Scripta Scientifica Medica, 2024;56(1):46-51
DOI: 10.14748/ssm.v57i1.10223

ISSN 0582-3250 (Print)
ISSN 1314-6408 (Online)

CASE REPORTS

ACUTE NECROTIZING ENCEPHALOPATHY WITH FATAL OUTCOME IN A PATIENT WITH FULMINANT INFLUENZA A (H1N1) INFECTION

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ABSTRACT

Influenza is a viral infection that spreads annually as an epidemic, and every few years as a pandemic. In most cases, the infection occurs with mild symptoms. However, severe illness with serious complications is possible, as certain subtypes of the virus, such as H1N1, are associated with a higher risk of more severe course of the infection. Neurological involvement, although rarely observed during acute influenza infection, is one of the serious complications with a risk of permanent damage or death. Children belong to the risk groups for whom vaccination after 6 months of age is of particular importance, both for limiting the spread of the infection and for preventing complications. We present a clinical case of a 6-year-old child with a fulminant course of infection with influenza A, subtype H1N1, with severe neurological involvement and fatal outcome.

Keywords: *influenza, H1N1, childhood, acute necrotizing encephalopathy*

INTRODUCTION

Influenza is an acute respiratory infection caused by influenza virus—an RNA virus of the Orthomyxoviridae family. Every year during the winter months, the virus spreads in the form of an influenza epidemic, and every few years pandemics occur. The infection can be clinically presented by mild respiratory symptoms within a few days. However, in some cases, especially in risk groups, such as the pediatric population, influenza can be severe with the development of serious complications and even death (1,2). The global mortality rate from complications of influenza infection reaches 500,000 people per year despite the fact that there is a vaccine against the infection (3). During the COVID-19 pandemic, in 2020–2021, influenza incidence declined, likely due to global measures to contain the spread of COVID-19 (4). However, influenza cases increased in the 2022–2023 season, likely as a result of the lifting of restrictive measures and lower vaccination rates (4). The widespread adoption of combined rapid antigen tests for COVID-19, influenza A, and influenza B contributes to earlier diagnosis, which is of key importance, as specific therapy is most effective if started within the first 48 hours of symptom onset (5).

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Received: January 7, 2024
Accepted: March 18, 2024

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Ethical Considerations

The co-authors have the parents‘ consent to publish the clinical case. Parents were provided with sufficient information in order to make an informed decision on their child's participation. Ethical issues of consent, risk of harm, and confidentiality were clearly defined.

CLINICAL CASE

We present a clinical case of a 6-year-old girl who became acutely ill the day before hospitalization with a high-grade fever of up to 40°C. On this occasion, an examination was performed by the family doctor and symptomatic therapy was prescribed for treatment at home. On the second day of the acute illness, the parents reported repeated profuse vomiting, impaired consciousness, and a seizure. An emergency medical team was called due to the seizure, and a paracetamol suppository and phenobarbital were administered. The total duration of the seizure was about 40 minutes. During this period, the child was transported to the Pediatric Emergency Department and was urgently hospitalized in the Pediatric Intensive Care Unit (PICU) due to status seizure.

On admission, the patient was in a state of generalized tonic-clonic seizure with incontinence. After a single administration of midazolam, the seizure stopped, but without full recovery of consciousness. The patient remained somnolent with rapid, within minutes, progressive depression of consciousness to coma (Glasgow Coma Scale—3/15 points) and ineffective spontaneous breathing. The latter necessitated intubation and placement on invasive mechanical ventilation (IMV).

The initial laboratory tests showed mild decompensated metabolic acidosis (pH 7.28) with elevated lactate levels—4.4 mmol/L (≤ 2 mmol/L), and blood glucose of 7.3 mmol/L. The peripheral blood count showed normal hemoglobin and leukocyte values, but with a platelet count below the lower limit of normal. The biochemical tests performed showed no evidence of inflammatory activity. Kidney function tests were normal, but liver transaminases were elevated (ALT—608 U/l (10–49), AST—1079 U/l (0–34)). Creatine kinase values were also elevated—206 U/L (1–170), creatine kinase MB fraction (CK-MB)—123.9 U/l (0–25), and troponin—1.29 ng/mL (0.2–0.32). Deviations were found in the coagulation status with prothrombin activity 42.8% (70–130), INR—1.76 (0.9–1.15), aPTT—64.2 sec. (25.4–36.9), aPTT ratio—2.21 (0.88–1.28), and D-dimers—36.8 mg/L (<0.232).

Given the history for an acute infectious disease, a rapid antigen test for COVID-19, influenza A, and influenza B was performed upon hospitalization, which was positive for influenza A. A chest X-ray was performed, which did not reveal any areas of consolidation in the lungs, indicating inflammation.

The acute onset of neurological symptoms was a reason to perform a native computed tomography (CT) scan of the brain within the first hour after hospitalization. Hypodense areas in the hypothalamus were identified, the finding being nonspecific and possibly due to an inflammatory process or venous sinus thrombosis.

A contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed due to the insufficient informativeness of CT (**Fig. 1**). It was found that there was no blood flow in the main intracranial arterial vessels, no venous blood flow, pathological signal in the thalamus and brainstem as

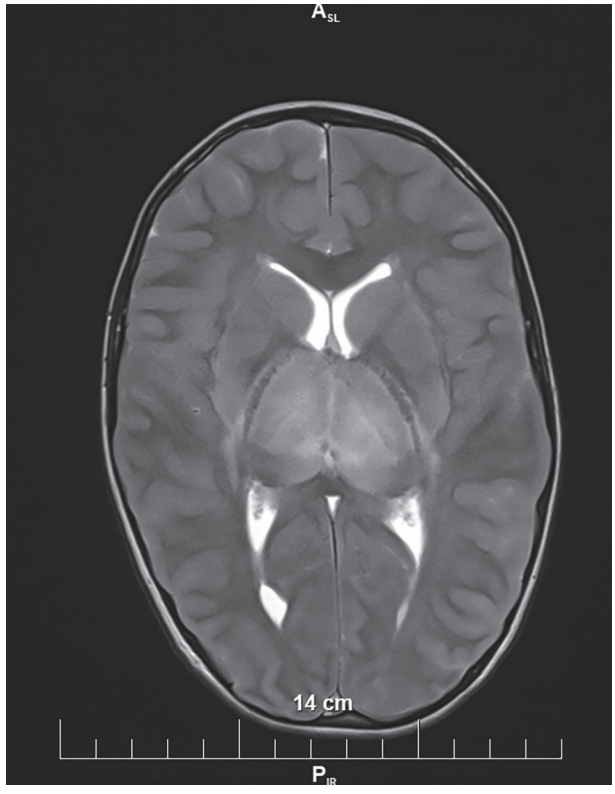


Fig. 1. Brain MRI.

seen in edema due to encephalitis or acute necrotizing encephalopathy, reduced cisterns and cerebrospinal fluid spaces. The changes corresponded to brain death as a result of encephalitis or acute necrotizing encephalopathy. These findings were established four hours after hospitalization.

ter an initial slight decrease in ALT values, there was a progressive increase in liver transaminases, LDH, creatine kinase and CK-MB, urea and creatinine. The deviations in the listed indicators speak in favor of multiple organ failure. Their values in dynamics are presented in **Table 1**.

Table 1. Dynamic changes in lab test results during the hospital stay.

Indicator	Reference Values	On Admission	3 Hours After Admission	Day 2	Day 3
Platelets (x10^{12}/L)	140–440	108	111	86	23
ALT (U/L)	10–49	608	561.2	740	2047
AST (U/L)	0–34	1079	1215.2	1869	4884
Creatinine (μmol/L)	18–62	87	109	119	121
Urea (mmol/L)	3.2–8.2	8.78	10.1	19.35	17.35
LDH (U/L)	208–378	2795	3441	4448	7171
Creatine kinase (U/L)	1–170	-	206	613	2302
CK-MB (U/L)	0–25	-	123.9	107	124
Troponin (cTnI, ng/mL)	0.2–0.32	-	1.29	16	55.2

A PCR result was obtained from a nasopharyngeal swab within 16 hours of admission to PICU, which confirmed infection with influenza A, subtype H1N1/2009, with a high viral load.

A lumbar puncture was not performed due to the pronounced cerebral edema and the risk of tonsillar herniation, and the proven influenza infection and the brain MRI data were sufficient to confirm the diagnosis of ***influenza A (H1N1) associated acute necrotizing encephalopathy.***

In the following days, the patient remained in a critical condition, with no improvement in neurological status and permanently areactive pupils. No stem reflexes were observed. Electroencephalography was performed, which showed no bioelectrical activity in the brain. On the third day of hospitalization, elevated blood glucose values up to 23 mmol/L were recorded, which necessitated intravenous administration of fast-acting insulin for several days, after which glucose levels normalized. Platelet values progressively decreased to 23x10^{9}/L, which necessitated multiple transfusions of platelet concentrate. Coagulation status indicators also worsened, for which plasma transfusions were performed. After an initial slight decrease in ALT values, there was a progressive increase in liver transaminases, LDH, creatine kinase and CK-MB, urea and creatinine. The deviations in the listed indicators speak in favor of multiple organ failure. Their values in dynamics are presented in **Table 1**.

The patient's initial treatment included empirical antibiotic therapy with ceftriaxone—100 mg/kg/day, anti-edema therapy with mannitol 10%—10 mL/kg/day and dexamethasone 0.5 mg/kg/day. Because of the coagulation disorders, administration of etamsylate 30 mg/kg/day and vitamin K1—5 mg/day, was started. Due to the increased liver function tests, administration of ademetionine was started at a dose of 10 mg/kg/day. Additionally, transfusions of bioproducts and fluid replacement were performed. After establishing brain death in the patient, supportive therapy and IMV were continued. Acute necrotizing encephalopathy and multiple organ failure led to a fatal outcome, despite the timely measures taken.

DISCUSSION

Influenza is a common respiratory infection caused by influenza virus which is RNA virus of the Orthomyxovirideae family . There are three main types of influenza virus—A, B and C. The structure of the virus includes the surface proteins hemagglutinin (HA) and neuraminidase (NA), as well as a viral matrix (1). Based on the different structures of the surface proteins HA and NA numerous subtypes such as H1N1, H1N3, H5N1, etc. are distinguished.

The influenza virus is characterized by frequent spontaneous mutations (antigenic drift), which lead to small changes in HA. Larger changes in segments of the RNA molecule are called antigenic shift (2). This type of mutation leads to the emergence of new virus strains unknown to the immune system. Their mass spread among the population can lead to an influenza pandemic (6). Type A viruses circulate both among humans and some animals (birds, pigs). One of the subtypes of influenza A, H1N1, also known as swine flu, caused a serious pandemic in 2009 (6).

The influenza virus is spread by airborne droplets, with children considered the main carriers (7). Approximately 10% of the adult population and 20% of the child population are infected with influenza each year (2). Studies show that children have a higher viral load and shed the virus for a longer period of time (4). Therefore, the use of influenza vaccine in children, which reduces the transmission of the virus, is of particular importance for reducing the incidence of influenza in the community (8).

The clinical presentation varies from asymptomatic course or mild respiratory infection to multiorgan failure (2). After an incubation period of 24–48 hours, symptoms such as fever, cough, headache, joint and muscle pain, and general weakness develop. Gastrointestinal symptoms—abdominal pain, vomiting, and diarrhea—can be observed less frequently and mainly in children (7). The infection is more severe in certain risk groups—children under 2 years of age, adults over 65 years of age, immunocompromised, and patients with concomitant chronic diseases (2). The presented patient had no known underlying diseases. The most common complications of influenza infection in children are bacterial pneumonia with the main causes being *Streptococcus pneumoniae* and *Staphylococcus aureus*, acute otitis media, exacerbation of bronchial asthma, Guillain-Barre syndrome, rhabdomyolysis, pericarditis and myocarditis, and encephalitis/encephalopathy (6,7). In 90% of cases, influenza encephalitis occurs in children under 5 years of age (7).

With regard to neurological involvement by influenza virus, it is known that different strains have variable tropism towards nervous tissue (9). Although rare, neurological manifestations occur significantly more frequently in the pediatric population, with children under 2 years of age being a particularly high-risk group (10). The clinical presentation of neurological involvement is variable, and impaired consciousness, seizures, acute necrotizing encephalopathy (ANE), Reye's syndrome, transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barre syndrome can be observed (9). In some cases, patients recover completely, while in others, permanent neurological damage occurs (9). In the most unfavorable cases with the development of ANE, the clinical course can be fulminant with rapid development of severe cerebral edema and lethal outcome (11). The H1N1 subtype of influenza A is characterized by a pronounced neurotropism in childhood, which was observed during the last pandemic in 2009 (9,10). The interval from the first symptoms of infection such as fever to the appearance of neurological symptoms is usually short—24 to 48 hours (12). The various forms of neurological involvement in influenza are united under the general name influenza-associated encephalitis/encephalopathy (11). New scientific data link this susceptibility to a genetic predisposition in some people. The RANBP2-gene is associated with an increased risk of developing ANE in seasonal influenza infections (11). It is also known that genetic variants in different components of the immune response (proinflammatory cytokines, the complement system, HLA alleles) are related to the different susceptibility of each organism to the H1N1 subtype of the influenza virus (13).

In the presented patient, the clinical picture unfolded fulminantly, within less than 24 hours from the first symptoms to the establishment of brain death. Leading in the clinical picture was the neurological involvement with status seizure, and after the seizure was stopped, consciousness remained impaired and rapidly worsened to GCS (Glasgow Coma Scale) 3/15 points. A genetic examination was proposed within the framework of an international study, which was refused by the parents.

There are several methods for diagnosing influenza infection. The fastest and most readily available method is rapid antigen test that detects influenza A and B in nasopharyngeal swab. In routine practice, serological tests are used to detect IgM antibodies against the influenza virus. The recommended method for detecting infection is reverse-transcription PCR (RT-PCR) testing of nasopharyngeal swab

(12). In the presented case, the diagnosis was made using a combined rapid antigen test for influenza A, influenza B, and COVID-19 and confirmed by PCR of nasopharyngeal swab.

There is specific treatment for influenza with medications such as rimantadine, amantadine, oseltamivir, and zanamivir. Oseltamivir and zanamivir are more commonly used. They are neuraminidase inhibitors and are suitable for the treatment of influenza A and B. Their use is highly recommended for the indicated risk groups with the treatment being more effective when started in the first days of the disease. Resistance of some influenza strains to antiviral therapy is observed. In these cases, the combination of two drugs with different mechanisms of action is possible. The H1N1 subtype is often resistant to neuraminidase inhibitors (6). The effectiveness of anti-influenza therapy in terms of neurological involvement and permanent neurological consequences has not been confirmed (9,10). The use of corticosteroids and intravenous immunoglobulin is also of uncertain effectiveness (9). According to some authors, during an influenza pandemic, in children with neurological symptoms, it is appropriate to empirically start treatment with oseltamivir even before confirmation of influenza infection (10,12). The patient was not started on oseltamivir treatment because the drug is hepatotoxic, and elevated liver transaminases were detected from the initial tests. The initial therapy was symptomatic and pathogenetic, and after confirmation of brain death—supportive therapy and IMV.

Influenza infection is vaccine-preventable. Vaccination is particularly recommended for risk groups. The effectiveness of vaccines can vary from 10–20% to 60% depending on its specificity against the circulating strain (3). In Bulgaria, an inactivated influenza vaccine is administered, with the administration period being from October to March. The administration is suitable for adults and children over 6 months of age. For children over 24 months of age, a live attenuated vaccine for nasal administration can also be used. Vaccination against influenza reduces the risk of severe course and complications of the infection. According to literature data, nearly 80% of cases with a fatal outcome in children with influenza are observed in unvaccinated patients (4). The presented patient was not vaccinated against influenza.

The presented clinical case demonstrates one of the rare, but unfortunately fatal complications of influenza infection—ANE. The interval between the first symptoms of viral infection and coma with imaging signs of ANE was less than 24 hours. The history of acute infection with high fever (febris continua), repeated vomiting, seizure and coma, as well as the initial laboratory data of metabolic acidosis, elevated liver transaminases and coagulation disorders, are grounds to discuss Reye's syndrome in the course of acute influenza A infection in the differential diagnosis. Reye's syndrome is defined as an acute non-inflammatory encephalopathy with pronounced cerebral edema, accompanied by liver failure or fatty infiltration of the liver (14). It mainly affects children aged 5 to 14 years (15). The etiology of the disease has not been clarified. It is often preceded by a viral infection, with influenza being among the most common ones (16). There is convincing evidence of the association of Reye's syndrome with salicylates, which is why aspirin is contraindicated in children (16). The clinical picture begins with symptoms of a viral infection, followed by persistent vomiting, impaired consciousness, seizures, coma and often fatal outcome. Laboratory tests demonstrate hypoglycemia, elevated liver transaminases, impaired coagulation status, metabolic acidosis. The examination of cerebrospinal fluid (CSF) is of diagnostic importance, which shows a leukocyte count <10 cells/mL. Imaging of the brain shows cerebral edema, but without inflammatory changes (15,16).

Reye's syndrome was ruled out in the first hours after hospitalization due to the fulminant course of the disease, the initial slight decrease in liver transaminase values, the lack of hypoglycemia on admission, and the inflammatory changes in the brain seen from the imaging studies performed.

CONCLUSION

Although often considered a mild seasonal infection, influenza can be extremely severe, fulminant, with multiple complications and fatal outcome. Influenza vaccine can be administered to children over 6 months of age, thereby protecting the at-risk pediatric population from complications and fulminant course of the viral infection.

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