A rare case of H1N1 pdm09 infection with acute cerebellar syndrome – a case report

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ABSTRACT

Background: Influenza A H1N1 pdm09-associated neurological complications are rare, particularly in adults. This case report highlights one of the uncommon presentations associated with H1N1 pdm09 infection.

Case Presentation: We present the case of a 38-year-old male who was admitted to the hospital primarily with respiratory manifestations and developed acute cerebellar ataxia during hospital stay, causing a diagnostic dilemma, as his cerebrospinal fluid analysis and magnetic resonance imaging brain were unremarkable. Throat swab real-time reverse transcriptase polymerase chain reaction {rRT-PCR) turned out positive for influenza A {H1N1) pdm09 virus strain and a nontypeable influenza A strain. He showed the resolution of cerebellar signs and a remarkable recovery on oseltamivir therapy. Based on the acute onset, positive RT-PCR and recovery on antiviral, a diagnosis of H1N1-associated cerebellitis was made.

Conclusion: This report highlights an extremely rare complication of influenza infection with only five reported cases in adults and case series in children. Vigilance and a high index of suspicion for patients presenting with rapid onset neurological deterioration during pandemics and seasonal epidemics can prevent devastating sequelae.

Keywords: Cerebellitis, influenza, cerebellar ataxia, influenza-associated encephalopathy, case report.

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Background

H1N1 influenza continues in the post-pandemic phase as seasonal influenza, after its initial outbreak in Mexico in the year 2009. Annual influenza epidemics result in 3–5 million cases of severe illness and an estimated 250,000–500,000 deaths each year [1]. Neurological manifestations in influenza infections are diverse and rarely seen. The estimated incidence of influenza-related neurological complications (INCs) was 1.2 per 100,000 symptomatic pdm09 H1N1 illnesses, as they were observed in 4% of patients with fatal or severe H1N1 infections in one study; however, more than three-fourth of these cases were in the paediatric age group [2].

There is a considerable overlap between acute cerebellar ataxia and acute cerebellitis as both are characterised by parainfectious, postinfectious, or postvaccination cerebellar inflammation [3]. Cerebellitis cases in H1N1 infection in children have been reported in the form of case series; however, there are few case reports in adults. In the PubMed-based literature review, there were five reported cases of influenza-associated cerebellitis [4–8] in adults and only two in association with H1N1 pdm09 strain in adults [6,8]. To the best of our knowledge, this is the first reported case in Pakistan with this presentation in an adult.

Case Report

The patient was a previously healthy 38-year-old man having no known comorbid conditions who presented to the Emergency Department of Military Hospital Rawalpindi on 3/1/18 with a 3-day history of fever, cough, sore throat and vomiting. The cough was productive, containing scanty mucoid sputum; fever was high grade associated with rigors and chills. The patient had taken co-amoxiclav but had found no relief. The past medical history was unremarkable. He was a non-smoker, with no recent contact with sick persons and no recent history of immunisation against influenza vaccination.

Physical examination revealed that he had a fever of 102°F, blood pressure of 100/70 mm Hg, pulse rate of 104 beats/minute and respiratory rate of 24 breaths/minute; he was maintaining saturation on room air (97%). The throat was erythematous and congested. Chest auscultation revealed bilateral crepitation. The cardiovascular examination was unremarkable. The neck was supple, there was no rash noted and no lymph nodes were palpable.

Baseline blood count revealed a total leucocyte count of 10,900/mm^3 with neutrophilia (90%), and his renal function tests, electrolytes and liver enzymes were within normal limits. High-resolution computed tomography (HRCT) scan chest showed bilateral patchy consolidations, ground-glass opacities and airspace nodules. He was hospitalised, and the treatment was started on lines of atypical pneumonia with antibiotics and supportive therapy.

On day 2 of admission, the patient developed slow intentional tremors and complained of headache and

sudden onset difficulty in balance and walking. There was no associated history of fits or previous history of neurological disease. He had no cognitive or behavioural deficits. Neurological examination revealed GCS 15/15, no neck stiffness, intact deep tendon reflexes and bilaterally down going planters. Gait was broad based and ataxic, and he had impaired coordination manifesting as bilateral past pointing, nystagmus, dysdiadochokinesia and dysmetria. Cranial nerve examination was unremarkable.

His cerebrospinal fluid analysis opening pressure was normal, cell count was 1 cell/mm^3, with occasional lymphocytes, glucose was 63 mg/dl (serum, 139 mg/dl) and total protein was 26 mg/dl. Gram stain and AFB stain were negative. Urine, sputum and blood cultures were negative for any pathogens. Urine antigen tests for *Legionella pneumophila* and Mycoplasma serology were also negative. Anti-glutamic acid decarboxylase antibodies and anti-neuronal profile were negative. Extractable nuclear antigens were also negative. Serum CK levels were 1479 U/l. A thorough review of drug intake was made, and drug-induced ataxia was excluded.

Magnetic resonance imaging (MRI) brain with contrast showed no abnormality to guide the diagnosis other than a persistent cavum septum pellucidum and cavum verge which are considered as normal variants.

A throat swab had been collected and sent to the National Influenza Center, National Institute of Health, Islamabad, for real-time reverse transcriptase polymerase chain reaction (rRT-PCR). The sample was tested based on Center for Disease Control and Prevention (CDC) rRT-PCR protocol for the detection and characterisation of swine influenza. It was positive for influenza A (H1N1) pdm09 virus strain and a nontypeable influenza A strain. The patient was given a course of oseltamivir 75 mg twice daily for 5 days, Intravenous immunoglobulin, plasmapheresis and admission to intensive care unit were kept under consideration due to patient's rapid onset of symptoms and sudden deterioration. However, his tremors improved over the next 3 days and ataxia resolved over the next 1 week. Based on positive H1N1 RT-PCR and onset of acute cerebellar syndrome, a diagnosis of H1N1-associated cerebellitis was made.

He had no permanent or residual neurological sequelae and was discharged after a hospital stay of 22 days. Follow-up neurological examination after 3 months revealed no residual neurological deficit.

Discussion

Acute cerebellitis in adults is a rare entity with a wide range of aetiology, clinical presentation and outcomes. The patient developed neurological symptoms 4 days after disease onset. The median time from the onset of influenza symptoms to the onset of neurologic symptoms ranges from day 1 to 5, and almost all cases had onset of neurologic symptoms within 5 days of illness onset in one study [9]. Direct invasion and cytokines have been proposed as the likely mechanisms behind acute onset neurological complications, whereas adaptive immune responses in subacute onset [9].

A diagnosis of H1N1 infection requires confirmation by RT-PCR of throat/nasopharyngeal swabs, viral culture, or four-fold rise in new influenza A (H1N1) virus-specific neutralising antibodies [10]. The cerebrospinal fluid (CSF) was abnormal in only 4 (22%) patients in another study on INC [9]. In this case, CSF was not tested for viral influenza RT-PCR, whereas it was positive in CSF for one of the H1N1-associated cerebellitis cases [8]. Although testing CSF for influenza virus RNA may help to establish influenza-associated encephalopathy (IAE), a negative PCR does not rule out the diagnosis. In a study by Meijer et al., the influenza virus was detected in CSF of minority (16%) of patients [11].

MRI is the most sensitive imaging modality and is used to either confirm a diagnosis or rule out other likely differentials; however, in this case and in other various cases in literature, it was unremarkable [3,4]. Only 43% (10/23) had imaging abnormalities in one study [9], and 55% of patients had normal imaging studies in a literature review on INC [12]. Regardless of pathogenesis, the most characteristic finding by MRI in cerebellitis is diffuse cortical swelling of the cerebellum which can be complicated in the form of hydrocephalus/tonsillar herniation. Imaging and CSF findings are summarised in Table 1.

The treatment of acute cerebellitis depends on the aetiology and complications. Antimicrobials and antivirals are the mainstay in infectious aetiologies. When brain MRI shows diffuse cerebellar swelling, patients should also be treated with corticosteroids to prevent further swelling and brain herniation [13]. Surgical interventions such as external ventricular drain might also be required in hydrocephalus. In H1N1-related neurological complications, antivirals should be ideally started within 48 hours of the onset of clinical symptoms [10]. The patient's condition also improved after initiation of antiviral. Almost 25 (86%) patients had received antiviral within 48 hours of hospitalisation in the United States study, but all had received such treatment after neurologic symptoms had begun [2].

Almost half of the patients ended up with neurological sequelae in a review on adult cases of cerebellitis, with cerebellar atrophy given as a plausible explanation for the cause [13]. CSF analysis and MRI appear to have a prognostic value in patients with acute onset neurological complications of influenza virus infection [11]. In a study by Meijer et al. [11], all the patients with normal CSF analysis (chemistry and/or PCR) and 7/9 (78 %) patients with normal MRI made a full recovery. This is consistent with the normal CSF and MRI imaging in this case and the patient's remarkable recovery without any permanent neurological sequelae.

Table-1. Summary of literature review on case reports on Influenza associated cerebellitis

CASE REPORT-TITLE/YEAR OF PUBLICATION	CLINICAL CHARACTERISTICS	CSF ANALYSIS	TREATMENT	IMAGING	OUTCOME
Probable post-influenza cerebellitis 1997 **[4]**	31 -year-old woman presented with ataxia 1 month after flu symptoms	Normal cell count, glucose and protein Type B influenza virus was detected by RT-PCR from the CSF at 7 and 9 weeks from onset of flu symptoms	Not specified/NA	CT-scan and MRI Brain essentially normal	Resolution of symptoms over three-month period
An adult case of acute cerebellitis after influenza A infection with a cerebellar cortical lesion on MRI 2006 **[5]**	A 25-year-old woman with fever and headache	Cerebrospinal fluid showed pleocytosis	Received Oseltamivir and steroid pulse therapy	T2-weighted brain MRI demonstrated a high signal lesion in the cerebellar cortex.	MRI lesion disappeared 80 days after hospitalization, truncal ataxia and CSF pleocytosis resolved three months later.
POI02 Fulminant cerebellitis related to H1N1: a first case report 2010 **[6]**	Teenage girl developed fulminant cerebellitis after taking anti-viral	Influenza RT-PCR in CSF was negative	Neurosurgical intervention for placement of an external ventricular drain	Hydrocephalus	Residual left-sided ataxia after 3 months
Sub-acute hydrocephalus in a patient with influenza A (H3N2) virus-related cerebellitis 2012**[7]**	A 47-year-old man with HCV hepatitis, CKD-5D developed rapidly worsening headache resulting in a coma	CSF Glucose, proteins & cells unremarkable. H3N2 influenza virus type A identified in CSF culture, also isolated from nasopharyngeal specimens.	Suboccipital decompressive craniotomy was performed for raised ICP patient was mechanically ventilated; received oseltamivir after diagnosis	Tri-ventricular hydrocephalus & posterior cranial fossa swelling on CT brain. MRI showed areas of hyperintense signal on T2-WI in in the cortical-subcortical region of cerebellar hemispheres	Weaned from mechanical ventilation and Discharged from intensive care unit on day 17 in a persisting coma state
Cerebellitis associated with influenza A(H1N1) pdm09, United States, 2013 **[8]**	37-year-old female patient Onset day 4 after onset of flu symptoms	Elevated leukocytes 330/mm (13% neutrophils and 62% lymphocytes) Glucose and protein levels in CSF 61 mg/dL and 41 mg/dL, RT-PCR for influenza A(H1N1) pdm09 virus RNA was positive.	Given oseltamivir, 75 mg orally twice daily for 5 days.	Enlarged bilateral cerebellar hemispheres with evidence of hypo intensity of the affected thoracic vertebral segment on T1 image and hyperintensity on the T2 image.	Discharged after 1 week with complete recovery

Conclusion

This case highlights a rare and potentially devastating manifestation of influenza infection. Clinicians should maintain a high index of suspicion particularly in peak seasons and high-risk populations. A national surveillance study, such as those done in the UK and US regarding neurological manifestations and their outcomes in the population, can further guide clinicians in diagnosis and management of thesecomplications.

What is new?

This case report is based on a rare manifestation of H1N1 2009 pandemic strain or swine flu. To the best of our knowledge, this is the first such reported case in an adult in Pakistan; the case highlights the importance of early recognition and treatment of influenza-associated cerebellitis/ acute cerebellar syndrome and gives a brief review of other reported cases in literature.

List of Abbreviations

CSF	Cerebrospinal fluid
HRCT	High-resolution computed tomography
IAE	Influenza-associated encephalopathy
MRI	Magnetic resonance imaging
RT-PCR	Reverse transcriptase polymerase chain reaction

Consent for publication

Informed consent was taken from the patient.

Ethical approval

Ethical approval was obtained from the institute.

Author details

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Summary of the case

1	**Patient (gender, age)**	Male, 38-year-old
2	**Final Diagnosis**	H1N1 pdm 2009 infection with acute cerebellar syndrome
3	**Symptoms**	Headache, fever cough, acute onset gait disturbance
4	**Medications**	Oseltamivir
5	**Clinical Procedure**	HRCT scan chest done, Contrast-enhanced MRI brain, throat swab H1N1 RT-PCR was positive for H1N1 influenza A pdm 2009 strain, improvement in neurological symptoms with oseltamivir therapy 75 mg twice daily for 5 days, clinical follow-up done
6	**Specialty**	Pulmonology, Neurology