

**CASE REPORT**

Progressive Encephalomyelitis with Rigidity and Myoclonus in an Intellectually Disabled Patient Mimicking Neuroleptic Malignant Syndrome

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ABSTRACT

We present a case of 32-year-old male with profound mental retardation and autism spectrum disorder who had presented with seizures, rigidity and elevated creatine kinase and was initially diagnosed as neuroleptic malignant syndrome (NMS). The patient subsequently had a complicated clinical course, developing refractory status epilepticus, which led to the eventual diagnosis of progressive encephalomyelitis with rigidity and myoclonus (PERM). We discuss the clinical similarities and differences between NMS and PERM, and highlight the need to consider alternative diagnoses when the clinical picture of NMS is atypical, particularly in this patient group where the history and clinical examination may be challenging.

Key Words Progressive encephalomyelitis with rigidity; neuroleptic malignant syndrome; autistic disorder.

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare disorder presenting with a combination of rigidity, stimulus-sensitive spasms, myoclonus, hyperekplexia, dysautonomia, encephalopathy, seizures, and brainstem dysfunction associated with the anti-glycine receptor antibody.¹ The diagnosis is challenging and typically delayed, as ancillary investigations are frequently normal and clinical features can overlap with other conditions, such as neuroleptic malignant syndrome (NMS).¹ Herein, we present a case of PERM in a severely intellectually disabled patient who had been initially diagnosed with NMS and highlight the unusual clinical features that led to the diagnosis.

CASE REPORT

A 32-year-old male with profound intellectual disability and autism spectrum disorder presented to us from a psychiatric unit following seizures in the context of a new fever. He was minimally communicative and normally taken care of at home.

However, in the last 4 months, he required institutionalized psychiatric care due to new behavioral changes, including aggression, shouting fits, and self-injurious behavior, and had developed a tendency to turn his neck from side to side. He received risperidone and chlorpromazine, but these were stopped prior to transfer.

Examination revealed he had a fever of 39.4 degrees Celsius and a heart rate of 107/minute and could follow one-step commands. There was marked neck rigidity. He was observed to have repetitive rotational movements of the neck and brief myoclonic movements in which he would extend his neck and posture his limbs. Creatine kinase (CK) was elevated at 4,779 U/L, C reactive protein was normal and white cell count was marginally elevated at $11.79 \times 10^9/L$. MRI brain and cerebrospinal fluid (CSF) studies were normal. Following the exclusion of other related conditions, including nonconvulsive status epilepticus and intracranial infections, a diagnosis of NMS was made, and he was treated with lorazepam and bromocriptine. No further seizures were observed following treatment with le-

Received: November 28, 2016 Revised: January 20, 2017 Accepted: February 17, 2017

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vetiracetam; however, fever, tachycardia, and blood pressure lability persisted. CK peaked at 17,847 U/L 3 weeks into admission before normalizing. Rigidity continued to persist for a month, despite the normalization of CK, before improving.

Two months after admission, he developed hypercapnic respiratory failure from pneumonia. Two weeks later, he developed status epilepticus manifesting with gaze deviation and twitching of the hands and jaw. Electrographic seizures were also noted on electroencephalography. MRI brain and CSF studies were again unremarkable. Status epilepticus was abolished with midazolam infusion, levetiracetam, phenytoin, valproic acid, carbamazepine, and lamotrigine; however, he still had intermittent episodes of clinical seizures and tachycardia.

Further investigations were performed, as the development of status epilepticus was unexpected. Anti-glycine receptor antibodies were positive in the serum (Oxford Neuroimmunology testing service, Oxford University Hospitals, United Kingdom). This

finding, together with his clinical features, was consistent with a diagnosis of PERM. Glutamic acid decarboxylase, voltage gated potassium channel complex (VGKCC), and N-methyl-D-aspartate receptor (NMDAR) antibodies were negative. A computer tomography scan of the chest, abdomen and pelvis was negative for malignancy. The patient was treated with intravenous immunoglobulins (IVIG). 2 weeks later, no further seizures or dysautonomia were observed. After discharge, he returned to his pre-morbid status with no further seizures, rigidity or head turning.

DISCUSSION

PERM has significant clinical overlap with NMS (Table 1). The DSM-V diagnostic criteria for NMS requires the presence of rigidity, changes in mental status, dysautonomia, elevated CK and elevated temperature. These features, with the exception of CK elevation, are frequently present in cases of PERM

Table 1. Clinical similarities, differences and diagnostic features in PERM and NMS

	NMS ⁵	PERM ¹
Diagnostic criteria/features	DSM-V criteria: - Hyperthermia - Rigidity - CPK at least 4 times the upper limit - Changes in mental status - Autonomic disturbances	- Rigidity, painful spasms - Changes in mental status - Autonomic disturbances - Stimulus sensitive spasms, myoclonus, hyperekplexia, brainstem signs
Predisposing factors	NMS	Autoimmune disorders, malignancy
Prodromal symptoms	Alteration in mental status	Alteration in mental status
Onset	Acute onset (16%), subacute presentation (66%), within 30 days (18%)	Acute onset (20%), subacute presentation (44%), subacute with acute exacerbation (7%), chronic (11%), chronic with acute exacerbation (18%)
Other reported features	Blepharospasm, oculogyric crisis, nystagmus or trismus Dysphagia, dysarthria, aphonia Urinary incontinence (uncommon) Disseminated intravascular coagulation, multiorgan failure	Gait difficulties, excessive startle, limb paresis Diplopia, nystagmus, ptosis, trismus Dysphagia and speech difficulties Sensory symptoms and painful spasms Urinary incontinence (common) Respiratory failure
CK elevation	600–10,000 U/L	Not described previously
CSF	Normal (≥ 95%)	Pleocytosis (60%)
EEG	Generalized slowing	Generalized slowing Focal epileptic activity
Prognosis	63% resolve within the first week and nearly all within a month of stopping treatment	Generally good Relapses common

Characteristic features are summarized based on the following data. NMS: neuroleptic malignant syndrome, PERM: progressive encephalomyelitis with rigidity and myoclonus, CK: creatine kinase, CSF: cerebrospinal fluid.

described in the literature. It is therefore unsurprising that our patient was initially diagnosed with NMS: he had recent neuroleptic exposure, persistently elevated body temperature, elevated CK and white cell count, and an apparent initial treatment response to lorazepam and bromocriptine. The marked CK elevation up to 17,847 U/L seen in our patient was diagnostically in favor of NMS, as it has not been previously described in PERM. There was also no CSF leukocytosis to suggest a possible immune-mediated inflammatory process, even when repeated at the peak of his illness, whereas CSF pleocytosis has been observed in 60% of patients diagnosed with PERM.¹ Other NMS-mimicking conditions, including nonconvulsive status epilepticus, malignant catatonia, serotonin syndrome and intracranial infections, were also considered and excluded during the patient's initial workup before the diagnosis of NMS was made.

With time, it became evident that our patient's clinical course was atypical of NMS. Firstly, rigidity and dysautonomia persisted longer than would be expected in NMS, given the brief exposure to neuroleptics. NMS rarely persists beyond a month after stopping neuroleptics. Secondly, although seizures can occur in NMS, refractory status epilepticus is highly unusual. Our patient required multiple anti-epileptics, and seizure control was only achieved with IVIG. This observation is consistent with prior reports of status epilepticus associated with the anti-glycine receptor antibody.^{1,2}

In previously reported cases of PERM, a prodrome of painful sensory symptoms and muscle spasms were typically elicited, alerting clinicians to this rare diagnosis. This was particularly difficult to discern in our patient due to his severe intellectual disability. He presented with a 4-month history of behavioral changes and aggression, with new head movements that were thought to be a stereotypy. Stereotypies are common in autism and can manifest as violent

body rocking and head turning. In retrospect, the development of this new stereotypy was likely a behavioral response to relieve the painful neck rigidity due to PERM.

Besides PERM, there have also been increasing reports of other immune-mediated encephalitis presenting with an NMS phenotype, including anti-NMDAR^{3,4} and anti-VGKC⁵ encephalitis. These frequently present with neuropsychiatric manifestations. Therefore, there is the potential for neuroleptic use and initial misdiagnosis as NMS before progressing to a more fulminant clinical course that includes seizures, encephalopathy, dysautonomia, and movement disorders. Our case highlights the need to consider these alternative diagnoses when the clinical picture of NMS is atypical, particularly in light of the recent discovery of these antibody-associated disorders.

Conflicts of Interest

The authors have no financial conflicts of interest.

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