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Original Article

Clinical characteristics of influenza virus-induced lower respiratory infection during the 2015 to 2016 season

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ABSTRACT

Background: Influenza A(H1N1)pdm09 virus infections often manifest severe respiratory symptoms, particularly in patients with a past history of allergic disease. Most of these findings were reported during the 2009 pandemic. The purpose of this study was to detail the clinical characteristics of influenza virus-induced lower respiratory infection (LRI) during the A(H1N1)pdm09-predominant 2015–2016 season.

Methods: We retrospectively reviewed the clinical characteristics of influenza-induced LRI cases in children admitted to a tertiary children's hospital. Molecular diagnostic evaluation was performed on samples obtained from the most severe cases.

Results: We identified 66 patients with influenza-associated hospitalization and included 21 patients with influenza virus-induced LRI for analyses. Twelve patients (57%) were admitted to the pediatric intensive care unit, seven (33%) required mechanical ventilation, and three (14%) required extracorporeal membrane oxygenation. Plastic bronchitis (PB) was identified in six patients (29%), among whom a past medical history of asthma or food allergy were noted in all six patients. A past history of allergic disease was more common among patients with, than among those without, PB ($p = 0.009$). A(H1N1)pdm09 was detected from all the PB cases, and phylogenetic analyses of the hemagglutinin and neuraminidase genes demonstrated that this virus belonged to subclades 6B.1 and 6B.2. In the six PB cases, we found one patient with H275Y mutation in neuraminidase.

Conclusion: Allergic disease was a risk factor for developing PB due to influenza A(H1N1)pdm09 infection during the 2015–16 season.

1. Introduction

An influenza A(H1N1)pdm09 (H1N1pdm09) pandemic occurred in 2009, resulting in numerous deaths and cases of severe respiratory failure requiring intensive care, including mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [1,2]. Severe respiratory failure associated with plastic bronchitis (PB), a condition characterized by rigid branching mucus casts that obstruct the airway, was also reported in 2009 season [3–5]. Chronic lung disease, immunosuppressive status, cardiac disease, pregnancy, diabetes mellitus, obesity in adults, and asthmatic status in children were identified as risk factors for developing severe respiratory failure due to H1N1pdm09 infection during the 2009 season [6,7].

Seasonal influenza due to H1N1pdm09 occurred during the 2010–2011, 2013–2014, and 2015–2016 seasons worldwide [8–10]. National surveillance in Japan during the 2015–2016

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season reported that H1N1pdm09 accounted for 86% of cases of influenza A virus infection [9]. Although the clinical features of pediatric patients with H1N1pdm09 in the 2009 season have been documented, clinical information regarding H1N1pdm09 infections in other seasons is relatively scarce. In general, we hypothesize that influenza pandemics tend to be more severe than seasonal outbreaks due to the lack of host immunity. However, risk factors for developing severe complications during a pandemic might differ from those in seasonal outbreaks due to differences in host immunity or genetic changes in the circulating strain. These questions require further research to be answered.

We therefore performed a retrospective study to identify the clinical characteristics of lower respiratory infection (LRI) due to influenza in the 2015–2016 season, in which H1N1pdm09 was the predominant strain.

2. Materials and methods

This study was conducted at the National Center for Child Health and Development, a pediatric tertiary care hospital in Tokyo, Japan. We performed a retrospective chart review of all the patients in whom influenza was diagnosed. We included patients under the age of 18 years who were hospitalized for influenza-related LRI between December 2015 and April 2016. Patients hospitalized for acute encephalopathy, febrile seizure, febrile delirium or croup were excluded.

Clinical information including age, gender, underlying disease, past medical history, immunization history, clinical course, and prognosis was collected from patients' medical records. Underlying diseases were classified as allergic (asthma or food allergy), neurological, cardiac, renal, hepatic, or immunological. Patients with primary immunodeficiency and those receiving immunosuppressive agents were included. Each condition was counted separately in patients with multiple conditions.

2.1. Clinical definition of lower respiratory infection

LRI included pneumonia and bronchitis and was defined by cough as the principal respiratory symptom, accompanied by respiratory distress or desaturation. PB was diagnosed in patients in whom the disease showed rapid progression leading to severe respiratory failure and large consolidation on the chest radiograph, but whose respiratory status improved dramatically after suctioning of the mucous plug [5].

2.2. Diagnosis of influenza

All patients were diagnosed using a rapid antigen test for influenza (Espline Influenza A & B-N (FUJIREBIO, Tokyo, Japan)). The sensitivity and specificity of the test are reportedly 96.8% and 97.6% for influenza A, and 88.1% and 97.6% for influenza B, respectively when measured against a standard diagnosis by cell culture or nested reverse transcription polymerase chain reaction results [11]. Total nucleic acids were extracted from specimens, which were additionally taken from endotracheal tube aspirates, from all patients who had PB using the QIAamp DNA Mini kit (QIAGEN) and analyzed by real-time quantitative polymerase chain reaction (qPCR) using the Fast-track Diagnostics respiratory pathogens 21 (FTDRP21) multiplex assay kit (Fast-track Diagnostics, Luxembourg). The panel shows 21 respiratory pathogens including: influenza A, influenza A (H1N1) swl, influenza B, rhinovirus, coronavirus NL63, 229E, OC43, and HKU1, parainfluenza 1, 2, 3, and 4, human metapneumovirus A/B, bocavirus, respiratory syncytial virus A/B, adenovirus, enterovirus, parechovirus, mycoplasma pneumonia, and an internal control [12]. Genome sequencing for the hemagglutinin (HA) and neuraminidase (NA) genes was performed using specific primers (Supplemental table: Table S1). The determined sequences are available from DDBJ/EMBL/GenBank database under the accession numbers LC270874 to LC270885. The phylogenetic trees were constructed by the neighbor-joining method using MEGA 6 software [13]. The other sequences analyzed for phylogenetic trees were obtained from the EpiFlu database of the Global Initiative on Sharing All Influenza Data [14].

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver.22 (IBM, Tokyo, Japan). Fisher's exact test for categorical

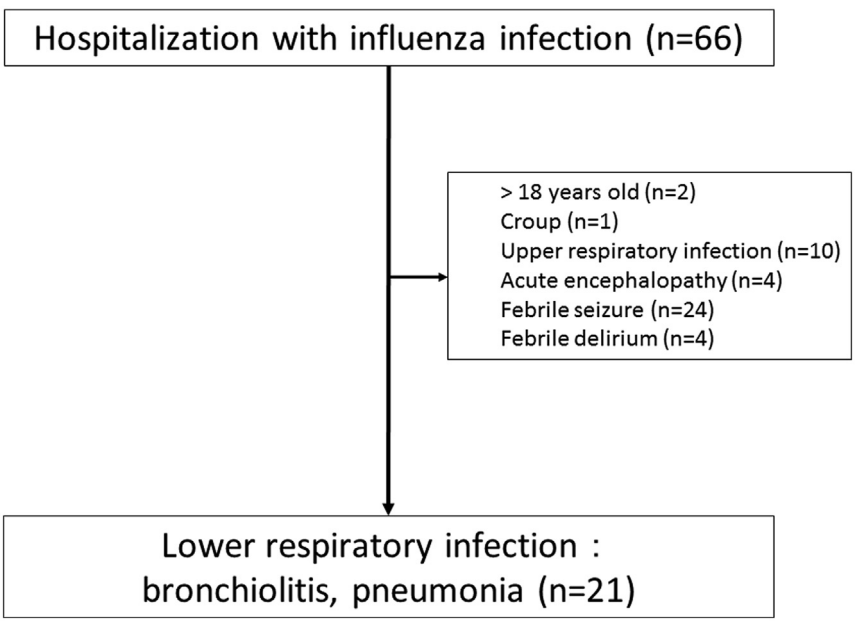

Fig. 1. Flow diagram for study inclusion. Sixty-six patients were hospitalized with the diagnosis of influenza. Lower respiratory infection was diagnosed in 21 patients after excluding patients >18 years old, and those with acute encephalopathy, febrile seizure, febrile delirium, croup, or upper respiratory infection.

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