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Case Report

A Fatal Case of Acute Encephalopathy in a 8-year-old girl from a Pandemic of Influenza A (H1N1) in 2009

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SUMMARY

We report on a case in which a child died from acute encephalopathy associated with Influenza A (H1N1) pdm. The case pertains to an 8-year-old girl, who was diagnosed with influenza A on the previous day and was prescribed zanamivir hydrate. She experienced abdominal pain and delirium the next morning, so she was referred to our hospital. Her level of consciousness at the time of consultation was JCS 200. In the brain CT scan, a swollen brain stem and bilateral middle cerebral artery were depicted. She was in a state of respiratory failure, and was admitted to the intensive care unit. She was diagnosed with acute encephalopathy caused by Influenza A, and therapeutic brain hypothermia as well as steroid pulse therapy were performed ; however, she died on the third day after hospitalization from multiple organ failure.

Key Words : Pandemic, Influenza A (H1N1), Acute encephalopathy, child, underlying disease

INTRODUCTION

In the year of 2009, there was a pandemic of H1N1 influenza, and there were several mortalities. In Japan also, this epidemic gradually expanded starting in May of the same year. Moreover, there was no detailed information regarding any serious life threatening complications, such as acute encephalopathy and severe pneumonia, which thus had a widespread impact on Japanese society.

We experienced a fatal child case in November of the same year, which was the middle of the influenza season, in which the death was caused by acute encephalopathy associated with Influenza A (H1N1). The course taken by the child was an extremely drastic course, even given our concept of acute encephalopathy associated with seasonal influenza, as far as we understand it. We herein report on the clinical course of the present case.

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CASE REPORT

An 8-year old girl consulted her local doctor as a result of having developed a fever. A quick test for Influenza A from the nasal cavity identified her as being positive, and so she was diagnosed with Influenza A. She was then prescribed zanamivir hydrate. The next morning, she was continually in a delirious state from the fever and strong abdominal pain, and consulted the emergency room of our hospital due to a sudden loss of consciousness. The level of consciousness of the child was 200 on the Japan Coma Scale. A swollen brain stem and bilateral middle cerebral arteries were observed in the brain CT scan (Fig. 1). No signs of pneumonia were observed in the chest X-rays. Spontaneous respiration was very shallow and she was in a state of respiratory failure, so tracheal intubation was

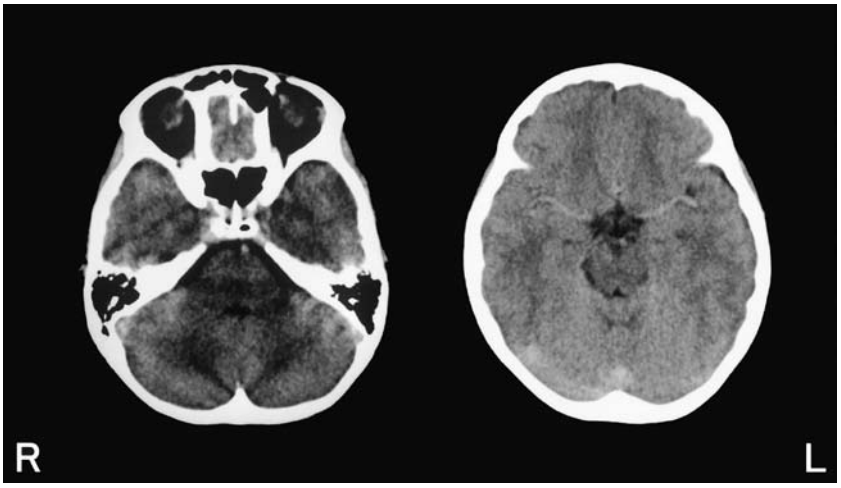

Fig. 1 Brain CT scan on admission

Table 1 Blood examination data on admission

WBC 9,900/μl	AST 369 U/L	Na 136 mEq/l	TP 8.0 g/dl	PT 26.0 sec	Fbg 129 mg/dl
RBC 622×10^4/μl	ALT 91 U/L	K 3.8 mEq/l	Alb 4.7 g/dl	PT-NC 12.2 sec	Hpt 38%
Hb 18.0 g/dl	LDH 1,392 U/L	Cl 104 mEq/l	CRP 0.82 mg/dl	PT% 27%	FDP 80.0 μg/ml (over)
Ht 52.8%	NH_3 86 mg/dl	Amy 1,826U/l	IgG 1,339 mg/dl	APTT 99.1 sec	D-Dimer 30.0 μg/ml (over)
Plt 10.4×10^4/μl	BUN 40 mg/dl	Glu 61 mg/dl	IgA 182 mg/dl	APTT-NC 30.4 sec	SFMC negative
	Cre 1.89 mg/dl	CK 572 U/l	IgM 146 mg/dl		AT-Ⅲ 61%

required immediately. In a blood test (Table 1) taken on admission, various abnormalities were observed in AST, LDH, CK, as well as coagulation tests, etc. Cerebral spinal fluid collection revealed normal data as follows, cell count 1/mm, protein 29 mg/dl, Glucouse 91 mg/dl. In generic testing of the influenza serotype, which used nasal secretions taken at the time of admission, she was diagnosed with an infection of pandemic Influenza swA (H1N1). Mild brain hypothermic therapy as well as steroid pulse therapy by methylprednisolone were commenced under the control of artificial respiration, however, the system vitals remained unstable, and it proved necessary to discontinue the therapeutic brain hypothermia after 36 hours. There was no improvement in the multiple organ failure from the blood test, and the child died on the 3rd day of hospitalization.

DISCUSSION

In April 2009, the WHO (World Health Organization) officially announced that the influenza A (H1N1) pdm-like symptoms which broke out in Mexico and sequentially spread in the form of an epidemic to the United States and Canada was H1N1 influenza. On May 9th of the same year, in Japan also, H1N1 influenza was detected in 4 airline passengers from Northwest of America. Subsequently, the epidemic rapidly spread throughout the country, and the number of infected patients increased to 370 people on May 30th and to 1266 people by the end of June. On August 15th, one of the first domestic cases of a death due to influenza A (H1N1) pdm was identified in Okinawa prefecture, and by December of the same year, the deaths of 135 people were reported within Japan. Furthermore, the pace did not even abate by the beginning of 2010, and ultimately, by March 15th, 2010, when the season came to an end, a total of 198 cases of influenza-related deaths had been confirmed[1].

Concerning the cases of death by infection during the influenza A (H1N1) pdm epidemic period from 2009 to 2010 published on the web site of the Ministry of Health, Labor and Welfare[1], when the breakdown

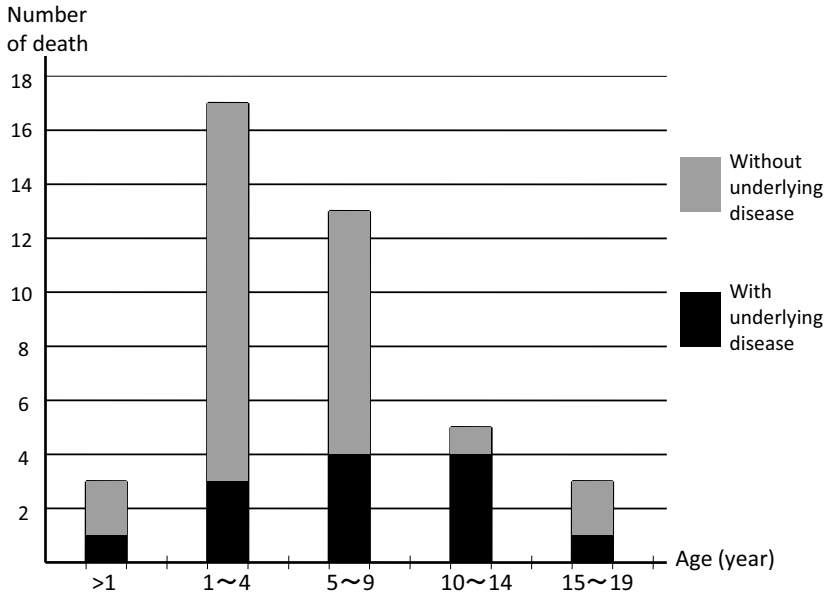

Fig. 2 The Child case of death by infection during the H1N1 influenza epidemic period from 2009 to 2010 in Japan

Table 2 The number of death by infection during the H1N1 influenza epidemic period from 2009 to 2010 in Japan

Age (year)	<1	1～4	5～9	10～14	15～19	20～29	30～39	40～49	50～59	60～69	70～79	80<	Total number
Number of death	3	17	13	5	3	11	14	31	31	25	23	22	198
With underlying disease	1	3	4	4	1	4	0	22	23	25	21	22	138

by age (Table 2) is examined, out of all 198 cases, mortalities involving children under 20 years old accounted for a total of 41 cases. In a breakdown of the child mortality cases (Fig. 2), the number of deaths was greatest, at 17 cases, for children over one year old to under 4 years old, and out of these, there were 3 cases in which the children had underlying diseases. There were 13 cases of death in children over 5 years old to under 9 years old, and out of those, there were 4 cases wherein the children had underlying diseases, which followed the preceding age range. Other than that, there were 5 cases of death in children over 10 years old to under 14 years old, 3 cases of death in children over 15 years old to under 19 years old, and 3 cases of death in children under one year of age. In view of this data, the number of child mortalities showed a trend, frequently occurring in nursery school and kindergarten, from older children to children in early schooling. Moreover, out of all 41 cases of child mortalities, 13 children (31.7%) had underlying diseases, and when the ratio of children with underlying diseases within the general population of this age range was considered, this indicated an exceedingly high percentage.

In addition, correlation between influenza A (H1N1) pdm and acute encephalopathy was reported on the web site of the Japan Infectious diseases surveillance center[2]. From the 28th week of 2009 until January 22nd, 2010, 120 cases of encephalopathy due to influenza A (H1N1) pdm were reported. The age distribution was 1 to 70 years of age (median : 7 years), and the cases included 74 males, and 46 females. An underlying disease and previous medical history were observed in 57 cases out of 119 cases, and there were 24 cases of febrile convulsion, as well as 16 cases of bronchial asthma. The period from the onset of fever until

the occurrence of an impaired consciousness was : 29 cases for 0 days, 66 cases for 1 day, 14 cases for 2 days, 4 cases for 3 days, and 2 cases for 4 days (median : 1 day). An impaired consciousness was observed before the onset of fever in 1 case. The duration of impaired consciousness was, out of 116 cases : 40 cases for over 48 hours, 17 cases for 24 to 48 hours, 30 cases for 12 to 24 hours, and 29 cases for less than 12 hours. Convulsions were observed in 66 cases (age : 1 to 24 years, median : 7 years), and among those, 26 cases were observed with status epilepticus. Abnormal behavior and abnormal speech were observed in 81 cases (age : 1 to 70 years old, median : 8 years). Treatment included steroid pulse treatment (97 cases), γ-globulin treatment (49 cases), hypothermic cerebral protection (12 cases), high dose antithrombin III treatment (5 cases), plasmapheresis (2 cases), and cyclosporine treatment (2 cases). No treatment was performed for 18 cases (15%). An artificial respirator was used for 32 cases. The number of days from the onset of fever to impaired consciousness in the 8 cases of mortality (age : 3 to 35 years, median : 4.5 years) was 1 to 3 days (median : 1 day), and the number of days from the onset of fever to death was 1 to 47 days (median : 3.5 days). Psychoneurotic disorders were observed in 13 out of the 14 cases that involved subsequent complications, and physical disabilities, such as motor paralysis, incontinence, etc., were observed in 8 cases.

The girl in the case we reported herein was an ordinary healthy child. The distinctive feature of this case is the intensity of the onset. Although the child was diagnosed with influenza A (H1N1) pdm, she remained at home a day before being hospitalized with no disturbance of consciousness. However, when she was conveyed to our hospital by ambulance, she fell into a severe disturbance of consciousness, and respiratory control at an intensive care unit was necessary in order to save her life. A high rise in AST and LDH values had already been observed at the blood test observation at the time of hospitalization, and this was similar to the reports on acute necrotizing encephalopathy and seasonal-type influenza encephalopathy trends[3]. In addition, a high cytokine state was indicated by such observations as the increase in ferritin value and sl-IL-2 value, etc. We performed therapeutic hypothermia and steroid pulse treatment, which are often reported to be useful as treatments for influenza-associated encephalopathy, with the patient under respiratory management[4,5] ; however, she did not respond to any to these treatments and, as a result, she died. There was no autopsy, and therefore, we cannot report on the detailed conditions of the disease. However, in the brain CT image taken just before she was admitted to the intensive care unit, the manifestation of a swollen brain stem and bilateral middle cerebral artery was observed. These are considered to be an indication of edema and angiitis. Perhaps this pathognomonic image manifestation is specific to influenza-associated encephalopathy caused by pdm.

Currently, the Ministry of Health, Labor, and Welfare is in the process of totaling child mortality cases caused by influenza A (H1N1) pdm in the 2009 to 2010 season by means of a national consultational investigation, led by 2 research teams : the Morishima team and the Kondo team. From 2011 onward, reports of acute encephalopathy in children caused by influenza A (H1N1) pdm show no signs of decline. Cases of acute encephalopathy in children caused by A (H1N1) pdm have been accumulated, and along with this, the overall picture has thus become clear. We eagerly hope for the early establishment of treatment as well as precautionary measures, as soon as possible.

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