomy was performed.

Magnetic resonance imaging (MRI) of the brain performed on the 10th day of hospitalization showed diffuse hyperintense signal in the cerebellar cortex on T2-weighted imaging and fluid-attenuated inversion recovery (Figure 1). In addition, there were symmetrical hyperintense signals in the cerebellar dentate nucleus, superior cerebellar peduncle, and thalamus on T2-weighted imaging. Brain MRI performed on the 27th day of hospitalization revealed the appearance of hyperintense signals in the bilateral substantia nigra and bilateral globus pallidus on diffusion-weighted imaging (Figure 2). However, at 3 months later, the signal intensities of the cerebellar and thalamic lesions had reduced and the basal ganglia lesions had disappeared (Figure 3). On the 149th day of hospitalization, she was transferred to another hospital for rehabilitation without an improvement in her disturbance of consciousness.

We obtained written consent for publication of this case report from the patient's daughter as her representative.

3. Discussion

NMS is induced by dopamine receptor blockade in the brain, specifically in the basal ganglia and hypothalamic circuitry [6]. Dysfunction in the basal ganglia motor circuit causes muscle rigidity and triggers muscle breakdown, producing a hypermetabolic state. This causes an intrinsic rise in body temperature from increased heat production. Hypothalamic regulation of body temperature, which is controlled by dopamine, also becomes disrupted, leading to hyperthermia.

MRI findings in NMS have not been well described [1]. Brain lesions appear in multiple areas, primarily in the cerebellum, but also in the basal ganglia and splenium of the corpus callosum. The cerebellum is particularly sensitive to thermal damage because Purkinje cells are believed to be vulnerable to heat [7]. An autopsy study also revealed cerebellar degeneration in patients with NMS [8]. Sustained hyperthermia can cause prolonged neurologic impairment and multi-organ failure; therefore, early active thermoregulation may satisfactorily improve convalescence.

Some researchers have reported reversible brain lesions on MRI in patients with NMS [1, 4, 9]. In these cases, brain MRI showed T2-weighted or fluid-attenuated inversion recovery hyperintense lesions in the cerebellum, brainstem, cerebellar peduncles, basal ganglia, thalami, internal capsules, and splenium of the corpus callosum. The severe neurologic impairments do not persist in NMS patients with reversible lesions. In our patient, the lesions in the cerebellum and basal ganglia initially detected on MRI disappeared, but the severe neurologic sequelae remained. Increased levels of protein in the patient's

cerebrospinal fluid suggested neurogenic degeneration in the central nervous system, which was consistent with the brain imaging studies. Our case shows that an improvement in brain MRI might not always reflect the neurologic prognosis in patients with NMS. In addition, Becker et al. [10] reported that NMS with concomitant renal failure was associated with a worse prognosis, although mortality from NMS alone is unusual. Therefore, the prolonged renal dysfunction in the present case also affected her prognosis.

In conclusion, we experienced a case with NMS in whom severe disturbance of consciousness was prolonged despite improved brain MRI findings. Therefore, brain MRI findings may not reflect the neurologic prognosis of patients with NMS.

Declarations

Author contribution statement

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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