Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: June 30, 2024

Citation: Badía F, Zurmendi EA, et al., 2024. Blindness Due to Severe Influenza B Infection: Case Report, Medical Research Archives, [online] 12(6). https://doi.org/10.18103/mra.v12i6.5311

DOI
https://doi.org/10.18103/mra.v12i6.5311

ISSN: 2375-1924

CASE REPORT

Blindness Due to Severe Influenza B Infection: Case Report

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ABSTRACT

Introduction: Influenza is an acute febrile infectious disease with respiratory manifestations, in a variable degree of severity, and a seasonal epidemic distribution. In healthy children, it usually presents as mild and self-limiting, but it can evolve into severe forms with significant morbidity and mortality. These include neurological manifestations such as influenza-associated encephalopathy and acute necrotizing encephalopathy. Objective: To report case of a previously healthy child who developed severe pneumonia due to influenza B and subsequent blindness associated with ANE. Case Report: previously healthy, five years old male, not vaccinated for seasonal influenza, was admitted with four days of fever and respiratory symptoms. Initial evaluation reveled respiratory impair and he was admitted to the critical care unit for respiratory distress syndrome. Influenza B antigen was detected in upper respiratory swab by immunochromatography. Initial laboratory: White blood count; 20300/L, C- protein reaction: 300mg/L, AST 176 U/L, LDH 2549 U/L. He required 11 days of invasive respiratory support due to severe hypoxemia. When support was withdrawn, severe bilateral visual impairment was observed without other neurological manifestations. Magnetic Resonance Image revels bilateral temporo-occipital cortico-subcortical lesions and in both cerebellar hemispheres, with a lacunar image in the left thalamus; no involvement of the optic nerve was observed. Close watching was workup without pharmacologic intervention. He starts recovering vision 5 month later. Discussion: influenza-associated encephalopathy and acute necrotizing encephalopathy are recognized as rare inflammatory complications associated with influenza and other virus infections. Cases of blindness associated with necrotizing encephalopathy are reported. Treatment with corticosteroids, intravenous immunoglobulin, hypothermia, and plasmapheresis are propose; roll of oseltamivir remain unknown. Tocilizumab represents a potentially rational approach to ANE management. Conclusion: Influenza infection could be severe, including neurological complication. Vaccination is the only primary prevention tool.

Introduction:

Influenza is an acute febrile infectious disease with respiratory manifestations, in a variable degree of severity, and a seasonal epidemic distribution.

In healthy children, it usually presents as mild and self-limiting, but it can evolve into severe forms with significant morbidity and mortality [1].

The neurological manifestations include influenza-associated encephalopathy (IAE) and acute necrotizing encephalopathy (ANE) [1].

First describe in 1979, ANE, was define as a novel disease entity in 1995, by a collaborating group, for the peculiar clinical, radiological, and pathogenic features. The most striking characteristic of ANE is the multifocal brain lesions. They propose that a systemic inflammatory response trigger by virus infection may be involved in the pathogenesis of this disease [2].

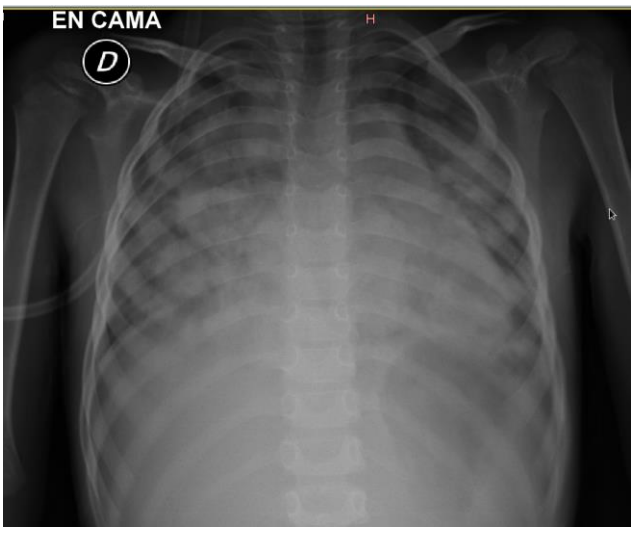
Most recent case definition describe ANE as: 1) acute influenza infection 2) Flu symptoms follow by onset of seizers, altered or loss of consciousness, altered mental status and/or coma 3) Cerebrospinal fluid (CF) assay with normal white cell count (WCC) and, normal or elevated proteins 4) TC scan or magnetic resonance imaging (MRI) with multiple, symmetric lesions in thalamus, brainstem, internal capsule, putamen and others 5) elevated transaminases, hyperammonemia, hypoglycemia, and 6) Exclusion of other causes of brain damage. For IAE case definition include: 1) acute influenza infection/detection in respiratory swabs 2) neurological symptoms: seizures, altered or loss of consciousness, altered mental status, 3) CSF proteins normal or elevate 4) neuroimaging: diffuse brain edema, and/or bleeding, bilateral lessons thalamus, others. 5) normal EEG [3].

During influenza epidemic in Japan between 1998-1999, 148 cases of encephalitis/encephalopathy were reported. Mayor clinic signs were, altered or loss of consciousness, seizures, motor palsy or sensory loss observed in 2,7% of cases [4].

In this case report we communicate a previously healthy child who developed severe pneumonia due to influenza B and subsequent blindness associated with ANE.

Case Report:

Previously healthy, five years old males, not vaccinated for seasonal influenza, was admitted to the hospital with four days of fever and respiratory symptoms. Initial evaluation reveled respiratory impair and he was admitted to the critical care unit for respiratory distress syndrome. Influenza B antigen was detected in upper respiratory swab, by immunochromatography. In the initial laboratory assay, he has white blood count (WBC) of 20300/L, C- protein reaction (CPR) of 300mg/L, aspartate transferase (AST) 176 U/L, lactate dehydrogenase (LDH) 2549 U/L. Chest radiography with findings of respiratory distress is shown in figure 1.



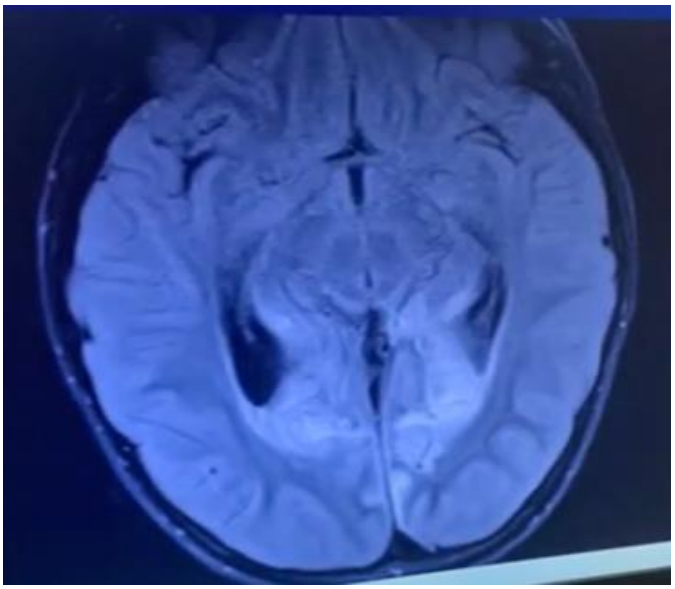
He required 11 days of invasive respiratory support due to severe hypoxemia.

When support was withdrawn, severe bilateral visual impairment was observed without other neurological manifestations.

The ophthalmological exam reveal a central visual loss. He has a right lateralized gaze, with deficit in leftward version and elevation, he doesn`t fix or follow gaze, neither persive light or identify light direction, nor differentiate light from darkness. The direct and consensual photo motor reflex was

present, he has no visual-motor coordination. The funduscopic examination was unremarkable. The visual evoked potential test was normal.

Magnetic resonance imagen (MRI) (figure 2) reveals bilateral temporo-occipital cortico-subcortical lesions and in both cerebellar hemispheres, with a lacunar image in the left thalamus; no involvement of the optic nerve was observed.



Considering clinical presentation and neuroimaging features, diagnose of ANE was propose.

Strict monitorization was performed without pharmacologic intervention because we considered out of opportunity by the length of evolution.

At the time of discharge, he has a complete recover of respiratory symptoms, but visual impairment persists. He started recovering vision 5 month later.

Discussion:

IAE and ANE are recognized as rare inflammatory complications associated with influenza and other virus infections [1, 2, 5].

First case report 1979, describe 50 patients with acute encephalopathy and a peculiar finding on computed tomography. Almost all patients have respiratory symptoms previous days, and Influenza A was most frequently virus detected. ANE seems to predominant in Oriental children, but cases from United Kingdom and United States were reported. Age of patients range between 5 month and 11 years old, previous healthy, without predominance of sex. First sign of brain dysfunction appears 0.5 – 3 days after onset of respiratory symptoms, convulsion in 40% of the patients, impairment of consciousness (somnolence or delirium) in 28% and vomiting in 20%. Blood examinations during the acute period reveal various abnormal findings, predominating elevation of serum aminotransferases and lactic dehydrogenase. Their values highly vary from case to case, and the degree of elevation appears to be correlated, in some extent, with the severity of the disease. Other findings were elevation of creatine kinase, urea nitrogen and amylase. In severe cases, hematological studies reveal changes resembling disseminated intravascular coagulation. An increase in CSF protein of variable degrees was noted in two-thirds of the patients and is characteristic of ANE [2]. These were the bases for case definition.

Our patient has a confirmed Influenza B infection, neurological manifestation with characteristic abnormalities in MRI, and elevated biomarkers as aminotransferases and lactic dehydrogenase. He was admitted at 4th day of symptoms with respiratory failure that required prompt AVM for 11 days, and neurologic manifestations were advise when support was withdraw. These findings agree with diagnosis criteria for ANE, and blindness the consequence of brain damage.

Since first descripted, multiple case reports have been published, and contribute to knowledge of this novel disease [3, 5, 6, 7, 8, 9, 10].

In a descriptive study examining cases of encephalopathy associated with Influenza, reported to the National Epidemiological Surveillance of Infectious Diseases of Japan, between 2010 and 2015, they estimated a median incidence rate in children of 2.83 cases/1million

inhabit., and 0.19/1million in adults; 74% of cases were < 18 y, and mayor frequency in children was seen between 5 and 12 years old [7].

Research in population <18y hospitalized for neurological complication associated to Influenza, describe a median age of cases between 3,7 and 4 y (range 9 m -12 y) [3, 6, 9], with mayor frequency in children < 5 years old (OR 4,6; p <0,001) [9].

Both Influenza A and B are associated to neurological manifestations. Influenza A seems to be more frequent, although ANE was most associated to Influenza B in a single center study [3, 8] Seizers and conscious delay are described to be the most frequent symptoms [2, 3, 5, 6, 7, 8]. The prevalence of influenza-associated neurological complications was 16.9% in a tertiary care center review, seizers represent 58,2% and encephalitis/encephalopathy 41,8% [10]. In a study cohort of children hospitalized for Influenza B, 10,8% (n=131, IC del 95 %: 9,1-12,6 %), have a neurological complication [9].

Blindness associated with ANE are reported. First publish of blindness associated to Influenza disease, date in from 1922; 17-year-old female, was admitted three weeks after influenza symptoms, as they recognize she was blind, she gradually recovers in 3 or 4 weeks without any pharmacological treatment [11]. More recently in 2020, 4-year-old toddler, healthy girl, not vaccinated for seasonal influenza, with 6 days of fever and respiratory symptoms, in which Influenza B was detected in respiratory swabs by RT-PCR, was admitted to critical care unit for respiratory frailer and seizures. CF was unremarkable and in MR bilateral affection of putamen and thalamus was observed. When respiratory support was withdrawn, they recognize she was blind without no other seculars. Methylprednisolone, IGIV and oseltamivir were administrated. At hospital discharge 16 days after she was still blind and recovered subjective vision one month later [12]. This last case report has much similarity with our patient. Visual recovery occurred earlier, and strong anti-inflammatory treatment was work up.

The pathogenic processes that lead to acute brain dysfunction in ANE remain poorly defined. It is suggested that an infection-triggered brain injury is neither due to CNS infection nor substantial brain inflammation; rarely viral RNA is detected in CF [7]. Dysregulation of cytokine production (IL6, 8, 10, TNFalpha), appears to be a common feature of ANE [7,10,13]. The finding of elevated cytokine levels, sometimes markedly, raised the possibility that cytokine storm may play a central role in disease pathogenesis. Intra-CNS production of pro-inflammatory cytokines may also occur in some cases; indeed, in one report levels of IL-6 that were over 100-fold greater in the CNS than serum during the acute phase of ANE and 8-fold higher during the late phase. Cytokines are known to affect neuronal function and high levels of CSF proinflammatory cytokines could directly contribute to the neurological damage seen in ANE. Furthermore, patients with lowest maximal level of IL-6 had the best outcomes and dose with over 15,000 pg/mL did not survive, also dysfunction involvement, which is risk factor for poor prognosis, was associated with IL-6 levels 6,000 pg/mL and over. Elevated IL-6 precedes neurological symptoms, and thus may not necessarily be elevated during or after encephalopathy [13, 14, 15].

Given the potential role of proinflammatory cytokines in driving the disease process, corticosteroids or intravenous immunoglobulin, hypothermia, and plasmapheresis, are describe in literature. The roll of oseltamivir in reduce neurological complications and improve the outcome of this patients remain unknown [3, 10]. It is possible that the timing of immunomodulatory therapy may be critical [14], patients who received steroid treatment within 24 h of symptom onset, good outcomes were notice comparing to patients without early steroid intervention. Use of IL-6 Blockade–Tocilizumab represents a potentially rational approach to ANE management and treatment, although no guidelines are available, and more research are needed [10, 15, 16].

Conclusions:

Influenza infection, even in healthy individuals, can lead to severe complications, including neurological issues. Vaccination is the only primary prevention tool, tetra-valent vaccine should be prioritized.

Conflict:

The authors to have no Conflicts of Interest for this publication.

Acknowledgments:

The team extends its gratitude to our colleague, Elizabeth Assandri, who give us encouragement for this publication.

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