인플루엔자 감염과 연관된 열성경련의 임상적 특징

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Impact of Influenza Infection on Febrile Seizures: Clinical Implications

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Purpose: Febrile seizures (FSs) are the most common type of seizure in the first 5 years of life and are frequently associated with viral infections. Influenza infection is associated with a variety of neurological conditions, including FSs. The purpose of this study was to evaluate the clinical implications of influenza infection in FSs.

Methods: In total, 388 children with FS were divided into two groups: FS with influenza infection (n=75) and FSs without influenza infection (n=313). Their medical records, including seizure type, frequency, duration, and familial history of FSs or epilepsy, were retrospectively reviewed and the clinical characteristics of the two groups were compared.

Results: In total, 75 of the 388 children (19.3%) had FSs associated with influenza infection; such children were significantly older than those with FSs without influenza infection (34.9 ± 22.3 months vs. 24.4 ± 14.2 months; $P < 0.001$). The children who had more than two febrile seizures episodes were more prevalent in children with FS with influenza infection [40/75 (53.3%) vs. 92/313 (29.4%); $P < 0.01$]. Children older than 60 months were more likely to have influenza infection compared to those aged less than 60 months [11/22 (50%) vs. 64/366 (17.5%); $P = 0.001$].

Conclusion: Influenza infection may be associated with FSs in older children, and with recurrence of FSs. Its role in the development of afebrile seizures or subsequent epilepsy requires further investigation with long-term follow-up.

Key Words: Febrile seizures, Influenza, Recurrence, Age

Introduction

Febrile seizures (FSs) are the most common type of seizure in the first 5 years of life and the prognosis is usually favorable¹⁾. FSs affect around 2–5% of children in Western countries^{1,2)}, while the average prevalence of FSs in children in Korea is reported to be as high as 6.92%³⁾. The peak incidence of FSs is in children aged 18 months, with the risk being markedly lower in those aged below 6 months or over 5 years⁴⁾. The most common causes of FSs are viral infections; among them, influenza infection is associated with a higher incidence of FSs than any other respiratory virus⁵⁾.

Influenza viruses belong to the Orthomyxoviridae family and influenza A and B viruses cause seasonal epidemics. The presentation of seasonal influenza ranges

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from an asymptomatic infection to a fulminant illness; neurologic complications associated with influenza infection are rare⁶⁾. There are several influenza-associated neurological conditions, including FSs, exacerbations in patients with epilepsy, and influenza-induced neurologic disorders⁷⁾. Among them, FSs have been reported to be the most common complication⁸⁻¹⁰⁾.

Previous studies have reported the association of influenza infection and FSs. The incidence of FSs is highest during the influenza season, when approximately 20% of young children experience seasonal influenza⁷⁻⁹⁾. In previous studies of the clinical characteristics of influenza-associated FSs, some studies showed a relationship between the influenza A virus^{7,9,11)}, complex FSs²⁾, and prolonged post-ictal status¹¹⁾. However, there is insufficient evidence regarding the role of influenza infection in, and clinical impact on, FSs occurring in the beyond-typical age group.

In this study, we retrospectively reviewed the medical records of children with FSs to determine the clinical implications of influenza virus in FSs.

Materials and Methods

This was a retrospective study of FS patients admitted to the Department of Pediatrics, Kyung-Hee University Hospital, Seoul, South Korea between December 2012 and February 2018. In total, 388 patients with FSs were included. All of patients underwent laboratory testing to confirm influenza virus based on throat, nasal, and nasopharyngeal secretions; a rapid antigen test or detection of respiratory viral RNA by reverse transcriptase-polymerase chain reaction was performed. FS patients without influenza infection were tested for mycoplasma or gastro-enteral virus antigen test, regarding to their disease entity.

FS patients were categorized into two groups according to the presence of influenza infection: FSs with influenza infection and FSs without influenza infection. Both groups were compared clinical characteristics (age, sex, peak body temperature at presentation, fever onset, length of hospital stays, any episode of neurologic sequelae and anti-epileptic drug administration at discharge) and seizure characteristics (including type, frequency, duration, familial history of FSs, and epilepsy status). The age distributions of each group and the rate of influenza infection in patients with FSs during four consecutive influenza seasons were also analyzed.

FSs were defined as seizures accompanied by fever $\geq 38^{\circ}\text{C}$ without central nervous system infection or metabolic disorders, and were classified as simple or complex. Simple FSs were generalized seizures lasting < 15 minutes, occurring only once in 24

h, and not provoking any neurologic abnormality after the episode in an otherwise neurologically healthy child. FSs were complex if they were focal, of longer duration (> 15 min), occurred more than once in 24 h, and/or caused any neurologic deficit¹⁾. Patients with a history of afebrile seizures, anti-epileptic drug use, neurologic deficit, or developmental delay were excluded from the study.

Patients with FSs were divided based on an age cut-off of 60 months, and compared according to the presence of influenza infection and seizure characteristics. A follow-up telephone survey was conducted to record any subsequent seizure episode or anti-epileptic drug use.

The data were analyzed using the SPSS statistical software (ver. 21.0; SPSS Inc., Chicago, IL, USA). A chi-squared test was used for data analysis of qualitative variables, and mean values were compared using an independent t-test. Differences were considered significant at P -values less than 0.05.

This research was approved by the Medical Sciences Ethics Committee of Kyung Hee University Hospital (IRB file No. 2018-10-005).

Results

1. Clinical characteristics

In total, 388 patients were included in the study. Of these, 75 (19.3%) were infected with influenza virus and 313 were not infected. The FS patients with influenza ($n=75$) were significantly older than those without influenza ($n=313$) (Table 1) (34.9 ± 22.3 months vs. 24.4 ± 14.2 months; $P<0.001$). Among the 75 cases with influenza infection, 56 had influenza A and 19 had influenza B. In a comparison of age distribution, the FSs without influenza group showed an age peak at 12 to 18 months, while the FSs influenza group showed a peak at 18 to 24 months, with a second peak at over 60 months (Fig. 1). There were no differences in sex, fever onset and length of hospital stays between two groups and no patients experienced any neurologic sequelae and anti-epi-

Table 1. Clinical Characteristics of Febrile Seizure Patients with/without Influenza Infection

	Febrile seizures without influenza (n=313)	Febrile seizures with influenza (n=75)	P-value
Age (Mean $\pm$ SD)	24.4 $\pm$ 14.2 months	34.9 $\pm$ 22.3 months	<0.001
Sex			
male	177 (56.5%)	42 (56%)	>0.05
female	136 (43.5%)	33 (44%)	
Peak body temperature ($^{\circ}\text{C}$)	39.0 $\pm$ 0.7	39.0 $\pm$ 0.6	>0.05
Fever onset (< 12 hrs)	163 (52.1%)	43 (57.3%)	>0.05
Length of hospital stay(days)	4.2 $\pm$ 1.5	4.3 $\pm$ 1.8	>0.05

leptic drug administration at discharge. The pathogen identified in FS patients without influenza infection was described in Table 2. In total, 283(90%) of FS patients identified pathogen, at least one pathogen was identified in 130/283 (45.9%) and co-infected pathogen in 153/283 (54%). Mycoplasma, Rhinovirus, Adenovirus and Parainfluenza were the commonly encountered pathogens (82/283, 29%; 65/283, 23%; 41/283, 14.5%; 37/283, 13.4%, respectively).

2. Seasonal occurrence of FSs associated with influenza infection

Influenza infection occurs mainly during the influenza season, which usually includes the 5 months from October to February of the following year. The rate of influenza infection in patients with FSs during four consecutive influenza seasons (October 2013 through February 2018) was higher than the overall incidence, and was highest in the 2015 season (23/49, 47%) (Fig. 2).

3. Comparison of seizure characteristics

Patients with FSs associated with influenza infection were more likely to have a previous history of FSs than were those with FSs without influenza infection; the difference was significant [92/313 (29.4%) vs. 40/75 (53.3%); $P<0.001$]. However, the type and dura-

tion of seizure, development of febrile status epilepticus, familial history of FSs, and epilepsy status showed no significant group differences (Table 3).

4. Clinical characteristics and short-term outcome of FS patients aged 60 months or older

Among the 388 patients with FSs, 22 patients (5.6%) were older than 60 months, with a mean age of 76.1 ± 13.9 months. There were no differences in sex or seizure characteristics by age group; however, the proportion of influenza infection was significantly higher in patients aged over 60 months than in those aged less than 60 months [11/22 (50%) vs. 64/366 (17.5%); $P<0.001$] (Table 4). A follow-up survey was conducted by telephone for 22 patients over a mean follow-up period of 29.5 ± 18.1 months; no episode of subsequent seizure, neurologic sequelae or anti-

Table 3. Seizure Characteristics of Febrile Seizure Patients with/without Influenza Infection

Semiology	Febrile seizures without influenza (n=313)	Febrile seizures with influenza (n=75)	P-value
History of previous febrile seizure			
First attack	221 (70.6%)	35 (46.7%)	0.001
More than two attacks	92 (29.4%)	40 (53.3%)	<0.001
Type of seizure			
Simple	265 (84.7%)	64 (85.3%)	>0.05
Complex	47 (15%)	11 (14.7%)	>0.05
Semiology			
Generalized tonic clonic	221 (70.6%)	60 (80%)	>0.05
Focal	60 (19.2%)	6 (8%)	>0.05
Flaccid	26 (8.3%)	6 (8%)	>0.05
Secondary generalized	1 (0.3%)	2 (2.7%)	>0.05
Seizure duration (min; mean $\pm$ SD)			
0 to <5 min	217 (69.3%)	59 (78.7%)	>0.05
5 to <15 min	79 (25.2%)	12 (16%)	
15 to <30 min	14 (4.4%)	1 (1.3%)	
≥ 30 min	3 (3%)	3 (4%)	>0.05
Familial history of febrile seizures	77 (24.6%)	19 (25.3%)	
Familial history of epilepsy	7 (2.2%)	0	>0.05
Abnormal electroencephalogram findings	27 (8.6%)	6 (8%)	

Table 2. Pathogens Identified in Isolation and in Co-infection in Febrile Seizure Group

Pathogen identified	Single infection	Co-infection	Total Cases (n=283)
Adenovirus	14/41 (34%)	27/41 (66%)	41 (14.5%)
Bocavirus	2/10 (20%)	8 (80%)	10 (3.5%)
Coronavirus	5/12 (42%)	7/12 (58%)	12 (4.2%)
Metapneumovirus	9/14 (64%)	5/14 (36%)	14 (4.9%)
Parainfluenzavirus	17/38 (45%)	21/38 (55%)	38 (13.4%)
Rhinovirus	34/65 (52%)	31/65 (48%)	65 (23%)
RSV A	1/9 (11%)	8/9 (89%)	9 (3.2%)
RSV B	5/8 (63%)	3/8 (27%)	8 (2.8%)
Mycoplasma	39/82 (48%)	43/82 (52%)	82 (29%)
Norovirus	3 (100%)	0	3 (1.1%)
Rotavirus	1 (100%)	0	1 (0.4%)

Fig. 1. Comparison of the age distribution of febrile seizure patients with versus without influenza infection.

epileptic drug use was reported.

Discussion

This retrospective study found that FSs associated with influenza infection were correlated with older age and recurrence of FSs. Among patients aged above 60 months, 50% had FSs that were associated with influenza infection, and tended to experience a history of FSs. A follow-up telephone survey revealed no subsequent afebrile seizures, neurologic sequelae or anti-epileptic drug use in these patients.

There has been considerable interest regarding the relationship between the influenza virus and neurologic manifestations. The most common neurologic complication is FSs^{8,9,11}. The overall incidence of influenza associated with FSs is approximately 20% in hospitalized infants and young children. During the influenza seasons of 1997 and 1998 in Hong Kong, Chiu et al.⁷ showed that, in children, influenza A infection associated with FSs was more prevalent than that associated with parainfluenza or adenovirus infections [81/415 (19.5%) vs. 36/347 (10.4%); $P=0.0004$]. In a study by Kwong⁹, 19.5% (34/177) of children diagnosed with influenza

A infection developed FSs during the course of their illness. Chung and Wong⁸ noted that 20.8% (163/785) of children under 15 years of age with influenza had FSs. In Korea, the incidence of influenza associated with FSs was reported to be 10.7–19.2%^{12,13}. The incidences were derived development of FSs from presence of influenza infection while our study drew the incidence of influenza infection from febrile seizure patients. We noted that 75 out of 388 patients (19.3%) had FSs that were associated with influenza infection, and that the infection rate was higher during the influenza season (range: 29–47%). Interestingly, Influenza associated FSs were less reported in western countries, 4.1% (35/842) in a study performed in Philadelphia, US¹⁰, and 3.1% (21/683) in Finland¹⁴. In a surveillance performed in 6 Australian tertiary pediatric hospitals, 4.5% (23/506) of influenza patient experience FSs and showed ethnical difference that influenza affect neurologic complications to Asian patients¹⁵.

The pathogenesis of influenza-associated FSs remains unclear. However, one possible explanation for the association between influenza and FSs is that the influenza virus itself has a neurological effect and induces expression of pro-inflammatory cytokine genes [interleukin (IL)-6 and tumor necrosis factor alpha], the anti-inflammatory cytokine gene, IL-10, has also been shown to be up-regulated in patients with influenza-associated encephalopathy and FSs¹⁶. Among them serum IL-6 level can be useful indicators in diagnosis and defining the severity of encephalopathy^{17,18}. Recent studies found that nervous system injury in influenza infection may be immune-mediated, or originate from vascular inflammation rather than direct viral invasion^{19–21}. Moreover, multiple studies suggest that a pathologic role of the host inflammatory response and hypercytokinemia^{16,22} may be responsible for the severity of disease in children with influenza infection²³. It is supposed that the age-related differences such as, ability to control influenza virus replication in children, the tendency to produce excessive inflammation, and a predisposition to a state of relative immunosuppression²⁴ may affect the development of febrile seizures in different age group. However, the role of cytokines in the pathogenesis of influenza associated neurologic manifestation is still unclear, further investigations are needed to clarify the association between age-related differences and cytokine responses.

Our study demonstrated that influenza infection may be associated with FSs in older children. Similar findings were reported by Son¹² (3.6 ± 2.9 years vs. 1.8 ± 1.4 years; $P<0.001$) and Moon¹³ (2.7 ± 0.6 years vs. 2.0 ± 1.0 years; $P<0.01$), and by Hara et al.¹¹ in a Japanese study (39.85 ± 22.16 months vs. 27.51 ± 17.14 months; $P<0.001$). In addition, the age distribution of the FS patients with influenza infection in our study showed a second peak at over 60

Table 4. Comparison of Febrile Seizures in Older Ages according to an Age Cut-Off of 60 Months

	<60 months (n=366)	≥60 months (n=22)	P-value
Influenza infection	64 (17.5%)	11 (50%)	<0.001
Type A	46	10	>0.05
Type B	18	1	
History of previous febrile seizure			0.013
First attack	247 (67.5%)	9 (40.9%)	
More than two attacks	119 (32.5%)	10 (59.1%)	
Sex			>0.05
Male	203 (55.5%)	16 (72.7%)	
Female	163 (45.5%)	6 (27.3%)	
Type of seizure			>0.05
Simple	309 (84.4%)	20 (91%)	
Complex	56 (15.3%)	2 (9%)	
Semiology			>0.05
Generalized tonic clonic	266 (72.7%)	15 (68.2%)	
Focal	65 (17.8%)	1 (4.5%)	
Flaccid	27 (7.4%)	5 (22.7%)	
Secondary generalized	3 (0.8%)	0	
Seizure duration (min; mean±SD)	3.8±5.0	5.0±8.6	>0.05
0 to <5 min	258 (70.5%)	18 (81.8%)	
5 to <15 min	90 (24.6%)	1 (4.5%)	
15 to <30 min	13 (3.6%)	2 (9.1%)	
≥30 min	5 (1.4%)	1 (4.5%)	
Familial history of febrile seizures	91 (24.9%)	5 (22.7%)	>0.05
Familial history of epilepsy	7 (1.9%)	0	
Abnormal electroencephalogram findings	32 (8.7%)	1 (4.5%)	>0.05

months. Overall, the proportion of patients with influenza infection was 50% (11 out of 22 patients) and was higher in those aged over 60 months. Ekstrand et al.²⁵⁾ reported that influenza-associated seizures can occur in older children, and the proportion of patients with influenza infection was significantly higher in the older age group (48 months and over) in another study [15/42 (35.7%) vs. 32/173 (18.5%); $P=0.015$].¹¹⁾ We suggest that influenza is more likely to be associated with FSs, particularly in patients who are older than the typical age for FSs.

Risk factors for FS recurrence include a first-degree relative with FSs, age below 18 months at seizure onset, high temperature, and long fever duration after seizure onset. Some studies have also suggested that influenza virus infection during the influenza season can be a risk factor for recurrence^{2,9,10)}. In studies of risk factors for recurrent influenza-associated FSs, a particular type of influenza virus²⁾ and a history of FSs^{9,13)} were independent risk factors.

FSs that occur in patients older than the typical age range are associated with an increased risk of subsequent epilepsy²⁶⁾. A follow-up telephone survey was conducted in patients older than 60 months to identify any episode of subsequent afebrile seizure, neurologic sequelae or anti-epileptic drug usage. No patients reported consecutive neurologic sequelae or medication use. This suggests that there is little cause for concern regarding the development of epilepsy in the short term in cases of FSs beyond the typical ages associated with influenza infection.

There were several limitations to the present study. First, it was designed as a retrospective review of the medical records of hospitalized patients. In addition, it was a single-center study that included a small study population. Moreover, these patients may not be representative of the pediatric population in South Korea. We also did not conduct a follow-up survey of all study patients. Finally, the follow-up period may have been too short to fully evaluate subsequent afebrile seizures and anti-epileptic drug use.

Despite these limitations, our study was consistent with previous studies in that influenza infection appeared to be associated with FSs per se, and their recurrence, in older children. Thus, for patients with a history of FSs, influenza infection may be a predictable risk factor for the development of the disease, particularly in children aged 60 months and over.

Further investigations of influenza-associated FSs in older children, including follow-up surveillance, are required, and whether administration of the influenza vaccine to children is beneficial for avoiding late-onset and recurrent FSs should be determined.

요약

목적: 열성 경련은 생후 첫 5년간 흔히 발생하는 경련성 질환으로 바이러스 감염과 관련이 있다. 인플루엔자 감염은 열성경련을 포함한 다양한 신경학적 증상과 연관이 있다. 이 연구에서는 열성 경련에 대한 인플루엔자 감염의 임상적인 영향을 평가하고자 하였다.

방법: 총 388명의 소아 중 인플루엔자가 동반된 열성경련 환자 75명, 인플루엔자가 동반되지 않은 열성경련 환자는 313명의 두 그룹으로 나누었다. 이 환자들의 의무기록을 후향적으로 분석하여, 발작 유형, 발작 빈도, 발작 기간, 열성경련의 가족력 및 간질의 발병과 임상적 특징을 비교하였다.

결과: 전체 388명의 열성 경련 환자 중 75명(19.3%)가 인플루엔자 감염이 동반되었다. 인플루엔자 감염이 동반된 열성경련 환자가 인플루엔자 감염이 동반되지 않는 환자보다 평균적으로 나이가 많았으며 (34.9 ± 22.3 개월 vs 24.4 ± 14.2 개월, $P<0.001$), 이전에 열성경련의 병력이 있는 경우가 더 흔하였다($40/75$ (53.3%) vs $92/313$ (29.4%), $P<0.01$). 또한 60개월을 기준으로 환자 군을 나누어 보았을 때 60개월 이상 열성경련 소아에서 인플루엔자 감염 비율이 60개월 미만인 소아보다 유의하게 높았다($11/22$ (50%) vs $64/366$ (17.5) %, $P=0.001$).

결론: 인플루엔자 감염은 연장아의 열성경련과 연관된 것으로 보이며, 열성경련의 병력이 있는 환자에서 재발과 관련이 있다. 인플루엔자 감염이 동반된 연장아의 열성 경련 환자에서 추후 뇌전증 발병이나 항경련제의 복용 여부에 대한 장기적 추적 관찰이 필요하다.

References

- 1) Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2008;121:1281-6.
- 2) van Zeijl JH, Mullaart RA, Borm GF, Galama JM. Recurrence of febrile seizures in the respiratory season is associated with influenza A. *J Pediatr* 2004;145:800-5.
- 3) Byeon JH, Kim G-H, Eun B-L. Prevalence, incidence, and recurrence of febrile seizures in Korean children based on national registry data. *J Clin Neurol* 2018;14:43-7.
- 4) Sugai K. Current management of febrile seizures in Japan: an overview. *Brain Dev* 2010;32:64-70.
- 5) Francis JR, Richmond P, Robins C, Lindsay K, Levy A, Effler PV, et al. An observational study of febrile seizures: the importance of viral infection and immunization. *BMC Pediatr* 2016;16:202.
- 6) Paules C, Subbarao K. Influenza. *Lancet* 2017;390:697-708.
- 7) Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. *Pediatrics* 2001;108:E63.
- 8) Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. *Arch Dis Child* 2007;92:589-93.
- 9) Kwong KL, Lam SY, Que TL, Wong SN. Influenza A and febrile seizures in childhood. *Pediatr Neurol* 2006;35:395-9.

- 10) Newland JG, Laurich VM, Rosenquist AW, Heydon K, Licht DJ, Keren R, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2007;150:306-10.
- 11) Hara K, Tanabe T, Aomatsu T, Inoue N, Tamaki H, Okamoto N, et al. Febrile seizures associated with influenza A. *Brain Dev* 2007; 29:30-8.
- 12) Sohn YS, Kwon SH, Moon JE, Ahn JY, Kim JE, Beak HS. Clinical analysis of the correlation between febrile seizures and influenza infection. *J Korean Child Neurol Soc* 2014;22:155-9.
- 13) Moon JW, Kang JH, Kim HJ, Byun SO. Risk factor of influenza virus infection to febrile convulsions and recurrent febrile convulsions in children. *Korean J Pediatr* 2009;52:785-90.
- 14) Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. *Clin Infect Dis* 2003;36:299-305.
- 15) Khandaker G, Zuryski Y, Buttery J, Marshall H, Richmond PC, Dale RC, et al. Neurologic complications of influenza A(H1N1) pdm09: surveillance in 6 pediatric hospitals. *Neurology* 2012;79: 1474-81.
- 16) Kawada J, Kimura H, Ito Y, Hara S, Iriyama M, Yoshikawa T, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. *J Infect Dis* 2003;188:690-8.
- 17) Aiba H, Mochizuki M, Kimura M, Hojo H. Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. *Neurology* 2001;57:295-9.
- 18) Fukumoto Y, Okumura A, Hayakawa F, Suzuki M, Kato T, Watanabe K, et al. Serum levels of cytokines and EEG findings in children with influenza associated with mild neurological complications. *Brain Dev* 2007;29:425-30.
- 19) Paksu MS, Aslan K, Kendirli T, Akyildiz BN, Yener N, Yildizdas RD, et al. Neuroinfluenza: evaluation of seasonal influenza associated severe neurological complications in children (a multi-center study). *Childs Nerv Syst* 2018;34:335-47.
- 20) Chen LW, Teng CK, Tsai YS, Wang JN, Tu YF, Shen CF, et al. Influenza-associated neurological complications during 2014-2017 in Taiwan. *Brain Dev* 2018;40:799-806.
- 21) Toovey S. Influenza-associated central nervous system dysfunction: a literature review. *Travel Med Infect Dis* 2008;6:114-24.
- 22) Oshansky CM, Gartland AJ, Wong SS, Jeevan T, Wang D, Roddam PL, et al. Mucosal immune responses predict clinical outcomes during influenza infection independently of age and viral load. *Am J Respir Crit Care Med* 2014;189:449-62.
- 23) Sun S, Zhao G, Xiao W, Hu J, Guo Y, Yu H, et al. Age-related sensitivity and pathological differences in infections by 2009 pandemic influenza A (H1N1) virus. *Virology* 2011;8:52.
- 24) Coates BM, Staricha KL, Wiese KM, Ridge KM. Influenza A virus infection, innate immunity, and childhood. *JAMA pediatrics* 2015;169:956-63.
- 25) Ekstrand JJ. Neurologic complications of influenza. *Semin Pediatr Neurol* 2012;19:96-100.
- 26) Verrotti A, Giuva T, Cutarella R, Morgese G, Chiarelli F. Febrile convulsions after 5 years of age: long-term follow-up. *J Child Neurol* 2000;15:811-3.