CASE REPORT

Persistent oromandibular dystonia and angioedema secondary to haloperidol

Ruziana Masiran

Department of Psychiatry,
Universiti Putra Malaysia,
Serdang, Selangor, Malaysia

Correspondence to
Dr Ruziana Masiran,
ruziana78m@yahoo.com

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SUMMARY

We report a case in a young man who developed acute, persistent and painful tongue protrusion followed by swelling for more than 24 hours. He had relapse symptoms of schizophrenia and had recently received a single dose of parenteral haloperidol to manage his agitation. His record showed history of similar event and he has been taking atypical antipsychotic for maintenance. Mental state examination on admission revealed an agitated man with disorganised speech, restricted affect, auditory hallucination and persecutory delusion. His dystonia and oedema improved after 3 days. His mental status also recovered with the maintenance of low-potency antipsychotic and anticholinergic antiparkinsonian medications.

BACKGROUND

Acute dystonia secondary to conventional antipsychotics is a common adverse event seen both in the outpatient as well as inpatient settings. Occurring abruptly in the early phase of treatment, this side effect is extremely uncomfortable to the sufferer. Young male patients with history of acute dystonia are particularly at risk. Although preventable, recurrent episodes of such distressing event are still being encountered. Patients who are on antipsychotics but have previously developed acute dystonia are commonly forgotten or dismissed, owing to lack of proper documentation or identification of such patients, the inability of patients themselves to inform the healthcare workers of such history or the failure of assessment of possible adverse reactions in situations where such medications are required to be administered urgently. Angioedema associated with antipsychotic is rare but potentially lethal when there are cardiorespiratory complications. In both conditions, early recognition of high-risk patients is crucial.

CASE PRESENTATION

A 27-year-old Middle Eastern student with a history of schizophrenia diagnosed just a year ago presented with commanding, second-person auditory hallucination and persecutory delusion, as well as made act for 2 weeks which impaired his academic performance and attendance. He started to wander around the city and was finally reported to have caused public commotion by screaming and verbally threatening the public near a hotel. He subsequently was brought by the police to the hospital, where he was noted to be agitated and

there was impending aggression to the staff at the emergency ward. As a result, he was sedated with parenteral haloperidol 10 mg and midazolam 10 mg and restrained over all four limbs. The physical restraints were taken off an hour later, during which he has already arrived in the psychiatry ward. However, 4 hours later, he developed sudden episode of painful tongue protrusion which was associated with gradual development of tongue swelling within the next 24 hours.

A further examination in the ward showed that he was fully conscious, alert and orientated but appeared anxious, diaphoretic and was tachycardic with pulse rate 110/min. His blood pressure was initially 150/90 mm Hg on admission but continued to be normal during his stay in the ward later. There was involuntary tongue protrusion associated with mild tongue oedema but without cyanosis. This was associated with muffled voice, and drooling of saliva ([figure 1](#)) and dryness over his mouth was seen. There was no stiffness noted over his limbs, trunk, neck or jaw. His muscles were soft on palpation. There were also no involuntary movements noted over his eyes or limbs. There was no airway compromise. His lungs were clear bilaterally while the remainder of the physical examination including the neurological assessment was normal.

A thorough check on his past psychiatric records revealed that he had experienced a similar episode the previous year, following an administration of parenteral haloperidol.

INVESTIGATIONS

His body mass index was normal.

Full blood counts, creatine kinase and the erythrocyte sedimentation rate were all within normal ranges. The renal, thyroid and liver function tests and infectious disease screening were also normal. Fasting sugars, cholesterol and triglycerides were not deranged.

ECG showed sinus tachycardia.

A plain CT brain showed no abnormalities.

DIFFERENTIAL DIAGNOSIS

There are a number of neurological conditions which resemble this patient's condition. In a prolonged state of dystonic reaction, status epilepticus should be ruled out. However, his presentation was not that typical of epilepsy; only 'tonic' stage was observed. In addition, he was fully conscious throughout the event and there had been recent administration of intramuscular haloperidol

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Figure 1 Acute dystonic reaction of the tongue (lateral view).

at the emergency department preceding the onset of muscle spasm.

Another condition which should be ruled out would be stroke or cerebrovascular accident. However, there was no altered consciousness and there were no other motor or sensory deficits elicited.

Among infectious diseases, meningitis must be ruled out due to the acute presentation of muscle spasm. However, the hallmark features, that is, fever, headache and neck stiffness were all absent in this patient, making the diagnosis rather unlikely. Pharyngitis was also another diagnosis in mind as patient presented with tongue protrusion and swelling and the associated dysphagia evidenced by hypersalivation. Nevertheless, lack of febrile reaction and other manifestations like rash and flu-like symptoms did not support this possibility.

Finally, amphetamine intoxication was also ruled out as the possible cause of acute dystonia. Amphetamines were thought to cause dystonia via the central dopaminergic effects. The patient's record did not show history of amphetamine use. His urine was assessed for this illicit substance and it was found to be negative.

TREATMENT

The offending drug, that is, haloperidol, was stopped immediately, and the patient was given parenteral orphenadrine 30mg twice but his condition only improve slightly; he was able to wiggle his tongue but it was still generally protruded and oedematous.

Intravenous dexamethasone 8 mg three times a day was initiated and continued for 4 days. Oral benzhexol 2 mg twice a day was commenced, and the previous maintenance of oral risperidone was replaced with sulpiride 200mg twice a day. Thymol gargle 15 mL was started. The patient had to receive intravenous hydration until his condition completely recovered.

OUTCOME AND FOLLOW-UP

Due to a high suspicion of meningitis, the patient was first admitted to the neurology ward before transferred to the psychiatric ward the next day. He had only received supportive treatment with intravenous fluids, without commencement of antibiotics. He was able to follow commands but his tongue protrusion and oedema persisted during the first 3 days of admission. His condition improved only to a minimum extent following the discontinuation of the offending agent and administration of intramuscular orphenadrine. It only resolved after 3 days, with the addition of oral benzhexol and intravenous dexamethasone.

On the fourth day, the tongue protrusion disappeared while the swelling subsided gradually. He appeared less anxious and his tachycardia improved. He was able to tolerate fluids and solid orally and showed no abnormality in speech. Concurrently, his psychotic symptoms also resolved and he was discharged well. The patient was advised about future haloperidol use, and he was given an identification card to warn the treating doctors and staff of potential similar reactions in the future.

DISCUSSION

Antipsychotic-induced acute dystonia is often manifested as an involuntary and sustained contractions of a muscle or a group of muscles producing an abnormal posturing or twisting movements of the body parts involved, as a result of taking antipsychotics, more commonly the conventional type. It may appear as upper or lower limb dystonia, oculogyric crisis, torticollis and tongue protrusion. The pathophysiology behind the onset of acute dystonia after hours of haloperidol ingestion or injection has been postulated to be due to a deficit in dopaminergic transmission resulting in overactive acetylcholine release in the striatum.¹ Similarly, other drugs like metoclopramide may also induce dystonia owing to its similarity with selective dopamine antagonists,² which has led to its initial use as an antipsychotic. Patients presented with acute dystonic reaction are frequently seen either in the emergency department (ED) or in the psychiatric wards. In the ED setting, this condition is often misdiagnosed, causing a delay in intervention,³ increasing morbidity and risk of mortality.

On the other hand, angioedema is a potentially life-threatening condition characterised by the swelling within the subcutaneous and mucosal tissue layers,⁴ with or without urticaria. The pathophysiology involves increased capillary permeability and plasma extravasation⁵ within these tissue layers in the body, including the respiratory and intestinal tract. Angioedema can be associated with IgE as part of an allergic reaction or bradykinin-mediated when an allergic reaction is not related.^{4,5} In the former, the prescription of an antihistamine might help. In a patient prescribed with haloperidol, the conventional antipsychotic acts on dopamine receptors and serotonin (5HT) 1A, histamine, muscarinic and alpha receptors. Despite the potential effect on the histaminergic receptors, the illustrated patient did not seem to exhibit urticarial reaction. Urticaria would be a common finding in allergic angioedema. Angioedema with haloperidol itself is uncommon but has been reported,⁶ along with other medications like ACE inhibitors,^{4,5} iloperidone,⁷ non-steroidal anti-inflammatory drugs⁵ and oestrogen-based contraceptive pills.^{4,5}

The combination of intramuscular haloperidol and midazolam has been recommended for rapid tranquilisation among patients with schizophrenia.⁸ Alternatively, lesser occurrence of dystonia associated with second-generation antipsychotics cannot be denied. This has even been reviewed using the Clinical Antipsychotic Trials of Intervention Effectiveness Schizophrenia Trial which showed the use of latter significantly reduced extrapyramidal side effects (ESPE) compared with haloperidol.⁹ Nonetheless, it has been suggested that the use of antipsychotics in schizophrenia and their tendency to cause spectrum of movement disorders might be better reviewed from their receptor binding affinities and the susceptibility of individual patients to develop ESPE rather than the type antipsychotics alone.

In the illustrated case, the development of oromandibular dystonia began 4 hours after the intramuscular administration of haloperidol. This was accompanied with tongue swelling,

triggered by angioedema involving the deeper subcutaneous tissues and mucosal surfaces of the tongue. Although these two incidents manifested abruptly, they seemed to have occurred in a minimal fashion without compromising the patient's airway. Unfortunately it took him 3 days to recover from the reactions. But this was not surprising as the maximum plasma levels of haloperidol can be reached within 20 min after injection while its half-life is longer; 12–36 hours.¹⁰ Thus further observation of patients with acute dystonia should actually be longer although the initial episode may occur for just minutes.

In conclusion, both acute dystonia and angioedema are distressing experiences a patient could suffer from. Prevention of these phenomena could be achieved through identification of risk factors in individual patients. Therefore, getting a thorough patient history is indispensable to determine previous episode or

episodes of such adverse events. It is highly recommended that any patient with similar history be provided with a medical identification bracelet, chain or card as a preventive measure against the administration of the same medication.

Competing interests None declared.

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Learning points

- ▶ Neuroleptic-induced acute dystonia has an abrupt onset but may takes up to 36 hours to resolve completely, hence requiring a longer patient monitoring.
- ▶ Persistent oromandibular dystonia accompanied with angioedema is rare and potentially lethal as it may be associated with laryngeal oedema.
- ▶ A high degree of clinical suspicion of acute dystonia and a better identification of high-risk patients are strongly recommended especially in places where conventional antipsychotics are more easily available and affordable compared with the atypical ones.

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