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ORIGINAL ARTICLE

Influenza-associated neurological complications in hospitalized previously healthy children: a retrospective study at a tertiary center in Saudi Arabia

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ABSTRACT

Background: Influenza in children is usually a self-limited respiratory illness but can cause central nervous system (CNS) complications ranging from simple febrile seizures to acute necrotizing encephalopathy. We describe the prevalence, clinical features, and short-term outcomes of influenza-associated CNS complications in previously healthy children at a Saudi tertiary center.

Methods: We retrospectively reviewed the records of children younger than 14 years admitted with laboratory-confirmed influenza to King Abdullah Specialized Children's Hospital, Jeddah, between November 2016 and December 2023. Children with a pre-existing CNS comorbidity or concurrent coronavirus disease 2019 were excluded. Data were extracted from electronic health records and analyzed descriptively.

Results: Of 509 children admitted with influenza, 449 had no pre-existing CNS comorbidity, and 19 of these (4.2%; 95% confidence interval, 2.6%-6.5%) presented with CNS symptoms. All 19 had seizures, most often generalized tonic-clonic (15/19, 79%), and all had a normal neurological examination in the emergency department. Influenza A was detected in 16 children (84%). Neuroimaging (seven children) was normal, and all cerebrospinal fluid (eight children) and blood cultures were negative. Discharge diagnoses were simple febrile seizure (12, 63%), complex febrile seizure (3, 16%), and clinically diagnosed meningitis or meningoencephalitis (4, 21%). Median length of stay was 3 days (interquartile range, 3 days); none required intensive care or died.

Conclusion: In previously healthy children hospitalized with influenza at our center, CNS involvement was uncommon, presented as seizures, and had good short-term outcomes. These single-center data add to limited regional evidence and need confirmation in larger, multicenter studies.

Keywords: Influenza, child, seizures, febrile, central nervous system diseases, hospitalization, Saudi Arabia.

Introduction

Influenza is a common cause of acute respiratory infection in children and is usually self-limited, with mild to moderate symptoms. Seasonal epidemics nevertheless cause an estimated 3 to 5 million cases of severe illness [1] and 290,000-650,000 respiratory deaths worldwide each year [2]. In Saudi Arabia, few studies have described children hospitalized with influenza [3]. Central nervous system (CNS) complications of influenza are less common but can be serious. They include febrile and afebrile seizures, encephalopathy, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and acute necrotizing encephalopathy (ANE) [4]. The more severe forms carry considerable morbidity and mortality. In a Chinese cohort of children admitted to intensive care with severe influenza, 30.8% of those who died had influenza-associated encephalopathy [5]. In a United Kingdom national surveillance study of 25 patients (21 children) with influenza-associated neurological disease, 80% required intensive care, 68% had a poor outcome,

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and 16% died [6]. Published cohorts have often included children with pre-existing neurological disease, who are at the highest risk of these complications [7,8]. Less is known about previously healthy children, and regional data are scarce. This study aimed to describe the prevalence, clinical features, and short-term outcomes of influenza-associated CNS complications in previously healthy children admitted to a tertiary pediatric hospital in Saudi Arabia.

Subjects and Methods

Study design and setting

We conducted a retrospective chart review at King Abdullah Specialized Children's Hospital, Jeddah, a tertiary pediatric hospital of the Ministry of National Guard Health Affairs. The study period was November 2016 to December 2023.

Participants

All children younger than 14 years who were admitted with laboratory-confirmed influenza during the study period were identified, and their records were retrieved from BESTCare, the hospital's electronic health information system. The upper age limit of 14 years corresponds to the age range admitted to our pediatric hospital. All eligible admissions were included consecutively (Figure 1). We excluded children with a pre-existing CNS-related comorbidity, such as a seizure disorder, CNS tumor, structural brain malformation, hypoxic-ischemic encephalopathy, or a genetic or metabolic condition with known CNS involvement, because these children are at higher baseline risk of neurological complications [7,8]. Children with concurrent coronavirus disease 2019 (COVID-19) and influenza were also excluded because COVID-19 can itself cause CNS complications. Among the remaining previously healthy children, those who presented with CNS symptoms were included in the detailed analysis.

Data collection

Data were recorded on a standardized collection form and included age, sex, medical history, routine immunization status, presenting symptoms and signs, initial investigations, imaging, cultures, diagnosis, management, and length of stay. Presenting features included fever, seizure type, altered mental status, lethargy, and coryzal symptoms. Antibiotic use in the 7 days before presentation was also recorded. We also recorded initial vital signs, neurological examination findings, white blood cell count with neutrophil and lymphocyte counts, C-reactive protein, procalcitonin, and nasopharyngeal polymerase chain reaction (PCR) results. When obtained, we recorded cerebrospinal fluid (CSF) culture and multiplex PCR results (the multiplex panel did not include influenza) and computed tomography (CT) or magnetic resonance imaging (MRI) findings. Febrile seizures were classified as simple (generalized, lasting <15 minutes, and not recurring within 24 hours) or complex (focal, prolonged, or recurring within 24 hours). Clinical meningitis and meningoencephalitis were adopted as it was documented by the treating physicians in the patient's clinical records.

Statistical analysis

Data were analyzed descriptively. Results were summarized and presented in tables and figures. No inferential statistical analysis was performed, as the study aimed to describe observed findings rather than test hypotheses. Tables and figures were prepared using Microsoft Word. Categorical variables are presented as frequencies and percentages and continuous variables as means with standard deviations (SDs); length of stay is presented as a median with interquartile range (IQR). Prevalence was calculated among previously healthy children and among all children admitted with influenza, with 95% confidence intervals (CIs) calculated using the exact (Clopper–Pearson) binomial method. Because of the small number of cases, the analysis was descriptive and no statistical comparisons were made.

Ethical considerations

The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (approval number 0000027824). Because data were collected retrospectively from existing health records, the requirement for informed consent was waived, and all medical record numbers were anonymized before analysis.

Results

Study population

Of 509 children admitted with laboratory-confirmed influenza during the study period, 60 (11.8%) had a pre-existing CNS-related comorbidity and were excluded, leaving 449 previously healthy children (Figure 1). Of these, 19 (4.2%; 95% CI, 2.6%-6.5%) presented with CNS symptoms, corresponding to 3.7% (95% CI, 2.3%-5.8%) of all influenza admissions.

Demographic and clinical characteristics

The characteristics of the 19 children are shown in Table 1. Eleven (58%) were male, and most were of preschool age. All were previously healthy apart from one child with sickle cell trait. Fifteen (79%) were up to date with routine childhood immunizations; influenza vaccination status was not documented for any child. Eight children (42%) had received antibiotics in the 7 days before presentation. All 19 presented with seizures, which were generalized in 18 (95%) and focal in one (5%) (Table 2). Five children (26%) had a reported history of altered mental status and eight (42%) a reported history of lethargy, but all had a normal neurological examination in the emergency department. One child was hypotensive and required fluid resuscitation.

Investigations and outcomes

Laboratory results are shown in Table 3; most values were normal or mildly elevated. Nasopharyngeal PCR detected

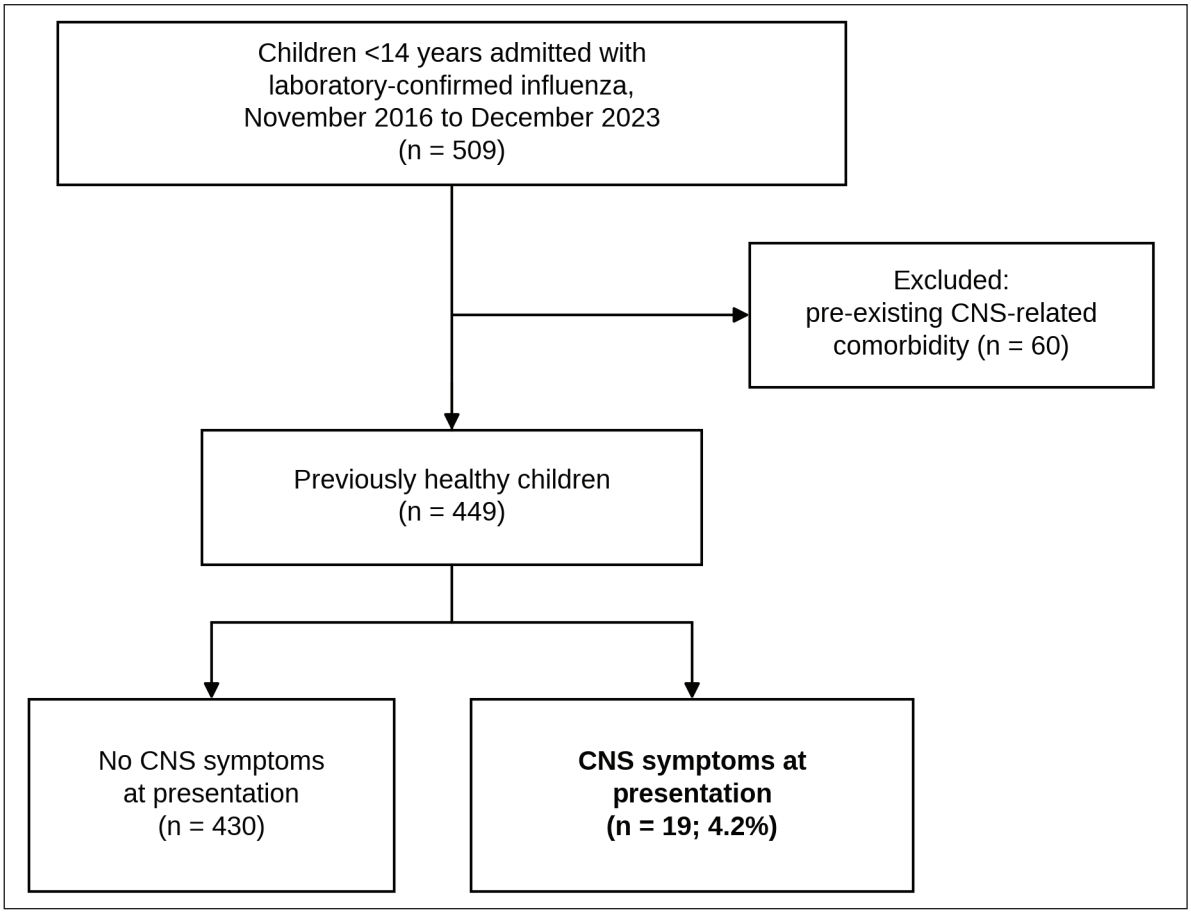

Figure 1. *Flowchart of patient selection.*

Table 1. *Demographic and baseline characteristics of previously healthy children with influenza-associated CNS complications (n = 19).*

Characteristic	Value
Age, months, mean ± SD	*19 ± 36.5*
Sex, n (%)	
Male	*11 (58%)*
Female	*8 (42%)*
Routine childhood immunization status, n (%)[a]	
Up to date for age	*15 (79%)*
Incomplete or unvaccinated	*4 (21%)*
Antibiotic use in the 7 days before presentation, n (%)	*8 (42%)*

[a]Influenza vaccination status was not documented for any child.

influenza A alone in 15 children (79%), influenza B alone in 3 (16%), and influenza A, influenza B, and rhinovirus together in one (5%). Neuroimaging was performed in seven children (37%) and was normal in all. CSF was examined in eight children (42%), and CSF culture and multiplex PCR were negative in all; all 19 blood cultures were also negative.

Fifteen cases (79%) occurred between October and March (Figure 2). No cases were recorded in 2020 or 2021, when COVID-19 restrictions were in place, and the four cases (21%) that occurred between April and September were all in 2022, after restrictions had been lifted.

Discharge diagnoses are listed in Table 4. Fifteen children (79%) had febrile seizures, 12 (63%) simple and 3 (16%) complex. Four children (21%) received a clinical diagnosis of meningitis (n = 3) or meningoencephalitis (n = 1); all four had received antibiotics before presentation, and their blood and CSF cultures and CSF multiplex PCR were negative. No child required intensive care. All children were discharged home, none died, and the median length of stay was 3 days (IQR 3).

Discussion

In this cohort of previously healthy children admitted with influenza, CNS involvement was mild. All 19 children presented with seizures, none had encephalopathy on examination, none required intensive care, and none died. This differs from the severe outcomes reported in other cohort studies. In a pediatric intensive care cohort, 30.8% of children who died had influenza-associated encephalopathy [5], and in the British national surveillance study, 68% of patients with influenza-associated neurological disease had a poor outcome [6]. Part of this contrast reflects case selection, because those studies included critically ill children or children with encephalopathy and encephalitis, whereas our cohort included all previously healthy children admitted with influenza. Even so, our findings suggest that in otherwise healthy children, influenza-associated CNS involvement usually takes the form of self-limited seizures.

Table 2. *Presenting signs and symptoms of the 19 children.*

Sign or symptom	n (%)
Seizure	19 (100%)
Generalized tonic-clonic	15 (79%)
Tonic with upward rolling of the eyes	3 (16%)
Focal	1 (5%)
History of altered mental status	5 (26%)
History of lethargy	8 (42%)
Coryzal symptoms	13 (68%)
Normal neurological examination in the emergency department	19 (100%)
Tachycardia for age	9 (47%)
Hypotension for age	1 (5%)
Tachypnea for age	8 (42%)

Table 3. *Laboratory, microbiology, and imaging findings of the 19 children.*

Investigation	Value
White blood cell count, $\times 10^9$/l, mean ± SD	10.26 ± 4.88
Neutrophil count, $\times 10^9$/l, mean ± SD	5.86 ± 4.13
Lymphocyte count, $\times 10^9$/l, mean ± SD	2.93 ± 1.80
C-reactive protein, mg/l, mean ± SD	17.51 ± 21.03
Procalcitonin, n (%)	
>0.5 µg/l	4 (21%)
<0.5 µg/l	7 (37%)
Not done	8 (42%)
Nasopharyngeal PCR, n (%)	
Influenza A	15 (79%)
Influenza B	3 (16%)
Influenza A, influenza B, and rhinovirus	1 (5%)
CSF culture and multiplex PCR[a], n (%)	
Done, negative	8 (42%)
Not done	11 (58%)
Blood culture, n (%)	
Negative	19 (100%)
Brain CT or MRI, n (%)	
Normal	7 (37%)
Not done	12 (63%)

[a] he CSF multiplex PCR panel did not include influenza.

Table 4. *Discharge diagnoses and outcomes of the 19 children.*

Outcome	Value
Discharge diagnosis, n (%)	
Simple febrile seizure	12 (63%)
Complex febrile seizure	3 (16%)
Clinical meningitis	3 (16%)
Clinical meningoencephalitis	1 (5%)
Length of stay, days, median (IQR)	3 (3)
Intensive care admission, n (%)	0 (0%)
Mortality, n (%)	0 (0%)

The prevalence we observed (4.2% of previously healthy children and 3.7% of all influenza admissions) was also lower than in previous reports. A large multicenter study from the United States found a neurological complication in 7.6% of children hospitalized with influenza [7], and a Thai tertiary hospital cohort reported a prevalence of 16.9% [8]. Both cohorts included children with pre-existing neurological conditions, who were at increased risk of complications. Because we excluded children with known CNS disease, our cohort represents a lower-risk group, and a lower prevalence would be expected.

Seizures were the main CNS manifestation in our cohort, and most were generalized tonic-clonic. Apart from the four clinical diagnoses of meningitis or meningoencephalitis discussed below, there were no cases of encephalitis, encephalopathy, Guillain-Barré syndrome, or ANE. Influenza A predominated (16/19, 84%). Influenza A has been associated with febrile seizures: in a Hong Kong study of hospitalized children aged 6 months to 5 years, febrile seizures occurred in 19.5% of those with influenza A, compared with 12.2% of those with parainfluenza and 9% of those with adenovirus infection, and repeated seizures were more common with influenza A [9].

All 19 children had a normal neurological examination, although some had a reported history of lethargy or altered mental status, which is consistent with a postictal state. This probably explains why only seven children (37%) underwent neuroimaging and 8 (42%) had CSF testing. The American Academy of Pediatrics advises that neuroimaging and electroencephalography are not needed in the routine evaluation of a neurologically healthy child with a simple febrile seizure, and that evaluation should focus on identifying the source of the fever [10]. In our cohort, all imaging studies were normal, which supports this selective approach in neurologically well children with influenza-associated febrile seizures.

The four children with a clinical diagnosis of meningitis or meningoencephalitis need separate comment, because all had received antibiotics before presentation. Antibiotic pretreatment lowers the yield of blood and CSF cultures. In a multicenter study of children with bacterial meningitis, those pretreated with antibiotics were less likely to have a positive culture, although pretreatment did not normalize the CSF white blood cell count [11]. A negative culture after antibiotics therefore does not exclude partially treated bacterial meningitis, and the American Academy of Pediatrics lists antibiotic pretreatment as a reason to consider lumbar puncture after a febrile seizure [10]. Because CSF testing for influenza was not available, we could not confirm direct CNS involvement by the virus.

Most cases (15/19, 79%) occurred between October and March. The absence of cases in 2020 and 2021, followed by out-of-season cases in 2022 (Figure 2), mirrors the global fall in influenza circulation during the COVID-19 pandemic, which a recent meta-analysis estimated at 92%, although the decline was smaller among children younger than 6 years [12].

This study has several strengths. It covered a 7-year period and included all eligible admissions consecutively, and restricting the cohort to previously healthy children

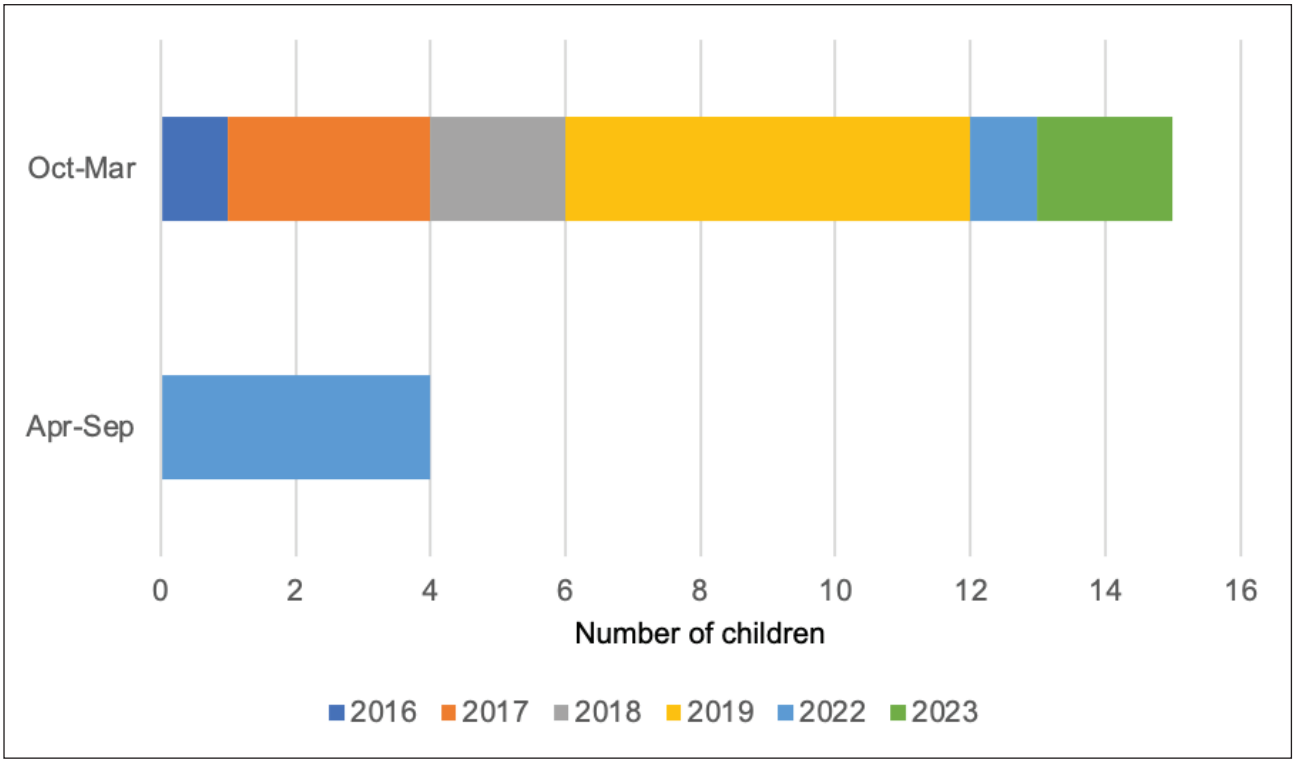

Figure 2. *Seasonal distribution of the 19 children with influenza-associated CNS complications, by year of presentation.*

reduced confounding by pre-existing neurological disease. Our estimates therefore apply to children who are not usually regarded as being at high risk of neurological complications, a group for whom regional data have been lacking.

An important limitation is that influenza vaccination status could not be assessed because it was not documented in any chart. This is a notable gap because vaccination is the main means of preventing influenza [1], and its effect on neurological complications in Saudi children is unknown. Routine documentation of influenza vaccination status would allow future studies to address this question.

The study also has other limitations. It was a small, single-center, retrospective study, which limits the precision of our estimates and precludes subgroup comparisons. Only admitted children were included, so children with influenza-associated seizures who were discharged from the emergency department were not captured, which may have introduced selection bias. Neuroimaging, CSF studies, and procalcitonin were not obtained in all children, which may have introduced ascertainment bias. The study period included the COVID-19 pandemic as well as changes in testing practice and data recording at our hospital, which may have affected influenza circulation and health care use. We relied on the completeness of the electronic records at the time of admission, so we cannot comment on seizure recurrence, later epilepsy, or subtle neurological sequelae. Finally, one child had sickle cell trait; unlike sickle cell disease, the trait is not an established risk factor for febrile seizures or CNS infection, so it is unlikely to have affected our findings.

Conclusion

In previously healthy children admitted with influenza to our center, CNS involvement was uncommon (19 of 449 previously healthy children, 4.2%), presented as seizures, and had good short-term outcomes, with no intensive care admissions or deaths. Clinicians should nonetheless remain alert to the rarer severe encephalopathic forms described elsewhere [4-6]. Prospective multicenter studies in the region, with standardized neuroimaging and CSF protocols, documented influenza vaccination status, and longer follow-up, are needed to define the full spectrum and long-term outcomes of influenza-associated neurological disease in Saudi children.

List of Abbreviations

ANE	Acute necrotizing encephalopathy
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
CT	Computed tomography
IQR	Interquartile range
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
SD	Standard deviation

Conflicts of interest

The authors declare no conflicts of interest relevant to this work.

Funding

This study received no external or internal funding.

Consent to participate
The requirement for informed consent was waived given the retrospective, de-identified nature of the data.

Ethics approval
The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (approval number 0000027824).

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Supplementary content (if any) is available online.

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