


Influenza A(H1N1)pdm09 Infection With Simultaneous Comorbidity of Severe Pneumonia and Acute Disseminated Encephalomyelitis: A Case Report

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Introduction

The 2009 H1N1 pandemic strain of influenza A(H1N1)pdm09 was first detected in Mexico and the United States in the spring of 2009 and, thereafter, spread to across the world. In Japan, the number of patients affected by the virus increased dramatically since September 2009.¹ The clinical profile of (H1N1)pdm09 infection varies from asymptomatic or mild to severe cases, resulting in severe respiratory failure, encephalitis or encephalopathy, and death in the worst scenario.²

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system following a viral infection or vaccination. The pathogenesis of ADEM is proposed to be autoimmune mechanisms triggered by infectious agents or vaccines. Childhood ADEM occurs more often after infection, and its prognosis is considered to be generally favorable.³

There are several reports of severe pneumonia caused by (H1N1)pdm09 infection, while there are only 7 pediatric case reports of ADEM following (H1N1)pdm09 until recently: none of these cases were complicated by pneumonia.⁴⁻⁶ Here we describe the case of 5-year-old boy who developed ADEM secondary to (H1N1)pdm09 severe pneumonia. To the best of our knowledge, this is the first case report of a pediatric patient with both comorbidities.

Case Report

A 5-year-old boy presented at the emergency department of our hospital with fever and dyspnea. He had no significant medical history except for allergic rhinitis. General examination revealed respiratory distress with cyanosis of the lips, and physical examination revealed prominent intercostal retractions and expiratory wheezing. A chest

X-ray revealed bilateral infiltration of the proximal bronchus (figure not shown). Blood examinations indicated a mild inflammatory pattern, and urine test revealed no significant abnormalities. A rapid antigen test of nasopharyngeal mucous specimen showed positive for influenza A. Only *Haemophilus influenzae* was detected in the nasal culture, and the mycoplasmal antibody titer was not elevated. He was admitted on the same day, and we immediately started treatment with intravenous hydrocortisone, cefotiam, and peramivir (an intravenous antiviral agent available in Japan). Within the first 12 hours following admission, his respiratory distress drastically deteriorated, so we started continuous isoproterenol inhalation therapy. However, this did not ameliorate his respiratory status, so we switched to respiratory management with intratracheal intubation and mechanical ventilation in the intensive care unit. During mechanical ventilation, a large amount of mucopurulent discharge was suctioned from the trachea. The discharge was highly viscous and resembled the casts in plastic bronchitis. A chest X-ray taken on the following day showed atelectasis of the right upper lobe, bilateral mediastinal emphysema, and subcutaneous emphysema (Figure 1). After suctioning a considerable amount of sputum, his respiratory status stabilized. On the fifth day the boy's respiratory status improved, so we extubated him and transferred him to the general pediatric ward.

On the sixth day his respiratory status was stable, but he had prolonged bradycardia and an altered consciousness: he was lethargic even after sedative withdrawal.

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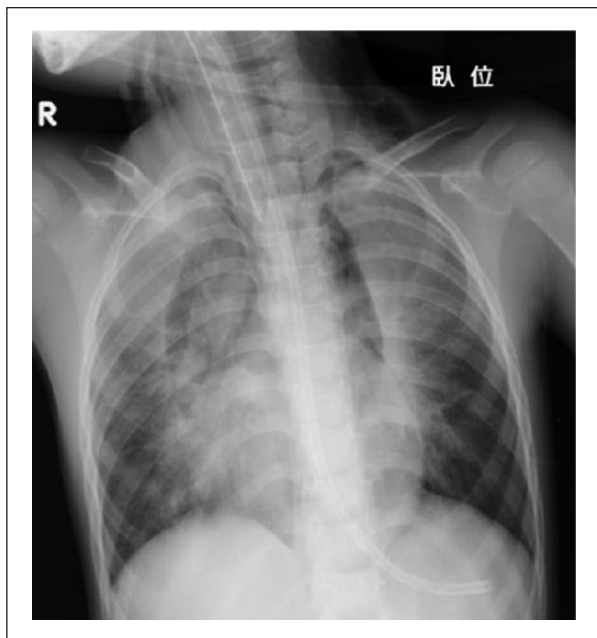


Figure 1. A chest X-ray study on the second day in hospital revealed right upper lobe atelectasis, bilateral mediastinal emphysema, and subcutaneous emphysema.

The situation remained unchanged the following day, so we conducted a more detailed examination. Electroencephalography revealed mild functional deterioration with frequent slow-wave activity. Lumbar puncture results were difficult to interpret because the procedure was traumatic. Cerebrospinal fluid was negative for oligoclonal bands and myelin basic protein. Brain magnetic resonance imaging (MRI) revealed asymmetric, bilaterally diffused, small, round patchy lesions within juxtacortical and deep white matter, where both T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) showed high signal intensity (Figure 2A). Distinct crescent-shaped areas in the left parietal lobe implicated a demyelinating pathophysiology. We diagnosed the boy with ADEM and administered intravenous methylprednisolone (30 mg/kg/day) for 3 days. On the eighth day, his pulse normalized and he became alert. A follow-up MRI on the 21st day in hospital showed no abnormalities, a significant improvement compared to previous studies (Figure 2B). He was discharged without any sequelae. After discharge, viral analysis revealed the causal virus was influenza A(H1N1) pdm09 strain, sensitive to peramivir. The patient remained well at his last visit 7 months after discharge.

Discussion

Influenza infection is usually self-limiting and most patients recover without severe complications, such as

seizure, pneumonia/bronchitis, or encephalitis/encephalopathy. It is therefore rare for 2 or more complications to occur concurrently in a single case. In the present case, (H1N1)pdm09 severe pneumonia led to mediastinal emphysema and plastic bronchitis, requiring mechanical ventilation, followed by ADEM. Uchimura et al reported 5 patients with encephalopathy out of 31 pediatric patients who required mechanical ventilation because of (H1N1)pdm09 severe pneumonia, but none developed ADEM.¹ To date there are 7 pediatric case reports of influenza A(H1N1)pdm09 followed by ADEM⁴⁻⁶; however, to the best of our knowledge, this is the first case of comorbid complications of severe pneumonia and ADEM.

We are unaware why this patient suffered from such severe pneumonia. Many researchers have been investigating the disease severity of (H1N1)pdm09 infection, and several factors, such as virulence of the virus, intrinsic host susceptibility, and host immune status, may be responsible. Rodriguez et al reported that (H1N1)pdm09 virus extracted from patients who died showed greater replicative capacity than virus from patients with mild disease course⁷; however, specific mechanisms of the virulence remain to be elucidated. A recent review by Horby et al indicates that there is limited evidence of an association between the identified genetic loci and host susceptibility in humans.⁸ Hall et al noted that hypercytokinemia and severe innate immune suppression could contribute to aggravation of (H1N1)pdm09 infections and proposed therapies including patient-specific immunomodulation.⁹ Unfortunately, we could not investigate these factors in the present case. Despite the accumulation of knowledge regarding disease severity of (H1N1) pdm09 infection, there is no standard therapy at clinical sites.

As ADEM is considered to be a heterogeneous entity, it remains a diagnostic challenge for many clinicians. A recent review proposed provisional definitions for pediatric-acquired demyelinating disorders of central nervous system (2012 IPMSSG criteria).¹⁰ In this report, we diagnosed the patient with ADEM because the clinical features met all the criteria. Pediatric ADEM preceded by infection has a monophasic clinical course, and prognosis is usually benign. However, Ozkale et al reported the case of a 7-year-old boy with neurological sequelae in spite of steroid pulse and intravenous immunoglobulin therapy.⁶ There is no standard therapy for ADEM at present, but high-dose intravenous corticosteroids are an accepted first-line treatment³; hence, we immediately administered intravenous methylprednisolone.

In our case, the onset of ADEM could not be determined because the neurological symptoms were obscured because of sedation, during mechanical ventilation. Uchimura et al reported 5 (H1N1)pdm09 patients with encephalopathy

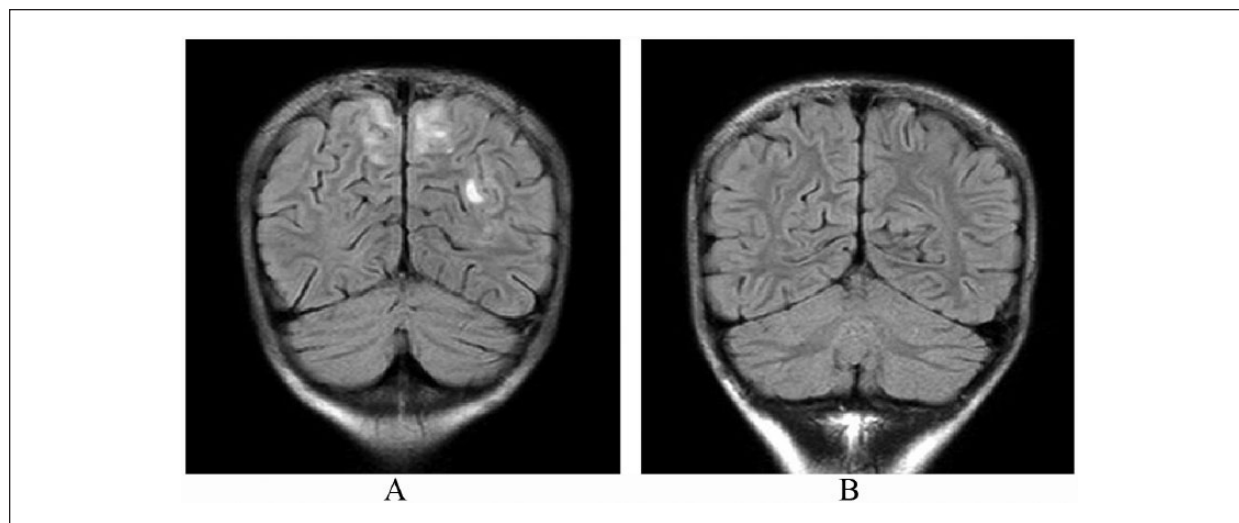


Figure 2. (A) MRI of the brain (FLAIR) on the seventh day showed diffused small round patchy lesions within juxtacortical matter. The periventricular white matter, corpus callosum, thalamus, basal ganglia, and infratentorial area (including the brainstem and cerebellar white matter) were not involved. (B) In the follow-up study on the 21st day in hospital, patchy lesions had disappeared completely.

complications who also required mechanical ventilation because of comorbid respiratory failure. Abnormal behavior was considered a symptom of encephalopathy, then diagnosed by electroencephalography, but they did not comment on the onset of encephalopathy.¹ Clinicians should be aware of concurrent neurological complications in patients with severe respiratory distress requiring controlled sedation, where neurological assessment is extremely difficult.

There has been a controversy about how to distinguish ADEM from a first attack of multiple sclerosis (MS). There are some patients who were once diagnosed with (monophasic) ADEM but later had a second attack, suggestive of MS rather than ADEM. Krupp et al noted that the interval between the first and second events was less than 2 years in 80% patients,¹⁰ but much later relapses were occasionally reported. Therefore, we need to observe patients for many years to confirm whether the event was truly monophasic.

Conclusion

To the best of our knowledge, this is the first case of 2 comorbid complications of influenza A(H1N1)pdm09 infection: ADEM and severe pneumonia. We performed mechanical ventilation for acute respiratory failure and treated the plastic bronchitis. After extubation, we diagnosed the patient with ADEM, treated it with methylprednisolone pulse therapy, and discharged him without sequelae. However, prolonged observation is necessary because of potential transition to MS. The factors that

induce severe complications with (H1N1)pdm09 infection are not fully understood. When working with influenza patients, pediatricians should keep in mind that one or more severe complications can develop.

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Author Contributions

YT contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MT contributed to conception; contributed to acquisition; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KA contributed to conception; contributed to acquisition; agrees to be accountable for all aspects of work ensuring integrity and accuracy. HF contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy. SS contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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