Therapeutics, Pharmacology and Clinical Toxicology
Vol XVIII, Number 1, March 2014
Pages: 29-32

CASE REPORT

SEVERE OUTCOME OF INFLUENZA A H1N1 RHOMBENCEPHALITIS IN A 6-YEAR-OLD CHILD CASE REPORT

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Abstract. Introduction: Influenza infection is extremely common, but despite being usually self-limited, the frequent occurrence of epidemics entails a considerable economic burden. Influenza-associated encephalopathy/encephalitis is relatively rare, but carries significant morbidity and mortality. Case report: We report the case of a 6-year-old girl admitted to the intensive care unit of the National Institute of Infectious Diseases "Prof. Dr. Matei Balș" with acute rhombencephalitis following influenza A H1N1 infection. The child survived but with severe neurological sequelae. Conclusions: Improving primary health care assistance from the point of view of prophylaxis through vaccination programs and improving patient management from the first signs of illness can lead to reducing the number of illnesses, but also to reducing the number of severe or complicated cases of influenza virus infection.
Keywords: influenza, child, encephalitis, neurological sequelae, vaccination

Introduction

Influenza (flu) is a contagious acute respiratory illness caused by influenza viruses A and B, manifested primarily with signs and symptoms of the upper and lower respiratory tract. Healthy immunocompetent children usually develop mild, self limited disease, but there are high-risk patients like children less than 1 year, patients with chronic illnesses, immunocompromised, or with poor social status that can develop severe forms of disease or life-threatening complications.[1,2]

Each year, about 20% of children worldwide develop symptomatic influenza A or B infections.[3]

The most frequent complications of influenza virus infection are acute otitis media, laryngotracheitis, bronchitis, bronchiolitis and interstitial pneumonia. Less often, influenza virus infection can lead to myositis, bacterial superinfection (most commonly Stafilococcus aureus and Streptococcus pneumoniae), neurologic complications, myocarditis, pericarditis, but also toxic shock syndrome associated to S. aureus infection.[1]

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Neurological complications associated to influenza include aseptic meningitis, acute cerebellar ataxia, transverse myelitis, Guillain-Barre syndrome, acute necrotizing encephalitis, acute disseminated encephalomyelitis, encephalopathy, febrile seizures, acute mental status changes. [1].

In the last two decades, in Japan, there was a significant increase in the number of cases of encephalopathy and encephalitis associated to influenza infection, most predominantly seen in children less than 5 years of age.[4]. An important number of these cases were followed by death or severe neurological sequelae. [5]

The first cases of influenza A H1N1 pandemic virus infections associated with neurological complications were reported by CDC (Centers for Disease Control and Prevention) in 2009, 24th of July. The 4 patients were from Texas and between 7 and 17 years of age. Influenza A H1N1 virus was detected from the nasopharyngeal swab, but not from the corticospinal fluid (CSF). [5]

CDC recommends rapid antigen testing for evaluating clinical suspicion of influenza infection, especially in a respiratory illness outbreak. Most of the rapid tests have high specificity (90-95%), but sensitivity varies a lot from 10% to 80% (compared to viral culture or RT-PCR). [6]

http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm)

The confirmation of an influenza infection can be done either on viral culture or RT-PCR.

Case report

We report the case of a 6-year-old-girl from a rural area, transferred from a county hospital to our intensive care unit on 12th of March 2014 with the clinical suspicion of acute encephalitis.

The onset of the disease was 4 days before the admission to our clinic with high fever, vertigo and vomiting (4-5 episodes/day). She was administered antipyretics by her family, without consulting their family physician. The day before admission to hospital she developed extreme agitation, visual hallucinations and then seizures.

Her personal and family medical histories were not significant, she was vaccinated according to our national schedule, but she was not vaccinated against influenza virus. In her family's recent history all members presented respiratory symptoms without consulting their family physician.

On admission the child was comatose, with a GCS of 5-6/15, afebrile, pale, without cutaneous eruptions, with signs of dehydration, hypotrophy (weight=17 kg), with cold extremities, with a heart rate of 120 beats per minute, a blood pressure of 120/60 mmHg, a respiratory rate of 40 per minute. Oxygen saturation measured by pulse oximetry was 90% while breathing ambient air, with bilateral pulmonary rales. Her abdomen showed no signs of peritoneal irritation; she had acute urinary retention and diarrhea. The child was in a decorticate posture, with flexion of the upper limbs and hyperextension of the lower limbs.

After assessing her extremely severe condition by an ICU physician, the child was intubated and mechanically ventilated under sedation with midazolam.

A neurologic examination was obtained after intubation and sedation which showed: pupils on the midline, of 2 mm diameter with poor reactivity, deep tendon reflexes were absent, slight movement of right shoulder to painful stimulus.

Laboratory blood tests showed inflammatory syndrome (slightly elevated white blood cell count, a procalcitonin of 20.4 ng/ml), hemoconcentration (due to dehydration), Hemoglobin=16 mg/dl, Ht=48%, blood urea = 91,5 mg/dl, moderate elevated transaminase level (AST/TGP=80 U/l; ALT/TGO=130 U/l), hypopoteinemia (5,2g/dl) with hypoalbuminemia (2,93g/dl,), LDH = 1226 U/L; CK=577 U/l. Imunogramme: IgG=2,12g/l, (normal value for age: IgG=6-15g/l); IgA=8,69, (normal value for age: IgA=0,35-2,4g/l); IgM=17,7g/l (normal value for age IgM=0,4-2,5g/l)

Rapid antigen testing for respiratory viruses using MariPOC test was positive for Influenza A virus from a nasopharyngeal sample. A confirmation test using **RT-PCR** from a nasopharyngeal sample was possible which tested positive for **influenza A H1N1- 2009 virus.**

A chest x- ray revealed bilateral bronchopneumonia.

Emergency cerebral MRI was performed and showed:

- T2 and FLAIR signal hyperintensity patches, with slightly T1 signal hypointensity, with infracentimetric restriction areas and progressive, intense, heterogeneous contrast enhancement areas localized in medulla, pons, midbrain, thalamus, posterior lenticular nuclei, supranuclear white matter; these lesions don't have a homogenous T2 signal, containing almost fluid T2 signal in the anterior part of the medulla, retro pyramidal, posterior internal capsule.
- T2 and FLAIR signal hyperintensity spots and semi lunar area, without restriction of diffusion, without gadolinium contrast, disseminated in the white hemispheric matter, predominantly sub cortical, especially at the genu of corpus callosum.
- normal symmetric ventricular system
- midline structures in normal position
- angiography of the intracranial veins and dural sinuses showed no abnormalities.

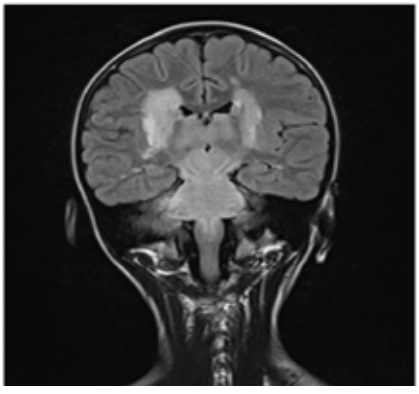

Figure 1. MRI cerebral showed contrast inhancement areas localized in medulla, pons, midbrain, thalamus, posterior lenticular nuclei, supranuclear white matter

Brain MRI and clinical presentation made a clear diagnosis of Acute Rhombencephalitis with upper extension to the sub cortical areas.

Oseltamivir (10 days through nasogastic tube), IV Acyclovir (until laboratory confirmation of etiology), IV solu-Medrol pulse-therapy (3 days) , IV mannitol and IV human immunoglobulins therapy was initiated. Broad spectrum antibiotics were also administered due to bronchopneumonia (meropenem and linezolid), and solu-medrol

therapy was continued with IV dexametazone in progressively descendent doses, under gastric protection with IV H2 receptor inhibitor and proton pump inhibitor.

Due to clinical and biological evolution with severe thrombocytopenia (21.000/mm^3), anemia (Hb 7,4g/dl) and hemorrhagiparous syndrome (blood through the nasogastric tube and macroscopic hematuria) administration of blood products was initiated (platelet concentrates, red blood cells, fresh frozen plasma)

The EEG showed beta rhythm, with symmetric hypo voltage. Hemoculture and nasal/pharyngeal cultures came back negative.

Serology testing was negative for HIV, Herpes simplex 1+2, Adenovirus, Coxsackie, Echovirus, Parainfluenzae viruses, Ebstein-Barr virus, Citomegalovirus. Serology for Mycoplasma p., Chlamydophila p., Borrelia burgdorferi, Yersinia spp were also performed and were negative.

After 14 days of mechanical ventilation (10 days in CPAP system) the patient was in a severe state, with hypotrophy, muscular atrophy, she had spontaneous respiration, cough reflex, pulmonary rales and rhonchi with periods of oxygen desaturation which necessitated oxygen therapy, a heart rate of 100 beats per minute, blood pressure of 100/70 mmHg, gastric tolerance through nasogastric tube, normal stool, urinary incontinence.

Neurologic examination revealed spontaneous opening of the eyes, lack of visual following or fixation, no execution of verbal commands, cranial nerve III paresis, pupils with anisocoria (left pupil>right pupil), mydriasis, diminished pupillary light reflex. Fundoscopic exam showed thin vessels with normal emergence. Spasticity was present with severe bilateral muscle contractures of pyramidal-extrapyramidal type, predominantly on the left side, brisk deep tendon reflexes, no plantar clonus, bilateral Babinski sign. The patient had suction automatism and no swallowing reflex. Nociceptive stimulation led to extension of the lower limbs.

The second brain MRI obtained after 20 days of hospitalization showed:

- extension of the T2 and FLAIR hiperintensity signal areas into the white matter of the hemispheres (semi-oval areas), in the parietal regions
- T2 and FLAIR hyperintensity signal bands located periventricular (lateral ventricles)
- moderate dilatation of ventricles V1, V2, V3,V4
- moderate enlargement of cortical sulci, especially of the sylvian fissure

The overall conclusion of the second MRI as compared to the first examination was the extension of the lesions into the white matter of the hemispheres, most probably due to a demyelinating process, and the development of diffuse cortical atrophy.

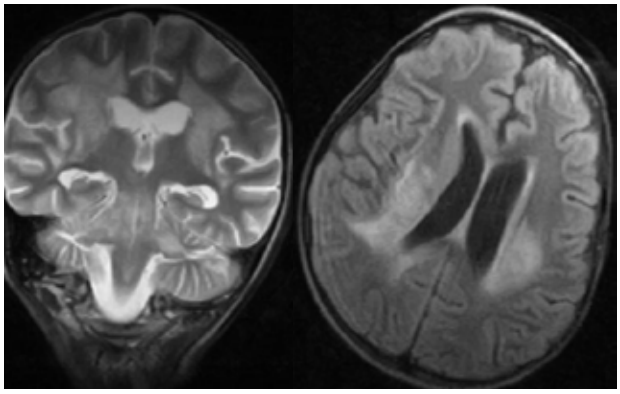

Figure 2. Extension of T2 and FLAIR hiperintensity signal areas into the white matter of the hemispheres in the parietal regions. Moderate dilatation of ventricles V1, V2, V3, V4

The patient was transferred to a medical rehabilitation clinic for children with neuromotor disabilities, and after that to a centre for children with severe motor handicap because her family could not provide adequate care and support.

Discussion

In our case report, the possible risk factors that we could identify for such a severe neurological outcome were malnutrition, poor social status and lack of primary care assistance.

Although the child's illness started 4-5 days before admission to hospital, her family approached medical assistance only after the child have had repeated seizures and became comatose.

Rapid antigen testing for respiratory viruses from a nasopharyngeal swab and RT-PCR confirmation from the same sample made an early (24 hours) and accurate diagnosis of infection with the pandemic strain of influenza A H1N1-2009 virus

Brain MRI evaluation was performed on admission and showed extensive, severe and early involvement of the neurologic system (medulla, pons, midbrain, thalamus, lenticular nuclei, supranuclear white matter) with influenza A H1N1 infection.

The treatment administered saved the child's life with the cost of severe neurological sequelae. Neuromotor disability required institutionalization of the patient in a specialized centre.

Having in mind the high rate of morbidity and mortality of influenza infection in the poor social status population, it is necessary to develop a medical strategy to vaccinate this high risk population against influenza infection.

Conclusions

Influenza infection is extremely common, but despite being usually benign and self-limited, the frequent occurrence of epidemics entails a considerable economic burden.[7]

The term „influenza-associated encephalopathy/encephalitis" (IAEE) is used because direct evidence of influenza virus in CSF is rarely demonstrated. In our case, the only noticeably finding was a positive PCR for influenza A from a nasopharyngeal swab;[8]

Acute encephalitis is one of the most severe influenza complications, responsible for high rates of mortality and morbidity with potentially severe neurological sequelae.[2]

Primary medical assistance can help diminish the economical burden of influenza infections through highlighting the importance of prevention methods like annual vaccination and by providing adequate medical care from the early stages of disease.

References

1. Munoz FM, Mallory GB, Eduards MS. Clinical features and diagnosis of seasonal influenza in children, *UpToDate,* **2013.**

2. Pieter LA, Fraaij Heikkinen T. Seasonal influenza: The burden of diseases in children, *Vaccine,* **August 2011.**

3. Pandemic influenza:a priority for the neurological community, *The Lancet Neurology,* **2009-10-01, vol 8, Issue 10, pages 869-869.**

4. Thorner AR, Hirsch MS, Baron EL. Clinical manifestations and diagnosis of pandemic H1N1 influenza ("swine influenza"), *UpToDate,* **2014.**

5. Henry J, Smeyne RJ, Jang H. Parkinsonism and neurological manifestation of influenza throughout the 20th and 21st centuries, *Rev. Parkinsonism and Related Disorders,* **June 2010.**

6. Nicholson KG, Wood JM. Influenza, *The Lancet,* **Nov. 2003, vol.362, Issue 9397,pag 1733-45.**

7. Fluss J, Ferey S. Mild influenza-associated encephalopathy/encephalitis with a reversible splenial lesion in a Caucasian child with additional cerebellar features, *Official Journal of the European Paediatric Neurology Society,* **2010.**

8. Hussain MI, Ming CT, Yin LL. Neurologic manifestations and complications of pandemic influenza AH1N1 in Malaysian children: What have we learnt from the ordeal?; *Brain and Development;* **March 2014.**