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# Encephalitis or Encephalopathy During an Influenza-A Epidemic

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**A B S T R A C T**

*Six female patients with encephalitis, mean age 36.5 (17–60) years, were admitted to the hospital during the 2000–2001 influenza A (H1N1) epidemic in the Osijek – Baranja County. In three (50.0%) patients, the manifestation of encephalitis occurred on day 4 or 5, and in two (33.3%) patients within 24–48 hours of the onset of influenza symptoms. The disease manifestations included headache, elevated body temperature, generalized fatigue, and consciousness disturbance through coma. Three (50.0%) patients had grand mal seizures. Pathologic electroencephalography findings were recorded in all six (100%) patients, whereas computed tomography showed cerebral edema in three (50.0%) patients. Elevated levels of hepatic enzymes and peripheral blood leukopenia were found in two (33.3%) patients in whom encephalitis developed early upon the onset of influenza. One (16.6%) of these patients died, whereas permanent sequels remained in the other two (33.3%) patients.*

***Key words:*** *cerebral edema, influenza A, epilepsy, coma, encephalitis, encephalopathy.*

## Introduction

Influenza A epidemics have almost regularly been accompanied by reports of central nervous system (CNS) impairments associated with influenza A[1,2]. CNS impairments usually occur in small children under the age of 5–6 years, however, they may also develop in adults. Encephalitis, encephalopathy and acute necrotizing encephalopathy have been related to the influenza virus invasion[6,7]. The interest in thorough research into the CNS effects of influenza A virus has

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been stimulated by recent reports from Japan on the ever increasing rate of encephalitis or encephalopathy in pediatric patients during the epidemics of influenza[8]. The CNS disease generally developed within 12–48 hours of the onset of influenza symptoms, and was accompanied by high body temperature, seizures, coma, and high mortality or permanent sequels in the survivors[8,9]. The patients had elevated levels of serum creatine phosphokinase (CPK), tumor necrosis factor alfa (TNF-α) and interleukin (IL-6) in blood and cerebrospinal fluid (CSF), abnormal hepatic enzyme findings, and CSF pleocytosis[9,10].

Brain radiological studies showed lesions of the thalamus, brain stem and cerebellum bilaterally[10,11]. The influenza virus (H3) genome was demonstrated in the CSF of some patients with encephalitis or encephalopathy[10–12].

The pathophysiology and pathogenesis of encephalitis and encephalopathy associated with influenza A virus has not yet been fully elucidated, however, this influenza A complication obviously shows a rising tendency[11,12]. Some 150 to 200 cases of encephalitis or encephalopathy per influenza epidemic are expected in Japan alone[12].

## Methods and Results

During the influenza A (H1N1) epidemic in the Osijek, Baranja County, from the end of December 2000 till March 2001, six female patients with encephalitis were treated at the University Hospital »Osijek«. The patients had neither received influenza A and B vaccination nor suffered from any neurological disorder. The clinical picture and epidemiological data pointed to influenza, whereas encephalitis of another etiology (Leptospira, tick-borne meningoencephalitis, cytomegalovirus, herpes simplex virus 1 and 2, and enteroviruses) were ruled out in all six patients. At least fourfold increase in the influenza A virus antibody titer was recorded in paired sera of all these patients.

The patients were aged 17–60, mean age 36.5 years. In two (33.3%) patients, the symptoms of encephalitis manifested within the first 48 hours, and in three (50.0%) patients on day 4 or 5 of the onset of influenza. In one (16.6%) patient, encephalitis manifested on day 11 of initial influenza symptoms. A very severe manifestation of encephalitis was recorded in the patients in whom it developed early in the course of the underlying disease, i.e. influenza A. In two patients, the initial abrupt manifestation of encephalitis included grand mal seizures and deep coma. They both had marked leukopenia (L $1.8 \times 10^9$ and $1.9 \times 10^9$) without granulocytopenia. One (16.6%) of these two patients died, whereas two (33.3%) patients sustained permanent sequels.

**TABLE 1**
CLINICAL AND LABORATORY FINDINGS OF ENCEPHALITIS DURING INFLUENZA A EPIDEMIC IN OSIJEK 2000–2001

| Clinical and laboratory findings | No. of cases | % |
|---|---|---|
| Elevated body temperature | 6/6 | 100.0 |
| Epilepsy | 3/6 | 50.0 |
| Consciousness disturbances | 4/6 | 66.6 |
| Headache | 6/6 | 100.0 |
| Vertigo | 5/6 | 83.3 |
| Cough | 5/6 | 83.3 |
| Fatigue | 6/6 | 100.0 |
| EEG abnormality | 6/6 | 100.0 |
| CT abnormality | 3/6 | 50.0 |
| ALT/AST elevation | 2/6 | 33.3 |
| Leukopenia | 2/6 | 33.3 |
| CSF pleocytosis | 4/6 | 66.6 |

EEG = electroencephalogram; CT = computed tomography; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSF = cerebrospinal fluid

Three (50.0%) patients were discharged from the hospital as fully recovered. All our patients (100%) had elevated body temperature (> 40 °C) (Table 1), and had previously suffered headache and generalized fatigue. Vertigo and cough were present in five (83.3%), and consciousness disturbances up to deep coma in four (66.6%) patients. Electroencephalogram (EEG) was normal in all (100%) patients. Computed tomography (CT) of the brain revealed severe cerebral edema and normal finding in three (50.0%) patients each. Elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were recorded in two (33.3%), and CSF pleocytosis in four (66.6%) patients.

## Discussion

Influenza viruses are obviously associated with encephalitis, encephalopathy and acute necrotizing encephalopathy[13]. These severe complications of influenza mostly occur in small children under the age of 5–6 years, but are by no means rare in adults either[13,14]. These CNS lesions have frequently been reported during influenza A epidemics caused by H1N1 and H3N2 virus strains. The neurotropic properties of these viruses, including H5N1, have also been demonstrated experimentally[15–17]. In all our patients encephalitis developed during the influenza A (H1N1) epidemic, as verified by clinical, epidemiological and serologic studies.

In five patients, the symptoms of encephalitis occurred during the course of influenza, whereas one patient probably developed postinfectious encephalitis. Interestingly enough, these were middle-aged women. This might be due to the higher rate of influenza A and B vaccination among men, because of more frequent travel and for occupational specificities.

Two of our patients with the onset of encephalitis within 24–48 hours of influenza symptoms had elevated serum AST and ALT levels, and marked peripheral blood leukopenia. There was no coagulation impairment, which is otherwise seen in small children with Reye's syndrome that has also been causally related with influenza virus. One of these patients died, whereas the others suffered permanent sequels. Three patients had severe brain edema, which has been associated with cytokines (TNF-α and IL-6) that lead to blood-brain barrier permeability, however, the contribution of local factors should also be taken in consideration[17].

The mechanism by which the influenza A virus penetrates the brain and causes encephalopathy and encephalitis has not yet been completely clarified. The influenza A virus is replicated in the nasopharyngeal epithelium. The virus takes invasive action to destroy the upper respiratory tract epithelium. Olfactory mucosa and its nerve endings are affected with the inflammation. The influenza A virus probably reaches the brain *via* the olfactory nervous system[18]. The virus interaction with glial cells results in the release of cytokines, especially TNF-α. TNF-α causes brain cell lesions by the inhibition of intracellular mitochondrial respiration[18,19].

Penetration of the influenza A virus into the brain by this route appears quite probable, because it obviously does not occur by the hematogenous route[18–20]. It is of utmost importance to distinguish whether these are manifestations of different diseases or pathophysiological sequels of the same disease entity.

## Conclusion

In the patients presented, the course of disease, clinical picture analysis, laboratory findings and radiological study results pointed to encephalitis or encepha-

lopathy caused by influenza A virus. The exact pathogenetic mechanism of the association between influenza virus and cerebral manifestations remains an open question, however, it should be admitted that a seemingly plain influenza could cause severe, permanent and even life-threatening sequels. Therefore, caution is warranted on approaching a patient with influenza A and B. Timely prevention of this seemingly simple but actually severe infection is of utmost importance. Results of the study pointed to the need of additional investigation aimed at a more distinct differentiation of biologically recognizable and objective features of the disease.

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## ENCEFALITIS ILI ENCEFALOPATIJA TIJEKOM EPIDEMIJE INFLUENCE-A

## SAŽETAK

Tijekom epidemije influence A (H1N1) u Osječko-baranjskoj županiji od 2000. do 2001. godine liječeno je 6 bolesnica s encefalitisom. Najmlađa bolesnica imala je 17, a najstarija 60 godina. Srednja životna dob je 36.5 godina. Tri (50%) su bolesnice dobile encefalitis 4-tog i 5-tog dana od pojave simptoma influence, a dvije (33.3%) tijekom prvih 24–48 sati od početka bolesti. Bolest se očitovala glavoboljom, visokom temperaturom, općom slabošću i poremećajem svijesti do kome. Tri (50%) su bolesnice imale epi napad tipa grand mal. U svih je bolesnica (100%) nađen patološki EEG, u tri (50%) je na CT-u nađen jači edem mozga. U dvije (33.3%) bolesnice u kojih se encefalitis javio prvih dana influence nađene su povišene vrijednosti jetrenih enzima i leukopenija u perifernoj krvi. Jedna (16.6%) je bolesnica umrla, a u dvije (33.3%) ostale su trajne sekvele.