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Clinical Presentations and Outcome of Hospitalised Paediatric Oncology Patients with Laboratory-confimed Pandemic H1N1 Influenza Infection in Hong Kong

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Abstract

Objective: The clinical course of hospitalised paediatric oncology patients and haematopoietic stem cell transplant (HSCT) recipients with laboratory-confirmed pandemic H1N1 influenza infection were studied. ***Methods:*** Data from oncology patients and HSCT recipients with hospitalised laboratory-confirmed pandemic H1N1 influenza infection in Hong Kong were collected. Parameters on initial presentations, clinical course, treatment regimens and outcome were studied. ***Results:*** Sixteen patients were studied, the median age was 12.4 years. Fever (100%), cough (75.0%), runny nose (56.3%) and sore throat (50.0%) were the most common presenting symptoms. Antiviral therapy was started at median 1 day after onset of fever. HSCT recipients were more common to require a repeated or prolonged course of antiviral therapy due to persistent respiratory symptoms. Our cohort recovered without severe complications. ***Conclusion:*** Fever, cough, runny nose and sore throat were the most common presenting symptoms. HSCT recipients were more likely to develop persistent or recurrent respiratory symptoms and required repeated course of antiviral therapy. The uncomplicated course of pandemic H1N1 infection of paediatric oncology and HSCT recipients might be related to the early initiation of antiviral therapy.

Key words Children; Influenza; Oncology; Pandemic

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Introduction

In April 2009, a novel influenza virus (H1N1) strain which was characterised by a unique combination of gene segments that derived from a quadruple reassortant of two swine species from North American and Eurasian lineages, one avian and one human origin influenza viruses was identified.[1] In June 2009, World Health Organization (WHO) declared the status of influenza A (H1N1) pandemic had reached phase 6 indicating widespread community transmissions on at least two continents.[2] The basic reproductive ratio, which defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period in a population of susceptible, of this novel influenza (H1N1) strain is similar to the spread of Asian pandemic influenza (H2N2) in 1957-1958 which is about 1.4-1.6.[2]

Although the reported case fatality rate of this influenza remains comparable to seasonal influenza in general population, the median age of reported confirmed cases is much younger than cases of seasonal influenza and the attack rate is highest among children which is quite different from seasonal influenza infection.[3] Prolonged viral excretion, lower respiratory tract infection and frequent development of anti-viral resistance during antiviral therapy are major additional concerns in immunocompromised paediatric population.[4]

The overall clinical picture of pandemic H1N1 infection in one of the most vulnerable patient groups – paediatric oncology and haematopoietic stem cell transplant (HSCT) recipients is not fully understood. Traditionally, immunocompromised patients are well-known to suffer from complications of influenza virus infection. By knowing this fact, appropriate and timely treatment strategy can then be tailored made to this patient group. We, therefore, performed this study to evaluate the symptomatology and clinical course of this infection in hospitalised paediatric oncology patients with laboratory-confirmed pandemic H1N1 infection in Hong Kong.

Methods

Recruitment Criteria

All hospitals including two university centres and three regional hospitals that are involved in managing paediatric oncology patients and haematopoietic stem cell transplant (HSCT) recipients in Hong Kong participated in this study.

The review period was started from the date which WHO declared the global pandemic of H1N1 infection, i.e. from 11th June, 2009 to 30th November, 2009. The following case definitions were used to select patients for review: (i) children aged ≦18 years old with oncologic conditions or haematopoietic stem cell transplant recipients who are receiving active treatment presenting with influenza-like illness (ILI) and laboratory-confirmed pandemic H1N1 influenza infection or (ii) children aged ≦18 years old with oncologic conditions or haematopoietic stem cell transplant recipients who have completed chemotherapy or discontinued immunosuppressants for less than 12 months, presenting with ILI and laboratory-confirmed pandemic H1N1 infection. The definition of ILI is fever (temperature ≧38°C) with either cough, sore throat or both for at least 24 hours. Laboratory-confirmed pandemic H1N1 infection was defined as (i) the detection of H1N1-H1 gene by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) in nasopharyngeal aspirate (NPA) or nasopharyngeal swab or combined oropharyngeal and nasal swab sample or (ii) isolation of pandemic H1N1 virus by viral culture.

Data collection

Medical chart abstraction was performed by the physician-in-charge of each participating site. They used the same standardised form that included (i) baseline demographic data; (ii) presenting symptoms/signs and laboratory results at diagnosis; (iii) clinical course; (iv) treatment offered; (v) outcome. All diagnostic tests and management were clinically driven and based on the recommendations of Hospital Authority of Hong Kong. For time calculations, the first day of onset of fever was considered to be day 0.

Results

Sixteen patients (12 male: 4 female) fulfilled the case definition and were recruited. All of them demonstrated positive pandemic H1N1 virus PCR. Twelve out of 16 patients (75%) were also culture positive. The median age was 12.4 years (range 3.4 years-14.6 years). The primary diseases included: (i) acute lymphoblastic leukaemia (n=7); (ii) brain tumours (n=4); (iii) acute myeloid leukaemia (n=2); (iv) lymphoma, (n=1); (v) adrenoleukodystrophy (n=1) and beta-thalassemia (n=1). Nine of them were receiving chemotherapy according to their disease-specific protocols. Seven of them have received haematopoietic stem cell transplant (HSCT) of whom six had chronic graft-versus-host disease (GVHD). Two patients (patient 10 and

15) developed moderate to severe chronic graft-versus-host disease of the lung and one of them (patient 15) had bronchiolitis obliterans and was on intensive immunosuppressive therapies.

The most common presenting symptoms were fever (100%), cough (75.0%) and runny nose (56.3%) and sore throat (50.0%). One patient (patient 13) with history of epilepsy presented with generalised convulsion and fever. One patient (patient 8) presented with vomiting but none presented with diarrhoea.

The median duration of fever was 4 days (range from 1 to 9 days). The median duration of hospitalisation was 5 days (range from 3 to 12 days).

Concerning antiviral therapy, oseltamivir was started at median 1 day after fever onset (range from 1 to 6 days). Eight patients (50.0%) received one 5-day course of oseltamvir. Patient 3, 10 and 15 had recurrence of fever and worsening of respiratory symptoms after a 5-day course of oseltamivir and required an extra 5-day of high dose antiviral therapy which defined as doubling of standard dose of antiviral therapy.

The median time of defervescence after starting antiviral therapy was 1.3 days (range 1-3 days) and 3.3 days (range 1-8 days) in oncology patients and HSCT recipients respectively.

Seven patients had repeated virologic studies, 4 turned negative by day 14 from diagnosis but 3 showed persistent positive PCR results up to day 24 of illness. No laboratory-confirmed secondary nosocomial spread of infection was recorded during the 5-month study period. The details are shown in Tables 1 and 2.

Three patients (patients 3, 4 and 15) developed changes

Table 1 Patients' characteristics

Patients	Sex / Age (years)	Primary disease	Treatment phase
1	F/3.4	ALL	Intensive chemotherapy
2	M/5.7	Cerebellar medulloblastoma	Intensive chemotherapy
3	M/13.7	Relapse ALL	Intensive chemotherapy
4	M/8.3	Relapse ALL	Maintenance chemotherapy
5	M/7.8	ALL	Maintenance chemotherapy
6	M/11.8	T-cell lymphoma	Maintenance chemotherapy
7	M/12.3	ALL	Maintenance chemotherapy
8	M/12.4	Oligodendroglioma	Intensive chemotherapy
9	M/13.2	CNS germinoma	Intensive chemotherapy
10	F/7.1	Beta-thalassaemia	Post-unrelated CBT 25 months with chronic GVHD of skin and lung on cyclosporine A
11	F/7.2	T-cell lymphoma, MDS	Post-unrelated CBT 23 months with chronic GVHD of skin on cyclosporine A
12	M/12.5	Ph+ve ALL, choroid plexus tumour	Post-unrelated CBT 36 months with chronic GVHD
13	M/13.3	Adrenoleukodystrophy	Post-unrelated CBT 45 months with chronic skin GVHD on prednisolone
14	F/14.1	Relapsed AML	HLA-identical sibling post-bone marrow transplant 9 months
15	M/14.2	Relapsed Ph+ve ALL	HLA-identical sibling PBSC transplant 20 months with extensive chronic GVHD of skin, lung (bronchiolitis, obliterans), gut and mucosa on prednisolone, cyclosporine A, sirolimus and mycophenolate mofetil
16	M/14.6	Refractory AML	Post-unrelated CBT 16 months with chronic skin GVHD on cyclosporine A

ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CBT: Cord blood transplant; CNS: Central nervous system; GVHD: Graft-versus-host disease; MDS: Myelodysplastic syndrome; Ph: Philadelphia chromosome; PBSC: Peripheral blood stem cell

Table 2 Clinical presentation and outcome of pandemic H1N1 infection

Patients	Presenting symptoms	ANC	CXR changes	Duration of fever (days)	Treatment	Antiviral therapy started on days of fever (days)	Duration of PCR remained positive (days)	Outcome
1	Fever, cough, runny nose, sore throat	5.7	No	6	Oseltamivir 2.5 mg/kg BD for 5 days; Empirical antibiotics for 2 days	6	Remained positive on day 14 of illness	Discharge on day 7 of illness
2	Fever, cough	0.7	No	3	Oseltamivir 3 mg/kg BD for 5 days; Empirical antibiotics for 7 days	3	10	Discharge on day 8 of illness
3	Fever, runny nose, cough, sore throat	0.1	Yes	5	Oseltamivir 2 mg/kg BD for 3 days then 4 mg/kg BD for 7 days; Empirical antibiotics for 7 days	3	ND	Required 2L/min O_2 supplement. Discharge on day 9 of illness
4	Fever, runny nose, cough	1.5	Yes	1.2	Oseltamivir 2.5 mg/kg BD for 5 days	1	ND	Discharge on day 3 of illness
5	Fever	3.1	No	3	Oseltamivir 2.5 mg/kg BD for 5 days	1	ND	Discharge on day 4 of illness
6	Fever, cough, runny nose, sore throat	4.4	No	2	Oseltamivir 2 mg/kg BD for 5 days	1	Remained positive on day 14 of illness	Discharge on day 4 of illness
7	Fever, cough, runny nose, sore throat	3.4	No	3	Oseltamivir 2 mg/kg BD for 7 days; Empirical antibiotics for 5 days	2	ND	Discharge on day 6 of illness
8	Fever, cough, runny nose, sore throat, chills, rigor, vomiting	3.1	No	2	Oseltamivir 2 mg/kg BD for 5 days	2	8	Discharge on day 4 of illness
9	Fever, sore throat, cough	0.2	No	4	Oseltamivir 1.5 mg/kg BD for 5 days	2	7	Discharge on day 7 of illness
10	Fever, cough, myalgia, chills, rigor, malaise	4.4	No	4	2 courses of oseltamivir 2.5mg/kg BD for 5 days; Empirical antibiotics for 5 days	1	ND	Discharge on day 6 of illness
11	Fever, runny nose	11.0	No	1	Oseltamivir 2.5 mg/kg BD for 10 days; Empirical antibiotics for 5 days	1	ND	Discharge on day 4 of illness
12	Fever	4.3	No	9	Oseltamivir 1.5 mg/kg BD for 10 days	1	ND	Discharge on day 10 of illness
13	Fever, cough, runny nose, tonic-clonic seizure	7.6	No	4	Oseltamivir 3.5 mg/kg BD for 10 days	1	ND	Discharge on day 6 of illness
14	Fever, sore throat, malaise	4.0	No	4	Oseltamivir 1.5 mg/kg BD for 10 days	1	ND	Discharge on day 5 of illness
15	Fever, cough, runny nose	2.3	Yes	2	2 courses of oseltamivir 3 mg/kg BD for 5 days; Empirical antibiotics	1	Remained positive on day 14 of illness	Required 2L/min O_2 supplement, discharge on day 12 of illness
16	Fever, cough, sore throat, chills	3.2	No	4	Oseltamivir 1.5 mg/kg BD for 10 days	1	ND	Discharge on day 6 of illness

ANC: Absolute neutrophil count; CXR: Chest X-ray; ND: Not done; PCR: Polymerase chain reaction

in chest X-ray suggestive of viral pneumonia. Patient 3 and 15 required oxygen supplement via nasal cannula. They did not require intensive care or requirement of mechanical ventilation. All of our patients recovered fully and none of them complicated with residual morbidity.

Discussion

Laboratory-confirmed cases of human infections with the novel influenza A (H1N1) virus mostly occur in children and young adults. A spectrum of disease ranging from non-febrile, mild upper respiratory tract illness to severe or fatal pneumonia has been described.[3] In our cohort of immunocompromised cancer children, the most commonly reported symptoms included fever, cough and runny nose. Gastrointestinal symptoms (nausea, vomiting and/or diarrhoea) previously reported with pandemic H1N1 influenza were not common in our series.[3]

To date, although the clinical presentation of patients who were hospitalised with 2009 H1N1 influenza were generally similar to those reported during peak periods of seasonal influenza, the epidemiology of mostly affected population is quite different. Jain et al studied 272 hospitalised patients with pandemic H1N1 infection in United States. During peak periods of seasonal influenza, hospitalisations are more common among persons 65 years of age or older and those under the age of 5 years, For pandemic H1N1 infection, up to 45% of the hospitalisations involved persons under the age of 18 years; more than one third of the patients were between the ages of 18 and 49 years, and only 5% were 65 years of age or older. Seventy-three percent of the patients had at least one underlying medical condition which included asthma; diabetes; heart, lung, and neurologic diseases; and pregnancy.[5]

Cao et al described the clinical features of 426 cases of pandemic H1N1 infection in China. Although they showed that majority of cases ran a benign course, independent risk factors for prolonged real-time RT-PCR positivity included patients' age of less than 14 years, male sex, and a delay from the onset of symptoms to treatment with oseltamivir of more than 48 hours.[6] Among the patients who required intensive care, about 93% were patients younger than 65 years old and 10% were pregnant women.[7] All these data suggested that young patient is one of the highest risk groups of pandemic H1N1 infection. To et al also showed that younger age was associated with prolonged shedding in the respiratory tract and higher viral load in the stool.[8] However, in our patient series, who was traditionally believed to be one of the highest risk groups of severe influenza infection, ran a relative uncomplicated clinical course and all of them recovered uneventfully from this infection. This was probably due to the early start of antiviral therapy (median 1 day after onset of fever) which halted the propagation of virus and decreased the viral load in the immunocompromised hosts. However, three patients (patient 3, 10 and 15) required additional course of high dose antiviral therapy due to recurrence of fever and respiratory symptoms. We also observed that the duration to achieve defervescence was longer in HSCT recipients and prolonged duration or recurrence of respiratory symptoms were more commonly observed in HSCT patients, therefore, we routinely prescribed a 10-day course of antiviral therapy in these patients in the latter half of the study period. Jain et al also demonstrated that the early use of antiviral drugs was beneficial in hospitalised patients.[5]

Apart from the potential role of early initiation of antiviral agent, whether there is a role of systemic immunosuppressents in accounting for the mild clinical course in our cohort still needs further evaluation. To et al recently demonstrated that patients who died from acute respiratory distress syndrome (ARDS) had a slower decline in nasopharyngeal viral load and higher plasma levels of proinflammatory cytokines and chemokines than in patients who survived without (ARDS) or mild disease groups.[9]

Despite the benign clinical course, the phenomenon of persistent symptoms and laboratory evidence of prolonged viral excretion after a standard course of antiviral poses a continuous threat in term of infection control policy in paediatric oncology and haematopoietic stem cell transplant unit.[4] We have reported a 15-month old patient with stage 3 neuroblastoma with persistent respiratory syncytial virus (RSV) shedding for 7 months after primary infection. Regular surveillance of the shedding of virus should be performed and confirmation of viral clearance should be obtained before discontinuing infection control measures (droplet and contact precautions) in order to prevent nosocomial outbreaks among high-risk patients.[10] As the pandemic H1N1 infection has become the major strain of influenza virus (90%) circulating in the local community, the same policy was adopted.[11]

Vaccination remains one of the most effective preventive measures to confine the infection in the community and especially among the high risk groups. Preliminary

immunogenicity data of injectable inactivated monovalent H1N1 vaccine in pediatric population showed that children aged 6 months - less than 9 years old should receive 2 monthly doses whereas children aged ≥9 years old can receive 1 dose.[12] To date, there is another intranasal preparation of monovalent H1N1 vaccine which is approved by Food and Drug Administration, USA.[13] However, it is a live-attenuated vaccine and is contraindicated in immunocompromised patients.

Case definition of influenza-like illness (ILI) for influenza surveillance schemes vary widely worldwide. Different ILI definitions will influence the case identification and indeed have implication in implementation of infection control measures. In our series, we adopted the definition from Centers for Disease Control and Prevention (CDC) which is simple and highly sensitive (98.4%-100%) definition. It is also the recommended influenza case definition of the World Health Organization (Department of Communicable Disease Surveillance and Control,1999b). However, the relatively low specificity (7.1%-12.9%) implies there is low accuracy in identifying influenza activity without laboratory confirmation.[14] Thursky et al propose a case definition of cough, history of fever and fatigue which has a higher positive predictive value (PPV) than the CDC definition.[14] This is a limitation of our study as the initiation of laboratory confirmation of pandemic H1N1 infection was based on the initial clinical presentation of patients. Different case definitions may leave some genuine cases with atypical presentation undiagnosed and skew the picture of clinical presentation of this infection in immunocompromised patients.

Conclusion

Fever, cough, runny nose and sore throat were the most common presenting symptoms. The uncomplicated course of pandemic H1N1 infection in our cohort of paediatric oncology and stem cell transplant recipients may have been related to the early initiation of antiviral therapy. HSCT recipients are more likely to develop persistent or recurrence of respiratory symptoms and required repeated course of antiviral therapy.

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