

CASE REPORT

Medication-induced acute dystonic reaction: the challenge of diagnosing movement disorders in the intensive care unit

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SUMMARY

A 62-year-old man presented with left middle cerebral artery stroke. 1 h postadministration of tissue plasminogen activator, he received a total of 4 mg of haloperidol for combativeness. He developed partial complex status epilepticus, requiring benzodiazepines, phenytoin, propofol and intubation. 5 h later, he developed recurrent stereotyped tonic movements involving arching of the back, extension of the arms and contraction of opposing muscle groups. Repeat CT scan of the head showed evolving insular infarct. Differential diagnoses for these movements included tonic/clonic seizures, extensor (decerebrate) posturing from haemorrhagic conversion, neuroleptic malignant syndrome, or dystonic reaction. Given the lack of response to antiseizure medications, the recent administration of haloperidol, and the prompt resolution of movements following diphenhydramine administration, an acute dystonic reaction was considered. This atypical case of a critically ill patient with stroke highlights the fact that these patients may have multiple abnormal movements requiring careful analysis to guide diagnosis-specific management.

BACKGROUND

Movement disorders in critically ill neurological patients are common, though diagnosis may be complicated by patients' critical state, complex monitoring and polypharmacy. In fact, the differential diagnosis for abnormal movements in these patients is broad and careful evaluation of the semiology of movements, as well as potential causative factors, may assist with proper diagnosis and correct treatment. Patients with acute stroke are at increased risk of seizures, which occur in 4–10%,¹ as well as delirium, which occurs in 13–48%.² Medications such as antipsychotics are often used to manage delirium and may lead to extrapyramidal side effects in up to 4.5% of patients.³ The management of movement disorders varies depending on the aetiology; antiepileptics such as benzodiazepines are the cornerstone of acute seizure management, while anticholinergics and withdrawal of offending agents are the management for dystonic reactions. Additionally, focal neurological deficits due to stroke can further complicate the analysis of abnormal movements, thereby delaying diagnosis and appropriate management.

We present an atypical case of a patient with acute stroke who exhibited three separate patterns of movement: focal neurological deficits, clonic

movements suspicious for partial seizure and a drug-induced acute dystonic reaction. This case will highlight the importance of careful evaluation of the semiology of movements to permit proper diagnosis and will discuss treatment-related issues that can minimise the risk of dystonic reactions in critically ill patients.

CASE PRESENTATION

A 62-year-old right-handed man presented with recurrent left middle cerebral artery (MCA) syndrome (National Institutes of Health Stroke Scale (NIHSS) 14) on a background of restless legs syndrome treated with pramipexole 0.5 mg nightly for the preceding 2 years. One-hour post-thrombolysis, he became agitated and received 1 mg of haloperidol. He continued to be very combative and was administered 5 mg of lorazepam, but continued to display dangerous behaviours. Over the following half hour, he received an additional 3 mg of haloperidol to attempt to control his agitated state. Minutes later, he developed suspected partial complex status epilepticus manifesting as clonic activity of the right arm and hand; this did not respond to an additional 4 mg of lorazepam and 6.5 mg of midazolam. The patient developed a reduced level of consciousness and was therefore intubated with propofol 320 mg as an anaesthetic, and administered 1.5 g of phenytoin, which led to resolution of the suspected seizure activity. Repeat imaging showed appropriate evolution of left parietal and insular ischaemia. Five hours later, the patient developed back arching and recurrent bilateral leg extensor muscle contraction ([video 1](#)). Each episode lasted less than 10 s and occurred 2–3 times per minute. There were no versive head or eye movements and no clonic activity was noted. Repeat CT scan of the head was unchanged. The movements persisted, despite an infusion of 8 mg/h of midazolam, but stopped abruptly following administration of intravenous diphenhydramine.

INVESTIGATIONS

In light of the evolution of three separate movement disorders, this patient underwent three CT scans of the head on the day of presentation: the first to confirm ischaemic stroke ([figure 1](#)), and the second and third to rule out haemorrhagic transformation after development of status epilepticus, followed by the movements seen in the [video 1](#), which were later recognised to be an acute dystonic reaction. The repeat CT scans only revealed



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Video 1 Acute dystonic reaction causing recurrent whole body extensor posturing. Episodes such as these would last several seconds and recur up to 2–3 times per minute.

evolving ischaemic stroke with no evidence of haemorrhagic transformation.

While EEG would have been useful to help rule out seizures as the cause of the abnormal movements, and may have led to a more rapid diagnosis, our centre does not have 24 h EEG capabilities and these episodes occurred exclusively at night. As such, examining the semiology of movement was of utmost importance and a trial of treatment for the leading differential diagnosis was required. EEG was, however, performed the following day once the dystonic reaction and seizures had been treated, and revealed no epileptiform activity, with slight slow activity in the left frontotemporal region due to left MCA stroke.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient's abnormal movements is broad. Considerations included tonic seizure (asymmetrical, sudden extension/flexion of extremities⁴), which occur in 4–10% of patients poststroke, with most occurring within the first 48 h.¹ The high NIHSS and cortical involvement in this patient further increased the risk,⁵ as did the administration of neuroleptics, which can reduce seizure threshold.⁶ However, seizure was thought to be less likely as the movements occurred despite the fact that the patient was receiving benzodiazepines, propofol and phenytoin. Extensor (decerebrate) posturing (arm adduction and extension, wrist pronation and back arching⁷) secondary to haemorrhagic conversion was considered, but thought to be less likely due to the symmetric presentation of movements and unchanged imaging. Neuroleptic malignant syndrome was thought to be less likely given that the patient was afebrile and not rigid between episodes. A creatine kinase level checked a few hours after the movements occurred was 824 U/

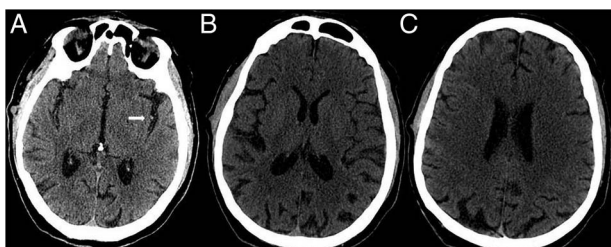


Figure 1 CT scan of the head. (A) Embolus in distal left M3 just superior to insula, and (B) and (C) Alberta Stroke Programme Early CT Score (ASPECTS) 10.

L, and, while elevated, could have been attributed to the patient's prior agitation. Finally, in light of recent administration of haloperidol and resolution with diphenhydramine, an acute dystonic reaction (involuntary, sustained, repetitive opposing muscle contractions⁸) was considered.

TREATMENT

In order to treat the suspected acute dystonic reaction, the patient received 50 mg of diphenhydramine and the abnormal movements quickly resolved. Two days later, the patient exhibited extreme agitation not responsive to benzodiazepines and was therefore started on quetiapine 50 mg every 6 h, a frequently administered medication in the intensive care unit (ICU) due to its ability to reduce duration of delirium and agitation without significantly affecting respiratory status.⁹ Another 2 days later, metoclopramide 50 mg every 6 h was initiated according to local ICU protocol for poor gastric absorption of feeds, given its prokinetic effects, while its central antidopaminergic actions and risk of associated dystonic reactions were not considered at the time.⁹ Over the course of the following day, the abnormal movements demonstrated in video 1 reappeared, but this time they were more quickly identified and were less severe. A total of 100 mg of diphenhydramine was administered, but movements did not completely resolve until 1 mg of benztropine was administered. This functioned as an unintended rechallenge with an antipsychotic for a patient who, prior to admission, had been antipsychotic naïve; the recurrence of dystonic movements confirmed that the patient was prone to develop an acute dystonic reaction with exposure to these medications. As such, all antipsychotics and antidopaminergics were withdrawn and no further dystonic reactions occurred. The patient continued on pramipexole for restless legs throughout the admission and after discharge.

OUTCOME AND FOLLOW-UP

The patient's course in the ICU was prolonged and complicated by vocal cord dysfunction requiring re-intubation shortly after extubation. He was eventually discharged with stroke rehabilitation completed in the community. Two years later, he has persistent mild dysarthria and focal neurological deficits consistent with his left MCA stroke.

DISCUSSION

Acute dystonic reactions are involuntary sustained, repetitive contractions of agonist and antagonist muscle groups.¹⁰ They occur in 2–3% of patients treated with antipsychotics, typically occurring within 48 h of drug exposure or dose change, and usually involve cranial, pharyngeal, cervical and axial muscles with limbs less frequently involved.³ While the propensity of dopamine-blocking agents to cause acute dystonia is related to blockade of D2 receptors, the exact mechanism by which dystonia results is unclear.¹¹ Rapid treatment with anticholinergic agents and removal of offending agents are cornerstones of management. It is unclear whether hyperacute stroke predisposes patients to acute dystonic reactions, but there have been rare reports of focal dystonia after motor area infarction.¹² In this case, the patient's exposure to antipsychotics and prompt response to intravenous diphenhydramine and benztropine were most suggestive of the diagnosis of drug-induced acute dystonic reactions.

Haloperidol, an antipsychotic medication widely used to treat agitation, has significant activity at type 2 dopamine receptors and is associated with acute dystonic reactions in 3–10% of patients.¹³ Compared with second-generation antipsychotics,

haloperidol is similarly efficacious but associated with more sedation, extrapyramidal symptoms and requirement for additional medications for agitation.¹³ In fact, a Cochrane Review comparing haloperidol with second-generation antipsychotics found similar severities of delirium with each, but also found that a higher dose of haloperidol (>4.5 mg/day) was associated with increased risk of extrapyramidal adverse effects.¹⁴ Furthermore, a recent clinical care practice guideline suggests that atypical antipsychotics may be more beneficial than haloperidol at reducing the duration of delirium in adult ICU patients, and should be the preferred first-line agent.¹⁵

In this case, seizures took place shortly after administration of haloperidol, and while antipsychotic medications can lower the seizure threshold, haloperidol is thought to be associated with a relatively lower risk of seizure induction,¹⁶ and it is therefore unclear as to whether this contributed to onset of seizure activity. Another interesting feature of the case was the occurrence of dystonic reactions after administration of quetiapine and metoclopramide, which may have acted synergistically, and highlights the importance of careful consideration of drug therapy to minimise side effects. There are several important learning points from this case. First, the involvement of back arching and leg muscles in this case make it an atypical presentation of an acute dystonic reaction and, therefore, more difficult to diagnose. Second, the patient's course was complicated by stroke and status epilepticus, and thus an anchoring bias may have made it more difficult for caregivers to consider alternative explanations for the new movements exhibited. For these reasons, careful clinical analysis of movements and attention to potential causes is crucial to the correct diagnosis (table 1). Perhaps if this atypical acute dystonic reaction had been recognised and treatment with benztropine attempted earlier, these movements may have resolved more promptly. Had this occurred, perhaps the third CT scan of the head may have been avoidable, and perhaps fewer antiepileptics, which can have harmful side effects, particularly in elderly and critically ill patients receiving many other medications, may have been administered. Finally, it should be recognised that while haloperidol can be effective in treating delirium, it is associated with a higher risk of extrapyramidal side effects compared with second-generation antipsychotics, which have been shown to be similarly efficacious in the

management of delirium.¹³ However, this case also demonstrates that care must be taken when prescribing second-generation antipsychotics and metoclopramide to patients at risk for dystonic reactions, as there is still a risk of extrapyramidal side effects, the presentation of which might be less pronounced.

In the ICU, seizures and dystonic reactions can be confused if careful attention is not paid to the quality of the movements and potential underlying causes. Patient assessment is often complicated by the use of sedation, invasive mechanical ventilation, monitoring equipment and the patient's underlying condition. While diagnosis in this case might have been assisted by continuous EEG monitoring, this technology is not universally available around the clock. Furthermore, our patient's course was complicated by both seizure poststroke and acute dystonic reaction, which warranted significantly different treatments. Careful evaluation of the semiology of movements permitted proper diagnosis and correct treatment.

Learning points

- ▶ Critically ill patients may have multiple abnormal movements, the assessment of which is often complicated by their critically ill state and associated care.
- ▶ Acute dystonic reactions are frequently drug related and typically occur within 48 h of drug exposure or dose change, and are treated with anticholinergic agents and removal of the offending drugs.
- ▶ Haloperidol has similar efficacy in the treatment of delirium as compared with second-generation antipsychotics, but is associated with a higher risk of extrapyramidal side effects, particularly in elderly patients.
- ▶ Careful evaluation of the semiology of movements may assist with proper diagnosis and correct treatment when patients are otherwise difficult to assess, and when EEG is not available.

Competing interests None declared.

Patient consent Obtained.

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Table 1 Abnormal movements in critically ill patients with neurologic disease

Movement	Characteristics of movement	Duration	Treatment
Seizure	Rhythmic	Intermittent (seconds–hours)	Antiepileptics
Acute dystonic reaction	Intermittent spasmodic or sustained involuntary contractions of muscles in the face, neck, trunk, pelvis, extremities	Prolonged and sustained	Anticholinergic agents, benzodiazepine
Myoclonus	Sudden, shock-like, involuntary movements caused by muscular contractions or inhibitions	Very short (milliseconds–seconds)	Antiepileptics, botulinum toxin
Paralysis	Flexors predominate in upper extremity, extensors in lower extremity Asymmetric in stroke	Fixed, slow to improve	Physical therapy

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Reminder of important clinical lesson

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