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ORIGINAL ARTICLE

Neurological complications of severe influenza a in children

Snezana Rsovac [1,2], Vesna Selakovic [1], Jasna Kalanj [1,2], Katarina Milosevic [1,2]

[1]University Children's Hospital, Intensive care unit, Belgrade,Serbia
[2] University of Belgrade, Faculty of Medicine, Belgrade,Serbia

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Correspondence to:
Snezana Rsovac
University Children's Hospital
10, TirsovaStreet, 11000 Belgrade, Serbia
Email: snezanarsovac@yahoo.com

Summary

Introduction: Neurological complications of Influenza infection in pediatric population vary in incidence and severity. The central nervous system is most often affected by encephalitis and encephalopathy. Acute necrotizing encephalopathy (ANE) is the most serious complication. The aim of this case study was to present a variety of severe cases of neuro-influenza in pediatric patients.

Methods: The study presents five children who were hospitalized in the pediatric intensivecare unit due to neurological complications of InfluenzaA infection during the winter season of 2022/2023. The identification of the causative agent was carried out by the reverse–transcription–polymerase chain reaction or by the detection of viral antigens in the samples of nasopharyngeal swabs.

Results: Four out of five presented patients were male. The average age at admission was 6 years (min. 7 months, max. 11 years). All patients had an acute disturbance of consciousness at admission and four of them had seizures. Neurological complications of Influenza A infection presented as acute encephalitis, posterior reversible encephalopathy syndrome, acute disseminated encephalomyelitis, encephalopathy, and ANE. Neurological signs appeared approximately four days after the first symptoms. There were no lethal outcomes. Younger patients had more severe brain damage and took longer to recover. None of the children had been vaccinated against the flu.

Conclusions: Children presenting with acute neurological deterioration during influenza season should be evaluated for influenza-associated central nervous system complications even if the respiratory involvement is mild or there are no respiratory signs at all. Magnetic resonance imaging is the most important tool for early diagnosis.

Keywords: Influenza, children, encephalitis, encephalopathy

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Table 1. Demographic data, vaccinal status and clinical presentation in five patients with Influenza A.

Case number	Age	Sex	Clinical presentation at the beginning of disease	Vaccinal status	Time from the onset of the disease to the appearance of neurological signs (days)	Neurological signs
1	8y 10m	F	Fever up to 39˚C Headache Photophobia Vomiting	No Vaccine	3	Seizures Loss of consciousness Disorientation
2	10y 4m	M	Cough Fever over 39˚C Headache Vomiting Hypertension	No Vaccine	11	Seizures Loss of consciousness Visual hallucinations Agitation
3	11y 2m	M	Fever over 40˚C Vomiting Diarrhea	No Vaccine	3	Seizures Altered consciousness
4	1y 4m	M	Fever up to 40˚C Vomiting Diarrhea Somnolence	No Vaccine	2	Seizures, prolonged disorder of consciousness
5	7m	M	Fever over 38˚C	No Vaccine	2	Cyanosis Apnea Episodes of altered consciousness

y-years, m-months, F-female, M-male

INTRODUCTION

Influenza A is a viral contagious infectious disease that is primarily manifested by symptoms and signs of acute respiratory disease. It is estimated that the causative agent of the disease, influenza A virus, infects tens of millions of people every year, mostly young children. A typical clinical presentation in this population includes high fever and gastrointestinal complaints such as reduced appetite, nausea, and vomiting. However, depending on the region and severity of the symptoms, some studies have reported that 10–30% of pediatric patients with influenza A may have neurological complications, including influenza-associated encephalopathy (IAE), encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, aseptic meningitis, Guillain-Barre syndrome, and cerebrovascular disease (1). Fever may cause febrile convulsions (1, 2). Acute necrotizing encephalopathy (ANE), which has mortality rate of about 30% and which affects about 70% of children, is the most severe brain complication of influenza (1, 3, 4). Similar results related to the incidence of neurological complications of the infection caused by influenza A were presented in a study in Croatia, but our study is the first report from Serbia in children (5). We present five pediatric cases of severe neurological complications caused by Influenza A. The goal of this case study was to present variations in neurological presentations and neuroimaging in pediatric patients.

METHODS

This retrospective casereport study included children with neurological manifestation of InfluenzaA virus who were admitted to the University Children's Hospital in Belgrade, during the winter season of 2022/2023, from December 2022 to April 2023. The identification of the causative agent was carried out by the molecular metho(reverse–transcription–polymerase chain reaction (RT-PCR)) or by detection of viral antigens in the samples of nasopharyngeal swabs, because molecular assay or viral culture are the "gold standard" for determining influenza A virus (6). We excluded COVID-19 infection in all patients by RT-PCR analysis of nasal swabs. The data were obtained by analyzing the existing medical documentation. Electroencephalography, magnetic resonance imaging (MRI), and computerized tomography (CT) were performed.

RESULTS

Four out of five presented patients were male. The average age at admission was 6 years and 6 months (ranging from 7 months to 11 years of age). Demographic data, vaccination status, and clinical presentation are shown in **Table 1**. Comorbidities in our patients were as follows: patient number 1 lost consciousness after a febrile illness at the age of 6; patient number 3 was diagnosed with type 1 diabetes mellitus and was well regulated; and patient number

Table 2. Neuroimaging, electroencephalography, disease course and outcome in five patients with Influenza

Patient	MR	CT	EEG	Diagnosis	Days at PICU	Day of discharge	Neurological sequels at discharge
1	Signal changes of the parietal and occipital cortex of both hemispheres	Cerebral edema	Encephalopathic	Acute encephalitis	6	12	None
2	Posterior reversible encephalopathy with supratentorial cortico-subcortical lesions of the holohemispheric type along the "watershed" zones	CT examination done in another institution described as normal	Encephalopathic	Posterior reversible encephalopathy syndrome (PRES)	4	15	None
3	Disseminated fronto-parietal supratentorial white matter lesions and lesions in the brainstem, basal ganglia and cerebellum	Indirect signs of cerebral edema, bilateral hypodensities of the thalamus	Encephalopathic	Acute disseminated encephalomyelitis (ADEM)	5	8	Decreased gross motor strength
4	Massive lesions of the white matter of both hemispheres of the cerebrum, cerebellum, thalamus and brainstem	Supra- and infratentorial lesions affecting the thalamus, dorsal pons, medial cerebellar peduncles and white matter of the cerebellar cortex	Encephalopathic	Acute necrotizing encephalopathy (ANE)	21	47	Altered state of consciousness with occasional spontaneous eye opening and preserved reaction to light and painful stimuli, uttering few meaningful words
5	Multiple bilateral cortico-subcortical changes in all cerebral lobes, signal changes in basal ganglia and thalamus	Cerebral edema	Focal epileptic activity	Encephalopathy	14	40	Generalized hypotonia, hyperreflexia, poor eye tracking

5 had macrocephaly without any neurological symptoms. Influenza A infection was confirmed in patients 1, 2, and 4 by RT-PCR and in patients 3 and 5 by rapid antigen test. All patients had flu-like symptoms with mild respiratory symptoms or with no symptoms. All of them also had acute disturbance of consciousness (ADOC) at admission, while four out of five had seizures. Neurological signs appearedapproximately 4 days (range 2-11) after the first symptoms. There were no lethal outcomes. All patients had different forms of neurological complications caused by virus influenza disease and required treatment in the pediatric intensive care unit (PICU). Diagnosis based on neuroimaging examinations, electroencephalography, and laboratory findings are shown in **Table 2**. MRI findings are shown in **Figures 1-5** for all the patients. Patients 4 and 5 were treated with plasmapheresis and intravenous immunoglobulins (IVIG) because they had severe liver dysfunction, while patient 4 was additionally treated with pulse doses of methylprednisolone. Both patients had increased levels of C-reactive protein (CRP) and significantly increased liver enzymes. Patient 2 also developed glomerulonephritis due to Influenza A infection. Laboratory examinations of all patients at admission are shown in **Table 3**.

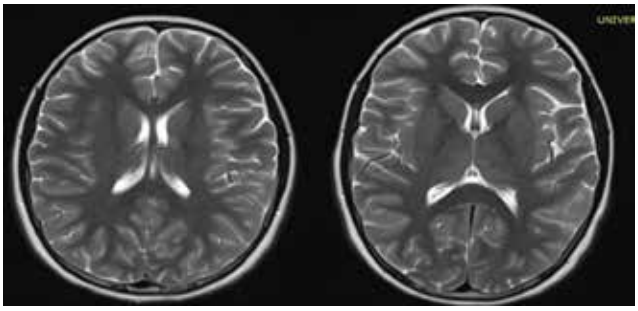

Figure 1. MRI findings of the endocranium of patient 1: signal changes of the parietal and occipital cortex of both hemisphere

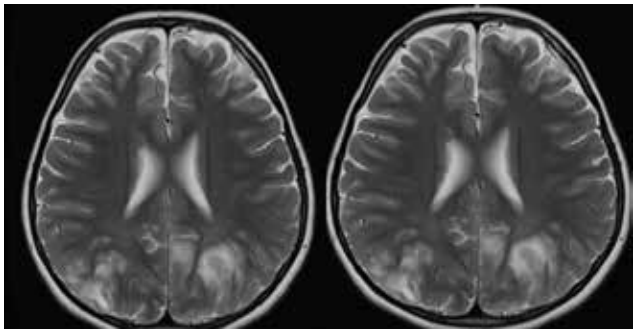

Figure 2. MRI findings of the endocranium of patient 2: posterior reversible encephalopathy with supratentorial cortico-subcortical lesions of the holohemispheric type along the "watershed" zones

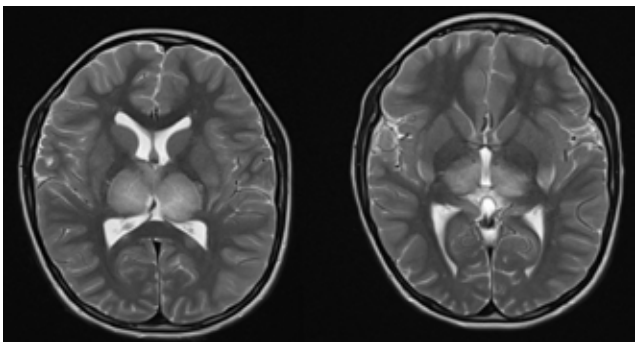

Figure 3. MRI findings of the endocranium of patient 3: Ddisseminated frontoparietal supratentorial white matter lesions and lesions in the brainstem, basal ganglia and cerebellum

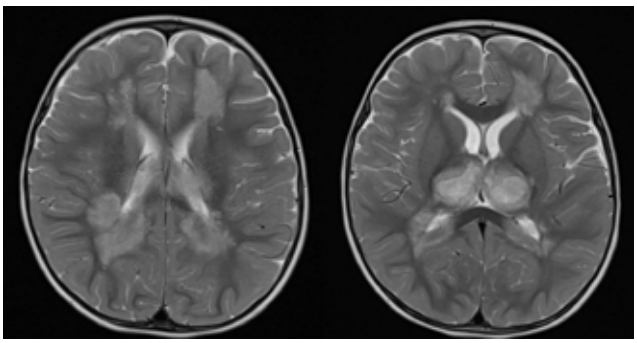

Figure 4. MRI findings of the endocranium of patient 4: massive lesions of the white matter of both hemispheres of the cerebrum and cerebellum, thalamus and brainstem

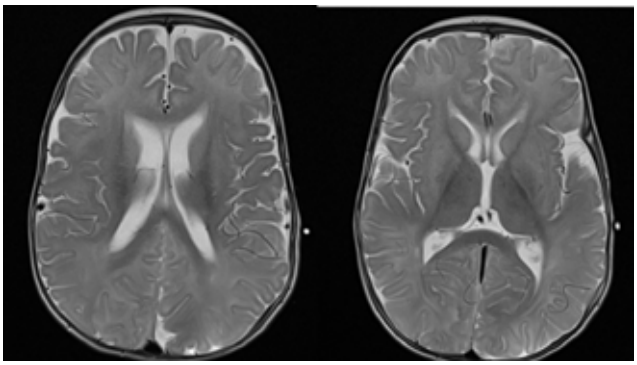

Figure 5. MRI findings of the endocranium of patient 5: multiple bilateral cortico-subcortical changes in all cerebral lobes, signal changes in basal ganglia and thalamus

DISCUSSION

All patients had different types of brain involvement which represent the diversity of neuroinfuenza, despite having relatively similar clinical presentations at admission. Although influenza viruses are known to increase the risk of secondary bacterial infections, particularly pneumonia and sepsis, our study group did not experience any of these complications (5). Acute necrotizing encephalopathy is described as the most severe form of influenza encephalopathy. It is acuteencephalopathy, with no inflammation and with symmetrical bilateral lesions of the thalami and other deep brain structures, and it presents with necrosis or hemorrhage (4).According to statistics, it affects about one-fifth of children with influenza encephalopathy, and the only documented case from our study is consistent with these figures (4). Acute necrotizing encephalopathy presents with fever, deteriorating consciousness, personality changes, seizures, focal deficits, and coma (6). Early steroid administration may be associated with a favorable prognosis, most likely as a result of the interruption of cytokine elevation and reduction of inflammation (7). The neuroinflammation-related brain edema can also be controlled by corticosteroids (8). This therapy had positive results for our patient and minimized brain sequelae.

Serious central nervous complications of the flu are more common in children under 2 years of age (2). Younger children in our study group (patients 4 and 5, aged 16 months and 7 months, respectively) presented with more severe clinical symptoms, recovered more slowly, and had neurological sequelae at discharge. Cerebral edema, signal changes in the cortical and subcortical white matter, bilateral lesions of the thalami and other deep brain structures, particularly in the brain stem, surrounding the white matter, and cerebellar medulla, are some of the neuroimaging changes of influenza-associated encephalitis and encephalopathy (2). The MRI scans of patients 1, 3, and 5 were comparable to previously published data (2). According to reports, significant MRI changes are associated with disease severity and have excellent prognostic value for outcomes (9–13). For IAE, there are no specific laboratory markers. Elevated enzyme levels are a common sign of liver dysfunction. An increased level of white blood cells and noticeably elevated liver enzymes are seen in ANE blood tests. These signs do not, however, exclusively point to the diagnosis of neuro-influenza (2). The results of our laboratory tests are not differentially symptomatic. Although acute necrotizing encephalopathy in children can result from other respiratory tract infections besides influenza A, it is most frequently caused by influenza A: rubella, measles, varicella, human herpes simplex virus, SARS-CoV-2, and

Table 3. Laboratory examination data of five children with Influenza A at admission

Laboratory examination	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
WBC count (10^9/L)	11,9	7,3	6,6	4,1	10,4
CRP (mg/L)	4,5	4	5,1	10,4	12,2
ALT (U/L)	34	39	40	78	97
AST (U/L)	35	58	80	105	241

WBC-white blood cell, PCT-procalcitonin, ALT- alanine aminotransferase, AST- aspartate aminotransferase

human herpes viruses 6 and 7. It was crucial to rule out SARS-CoV-2 infection as the cause of infection, especially since all patients in our study received care during the Covid-19 pandemic.

CONCLUSIONS

Changing consciousness and seizures are the main clinical signs of neuro-influenza. All children with neurological symptoms must be screened for CNS flu-related complications during the flu season. MRI is the most accurate tool for early diagnosis and treatment.This is a potent tool for the diagnosis of neurological damage to brain structures and serves as evidence of the brain diversity of the same virus, such as influenza A. The severity and course of the disease may be altered by the early administration of IVIG, corticosteroids, and plasmapheresis. The differential diagnosis of acute disturbance of consciousness following flu-like symptoms must take other viral infections into account.

Ethical approval

This research and publication were approved by the Ethical committee of the University Children's Hospital (approval number 018 19/02).

References

1. Chen Q, Li P, Li S, Xiao W, Yang S, Lu H. Brain Complications with Influenza Infection in Children. J Behav Brain Sci. 2020;10(03):129–52.
2. Kalil AC, Thomas PG. Influenza virus-related critical illness: Pathophysiology and epidemiology. Vol. 23, Critical Care. BioMed Central Ltd.; 2019.
3. Surtees R, DeSousa C. Influenza virus associated encephalopathy. Vol. 91, Archives of Disease in Childhood. 2006. p. 455–6.
4. Sarigecili E, Ucar HK, Havali C, Cansu A, Aydin K. Acute necrotizing encephalopathy associated with RANBP2 mutation: value of MRI findings for diagnosis and intervention. Acta Neurol Belg. 2023 Apr 1;123(2):571–82.
5. Tesovic G, Stemberger L. Influenza-associated complications in children. Medicus. 2011; 20: 39-44.
6. Phetcharakupt V et al. Clinical manifestations of influenza and performance of rapid influenza diagnostic test: A university hospital setting. Health Sci Rep. 2021 Dec; 4(4): e408.
7. Lee YJ, Hwang SK, Lee SM, Kwon S. Familial acute necrotizing encephalopathy with RANBP2 mutation: The first report in Northeast Asia. Brain Dev. 2017 Aug 1;39(7):625–8.
8. Levine JM, Ahsan N, Ho E, Santoro JD. Genetic Acute Necrotizing Encephalopathy Associated with RANBP2: Clinical and Therapeutic Implications in Pediatrics. Vol. 43, Multiple Sclerosis and Related Disorders. Elsevier B.V.; 2020. 3,
9. Okuno H, Yahata Y, Tanaka-Taya K, Arai S, Satoh H, Morino S, et al. Characteristics and Outcomes of Influenza-Associated Encephalopathy Cases among Children and Adults in Japan, 2010-2015. Clinical Infectious Diseases. 2018 Jun 1;66(12):1831–7.
10. Macdonald-Laurs E, Koirala A, Britton PN, Rawlinson W, Hiew CC, Mcrae J, et al. CSF neopterin, a useful biomarker in children presenting with influenza associated encephalopathy? European Journal of Paediatric Neurology. 2019 Jan 1;23(1):204–13.
11. 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 Aug;29(7):425–30.
12. Dadak M, Pul R, Lanfermann H, Hartmann H, Hehr U, Donnerstag F, et al. Varying Patterns of CNS Imaging in Influenza A Encephalopathy in Childhood. Clin Neuroradiol. 2020 Jun 1;30(2):243–9.
13. Nagao T, Morishima T, Kimura H, Yokota S, Yamashita N, Ichiyama T, et al. Prognostic factors in influenza-associated encephalopathy. Pediatric Infectious Disease Journal. 2008;27(5):384–9.
14. Jantarabenjakul W, Paprad T, Paprad T, Anugulruengkitt S, Pancharoen C, Puthanakit T, et al. Neurological complications associated with influenza in hospitalized children. Influenza Other Respir Viruses. 2023 Jan 1;17(1).

NEUROLOŠKE KOMPLIKACIJE TEŠKOG OBLIKA INFLUENZE A KOD DECE

Snežana Rsovac[1,2], Vesna Selaković[1], Jasna Kalanj[1,2], Katarina Milošević[1,2]

Sažetak

Uvod: Neurološke komplikacije infekcije virusom Influenza A u pedijatrijskoj populaciji javljaju se sa različitom učestalošću i ozbiljnošću kliničke slike. Centralni nervni sistem može biti zahvaćen na različite načine, najčešće u vidu encefalitisa i encefalopatije. Najozbiljnija komplikacija je akutna nekrotizirajuća encefalopatija (ANE). Cilj ove studije slučajeva jeste prikaz raznolikosti teških oblika neuroinfluence kod pedijatrijskih pacijenata.

Metode: Studija obuhvata petoro dece koja su zbog neuroloških komplikacija infekcije Influenzom tip A hospitalizovana na odeljenju pedijatrijske intenzivne nege tokom zime 2022/2023. godine. Identifikacija uzročnika sprovedena je reakcijom lančanog umnožavanja pomoću reverzne transkriptaze (RT-PCR) ili detekcijom virusnih antigena u uzorcima nazofaringealnog brisa.

Rezultati: Četiri od pet bolesnika bilisumuškog pola. Prosečna starost na prijemu bila je 6 godina i 6 meseci (min. 7 meseci, maks. 11 godina). Svi bolesnici su na prijemu imali akutni poremećaj svesti, a četvoro je imalo konvulzije. Neurološke komplikacije Influenze A manifestovale su se kao: akutni encefalitis, sindrom posterior nereverzibilne encefalopatije, akutni diseminovani encefalomijelitis, encefalopatija i ANE. Neurološki znaci su se pojavili u proseku četiri dana nakon prvih simptoma bolesti. Bolest se u svim slučajevima završila ozdravljenjem. Mlađa deca su imala veće oštećenje mozga i duži period oprovaka od starije dece. Nijedno dete nije bilo vakcinisano vakcinom protiv gripa.

Zaključci: Kod dece sa akutnim neurološkim pogoršanjem tokom sezone gripa treba razmotriti potencijalno postojanje neuroloških komplikacija infekcije gripom, čak i u slučajevima blagih ili nepostojećih respiratornih tegoba. Magnetna rezonanca je najvažnija dijagnostička procedura za blagovremeno postavljanje dijagnoze.

Ključne reči: Influenza, deca, encefalitis, encefalopatija

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