



Original article

Influenza-associated neurological complications during 2014–2017 in Taiwan

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Abstract

Introduction: Seasonal influenza-associated neurological complications had high mortality and morbidity rates in recent studies. We reported influenza-associated encephalitis/encephalopathy in children during 2014–2017 in Taiwan, focusing on neurological presentations, neuroimaging correlations, and critical care managements.

Materials/Subjects: During January 1st 2014 to June 30th 2017, pediatric patients reported to the Taiwan Centers for Disease Control surveillance system for severe complicated influenza infections in the hospital were retrospectively reviewed. Children with influenza-associated encephalitis/encephalopathy were inspected for clinical presentations, laboratory data, neuroimaging studies, treatment modalities, and neurological outcomes.

Results: Ten children with median age 5.9 years were enrolled for analysis. Influenza-associated encephalitis/encephalopathy appeared in the spring and summer, with a delayed peak comparing with the occurrence of pneumonia and septic shock. The neurological symptoms developed rapidly within median 1 day after the first fever episode. All patients had consciousness disturbance. Seven patients (70%) had seizures at initial presentation, and six of them had status epilepticus. Anti-viral treatments were applied in all patients, with median door-to-drug time 0.9 h for oseltamivir and 6.0 h for peramivir. Multi-modality treatments also included steroid pulse therapy, immunoglobulin treatment, and target temperature management, with 85.2% of the major treatments administered within 12 h after admission. Nine of the ten patients recovered without neurological sequelae. Only one patient had epilepsy requiring long-term anticonvulsants and concomitant cognitive decline.

Conclusions: In highly prevalent area, influenza-associated encephalitis/encephalopathy should be considered irrespective of seasons. Our study suggested the effects of timely surveillance and multi-modality treatments in influenza-associated encephalitis/encephalopathy.

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Keywords: Influenza; Encephalitis; Encephalopathy; Status epilepticus; Multi-modality treatments

1. Introduction

Influenza infection is well known for the neurological complications with high morbidity and mortality rates [1]. The manifestations are heterogeneous, from simple febrile seizure to the severe acute necrotizing

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encephalopathy (ANE) [1–3]. In contrast to the high morbidity and mortality rates, previous studies show that most patients of influenza-associated encephalitis/encephalopathy do not receive adequate vaccination, and some of them do not have anti-viral treatments [1].

The epidemiology of influenza-associated encephalitis/encephalopathy in East Asia is different from that in western countries. The fulminant ANE with distinctive thalamic necrosis was first reported in 1979 in Japan [4,5]. ANE is most prevalent in Taiwan, Japan, and South Korea, emphasizing the importance of treatment protocol for influenza-associated neurological complications in high-risk populations and countries [4,6,7].

In children, encephalitis/encephalopathy associated with pandemic H1N1 infection in 2009 and neurological complications in the post-H1N1 era during 2013–2015 are described in the literatures [2,8]. However, only a few studies addressed the emerging influenza-associated encephalitis/encephalopathy in recent years [9]. In the observational study, we reported clinical and neuroimaging characteristics of influenza-associated encephalitis/encephalopathy in children during 2014–2017 in Taiwan, emphasizing treatments during critical care and correlative neurological outcomes.

2. Materials/Subjects

2.1. Patients

During January 1st 2014 to June 30th 2017, patients less than 18 years old who were reported to the Taiwan Centers for Disease Control (CDC, Taiwan) surveillance system for severe complicated influenza infection in the hospital were retrospectively reviewed. Severe complicated influenza infection is defined as myocarditis or pericarditis, pulmonary complications, neurological complications, and superimposed invasive bacterial infections [10]. Patients reported for neurological complications were included. The demographic data, clinical manifestations, laboratory studies, neuroimaging studies, treatment modalities, and neurological outcomes were analyzed. The hospital's institutional review board approved the study.

2.2. Virology survey

The nasopharyngeal aspirates/throat swabs and cerebrospinal fluid (CSF) samples were sent for viral isolation and immunofluorescence staining assay. Real-time transcription polymerase chain reactions (RT-PCR) for influenza detection were also performed with the airway and CSF specimens. Rapid influenza diagnostic tests (RIDT) for antigen detection were tested with airway samples.

2.3. Definition of neurological complications

Encephalitis/encephalopathy was defined as alteration of consciousness due to inflammation [3]. Status epilepticus was defined according to the consensus of International League Against Epilepsy in 2015, with tonic-clonic seizure for more than 5 min, or focal seizure with consciousness impairment for more than 10 min [11].

2.4. Neuroimaging studies

Neuroimaging studies included computed tomography (CT) and magnetic resonance imaging (MRI) with T1 and T2-weighted images, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC, $b = 1000$). Neuroimaging studies were acquired by 1.5 T or 3 T MR machines. Gadolinium contrast medium was injected for better demonstration of inflammation, and post-contrast T1-weighted 3D images would be obtained.

2.5. Statistical analysis

The clinical data was analyzed with descriptive statistics. Numerical variables were presented in median and interquartile range (IQR). Fisher's exact test was performed for categorical variables. The statistical tests were performed with GraphPad Prism 5 and R version 3.4.2 software. The level of significance was set at $p < 0.05$.

3. Results

3.1. Epidemiology

During the study period, thirty patients younger than 18 years old were reported to the surveillance system for complicated influenza infection in the hospital. Among the thirty patients, fifteen were reported for pneumonia (including four combined with sepsis), and five for septic shock. Ten children were reported for neurological complications and fulfilling the definition of encephalitis/encephalopathy. The distribution of disease-onset month was shown in Fig. 1. In contrast to pneumonia and sepsis occurring during the winter to spring, encephalitis/encephalopathy tended to occur in later months with a peak in the spring to summer, which is not the typical flu season in Taiwan.

3.2. Demographic data

Five boys and five girls had influenza-associated encephalitis/encephalopathy at median age 5.9 years (range 0.4–17 years, IQR 2.3 years). Although four patients had past medical history, these diseases were not complicated (simple febrile convulsion in 1; asthma

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