

Influenza A-associated acute necrotizing encephalopathy

Encefalopatía necrotizante aguda asociada a influenza A

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What do we know about the subject matter of this study?

Acute Necrotizing Encephalopathy is a rare pathology, with characteristic alterations in neuroimaging, associated with high mortality and significant sequelae. There is no consensus on its treatment, and there is little information on the long-term evolution of these patients.

What does this study contribute to what is already known?

We report the case of a patient diagnosed with Acute Necrotizing Encephalopathy associated with Influenza A virus. Our patient was early managed with immunomodulatory and antiviral therapy, presenting favorable neurological evolution. This management could be considered as a valid treatment alternative.

Abstract

Acute necrotizing encephalopathy of childhood (ANEC) is a rare disease characterized by alteration of consciousness and multiple symmetric brain lesions mainly involving the thalamus. It presents a high mortality rate and severe sequelae. **Objective:** To describe a school-age patient with influenza A-related ANEC with favorable evolution. **Clinical Case:** Six-year-old boy with 3 days history of upper respiratory symptoms and fever (39 °C). One day previous to admission, he presented altered state of consciousness. A lumbar puncture was performed, showing a mild increase of protein level in CSF. MRI showed bilateral foci of symmetric restricted signal in the thalamus, mammillary bodies, periaqueductal gray, ventral tegmentum, hippocampus, and in both external capsules, which was compatible with ANEC. The patient received empirical treatment with methylprednisolone and oseltamivir. Subsequently, a positive result was received for influenza. Considering diagnosis and severity of illness, it was decided to administer immunoglobulin. The patient got better slowly but favorably. At discharge, he still was mildly bradypsychic with decreased visual acuity, spontaneous speech and walking with assistance. At 6 months of follow-up, the patient presented normal speech and gait,

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with persistent visual impairment in the right eye. **Conclusions:** Our patient presented ANEC, whose timely diagnosis and management were associated with a favorable neurological evolution in the long term. Although ANEC is an infrequent pathology, it has very high morbidity and mortality rates, so it is very important to have a high degree of suspicion in order to request a targeted imaging study, search for related infectious causes, and start proper treatment.

Introduction

Acute necrotizing encephalopathy (ANE) is a rare pathology, first described in 1995 by Mizuguchi et al, as a characteristic form of acute encephalopathy. Most cases have been described in Japanese and Taiwanese populations, but more and more have been observed in Western populations¹.

The clinical evolution of ANE is severe and has 3 stages: prodromal, acute encephalopathy, and recovery stage. In the first stage, symptoms include fever, respiratory and gastrointestinal symptoms, shock, and multiple-organ failure. Later, in the second stage, the patients develop encephalopathy, with manifestations of cerebral dysfunction (epileptic seizures in up to 40% of cases). Patients who survive, go to the recovery stage and most of them evolve with neurological sequelae².

In diagnostic images, ANE is characterized by the presence of multiple bilateral thalamic inflammatory lesions, as well as in the putamen, cerebral and cerebellar white matter, and in the brainstem tegmentum². Its physiopathology is not completely clear, and it has been associated with infectious (mainly viral), genetic (RANBP2 and CPTII), and environmental factors³.

To date, most of the reported cases are of Asian origin, with very little pediatric publication in Latin America². In Chile, there are only a few reports in congresses and one pediatric case published in 2010, which was a 7-year-old patient with brain death related to ANE associated with Influenza A virus⁴.

The objective of this report is to describe the case of a schoolchild patient with ANE associated with Influenza A virus, his management, and favorable evolution.

Clinical Case

6-year-old boy, without relevant morbid history, adequate psychomotor development, and up-to-date vaccination schedule.

He presented with a three-day clinical picture, initially with upper respiratory symptoms associated with a fever up to 39°C. On the second day, the patient had signs of weakness and asked reiterative questions. Twenty-four hours before the consultation, the patient

presented a qualitative-quantitative consciousness involvement, without achieving eye-opening, reporting dizziness, and incapacity to walk. He spoke repeatedly, presenting bradypsychia, and was disconnected from his surroundings. In the evaluation at the Emergency Service, the general examinations did not present any alterations. On the third day, the brain CT scan showed mucosal thickening in bilateral maxillary and ethmoid sinuses, with no other findings. Lumbar puncture was performed, obtaining colorless cerebrospinal fluid (CSF), with a slight increase of proteins (49 mg/dl), glycorrhachia 49 mg/dl, without leukocytes or red blood cells. Gram test negative for bacteria. The toxicological study in urine was negative, and the Test pack for Respiratory Syncytial Virus, Adenovirus, Influenza A and B was also negative.

Upon admission to the Critical Care Unit, the patient was unable to open his eyes, partially obeyed verbal orders, felt painful stimuli, and made unintelligible sounds. On neurological examination, he showed pupils equal and reactive to light, decreased visual acuity, and right ptosis, with preserved ocular motility, generalized hypertonia and hyperreflexia, bilateral plantar reflex, bilateral exhaustible clonus, and intention and resting tremor in upper extremities.

Treatment with vancomycin, ceftriaxone, and acyclovir was started, waiting for cultures, due to suspicion of meningoencephalitis, unable to rule out infectious causes. It was performed an electroencephalogram (EEG) with normal results, with no tremor electrical correlation. On the fourth day of the picture, Magnetic Resonance Imaging (MRI) plus Magnetic Resonance Angiography (MRA) of the brain showed bilateral diffusion restriction foci, with symmetrical distribution in the thalamus, mammillary bodies, periaqueductal gray, pontine tegmentum, hippocampus, and in both external capsules, with a hemorrhagic component, and images suggesting vasogenic edema in the hypothalamus, and splenium of the corpus callosum (see figure 1). Spinal cord MRI showed no pathological findings.

The findings of the brain MRI were compatible with ANE, therefore, a CSF study was performed, ruling out active infection, and we decided to add methylprednisolone (30 mg/kg/day for 3 days) and empiric treatment with oseltamivir. It was also requested a

study of free-living amoebae and rabies in CSF and was started antifungal therapy with deoxycholate amphotericin, azithromycin, fluconazole, and rifampicin, which were suspended after 48 hours due to negative reports. Additionally, at 72 hours, samples were collected for CSF, blood and urine cultures, and study for Cytomegalovirus, Epstein Barr virus, Herpes Simplex virus, and Parvovirus, which were all negative, suspending the treatment with vancomycin, ceftriaxone, and acyclovir. It was decided to maintain only oseltamivir for five days due to PCR positive for Influenza A virus.

Within 72 hours of admission, EEG was performed showing generalized diffuse slowing, compatible with his encephalopathy, but without epileptic seizures. The patient never presented respiratory involvement, without needing oxygen or ventilatory support nor did he present sphincter involvement or seizures during his ICU stay.

Regarding nutritional aspects, the patient required progressive feeding through a nasojunal tube from the second day of admission. General examination checks showed no evidence of involvement of other organs. He evolved with significant alteration in bilateral visual acuity, bradypsychia, without clear speech and pyramidal signs. Therefore, on the seventh day of evolution, it was decided to start the second-line treatment, with gammaglobulin 400 mg/kg/day for 5 days.

Finally, the patient completed treatment with methylprednisolone, gammaglobulin, and oseltamivir, maintaining therapy with prednisone (1 mg/kg/day).

He evolved favorably, with changes identified approximately every 48 hours. He was discharged after 17 days of hospitalization, presenting better connection with his surroundings, still with bradypsychia but achieving spontaneous intelligible speech. He was able to feed himself by mouth before discharge. He also showed an alteration in bilateral visual acuity and gross and fine motor skills, gradually decreasing pyramidal symptoms, and achieving walking with support.

In the follow-up, the patient received multidisciplinary rehabilitation, showing progressive recovery of neurological functions. Steroid therapy started with initial dose for 3 months, with gradual suspension afterward, without presenting relapses. After 6 months of evolution, the patient was able to return to formal education, with curricular adjustments. In the last clinical evaluation, his speech was normal, he was beginning to read and write, presented hyperreflexia of the lower extremities, upper limbs dysmetria, and normal gait. In relation to neuroophthalmological aspects, he had a severe decrease in visual acuity of the right eye.

Discussion

ANE is a rare disease, with unknown incidence. In an epidemiologic study from Japan, an incidence of 4% (39 patients) out of 983 pediatric patients with some type of acute encephalopathy was reported⁵. Mortality reports describe up to 30%, and severe neurological sequelae in up to 15% of survivors⁶.

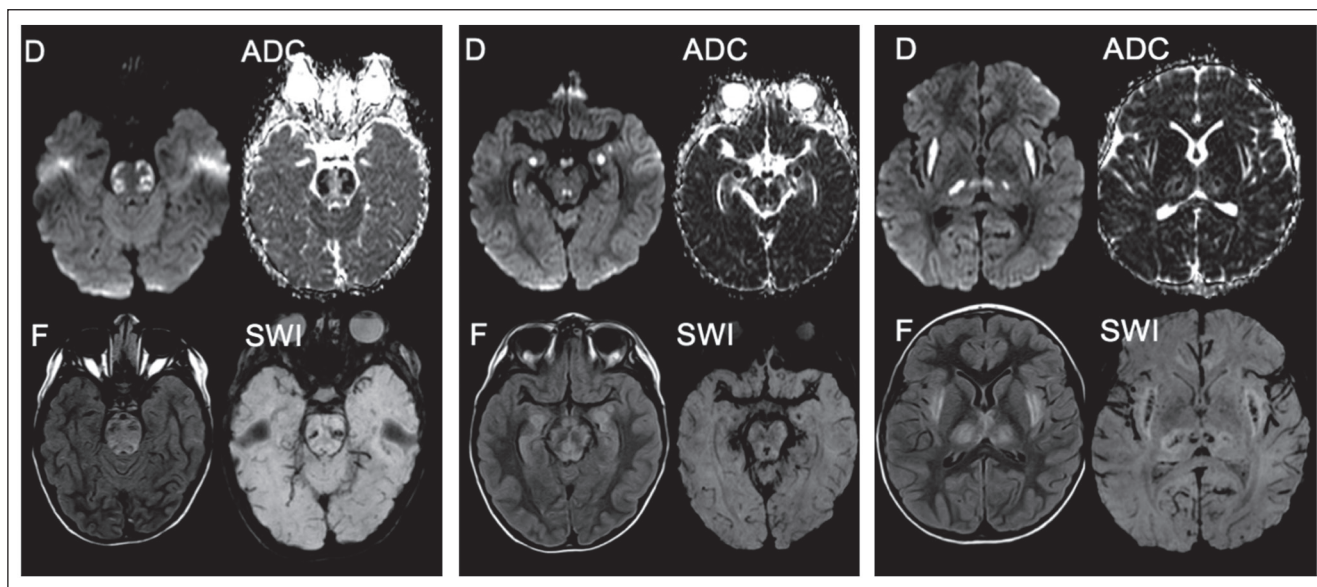


Figure 1. Bilateral diffusion restriction foci, of symmetric thalamic distribution, in mammillary bodies, periaqueductal, pontine tegmentum, hippocampus and in both external capsules. It is associated with a hemorrhagic component in these regions (SWI). The above, associated with hypersignal in F in these regions, including the hypothalamic region and splenium of the corpus callosum, explained by vasogenic edema. D (DWI); ADC (apparent diffusion coefficient); F (FLAIR); SWI (sequences of magnetic susceptibility).

So far, its etiopathogenesis is not clear. Certain studies indicate that in the presence of the virus, a pro-inflammatory cytokine storm is triggered, such as IL-6 and TNF- α ⁷. This produces proteolysis of the blood-brain barrier with increased vascular permeability, which causes cerebral edema, petechial hemorrhage, and necrosis^{8,9}.

In recent years, a familiar and recurrent form of ANE has been established, associated with RANBP2 gene mutations, autosomal dominant inheritance, and incomplete penetrance. This gene encodes the RAN-binding protein 2 of the nuclear pore complex, essential for neuronal function¹⁰. However, cases of recurrence, without alteration of the RANBP2 gene, have been described as those patients with CPTII deficiency, who present a viral infection, develop energy failure, and present a clinical picture of ANE¹¹.

The diagnostic criteria of Mizuguchi et al, include acute encephalopathy after viral febrile illness, with rapid deterioration of consciousness levels; increase of proteins in CSF, without pleocytosis; pathognomonic findings in brain MRI; elevation of aminotransferases without hyperammonemia; ruling out other diseases that explain the picture (such as viral or bacterial meningitis, fulminant hepatitis, Reye's syndrome, etc.)¹².

The most characteristic imaging finding is the symmetrical and bilateral inflammation of the thalamus, which can be associated with lesions in the putamen, cerebral and cerebellar white matter, and in the brainstem tegmentum¹². The classic image of ANE is the *tricolor* or *trilaminar* pattern in the thalamus observed in sequences of apparent diffusion coefficient. The trilaminar appearance is characterized by an internal layer of restriction caused by hemorrhagic necrosis (iso-hyperintensity), followed by an area with restricted diffusion by cytotoxic edema (hypointensity), and an external portion with restriction caused by vasogenic edema (hyperintensity)¹³. Our patient's MRI presented findings consistent with ANE, the symptoms were compatible with acute encephalopathy, and other diseases that would explain the picture was ruled out, in agreement with these criteria.

To date, there is no proven therapy. Reports and studies propose symptomatic management, empirical antiviral therapy (oseltamivir), immunomodulating agents, and hypothermia⁶. However, treatment guidelines have not been described, and there is no consensus on the actual usefulness of these therapies. Some studies have reported that administration of steroids within 24 hours of onset or early stage of the disease would be associated with a better prognosis in people without brainstem involvement¹⁴. However, some reports propose steroid administration at any stage and others have concluded that they would not influence the evolution of the disease¹⁵.

Given the physiopathology of ANE, the use of therapies against the cytokine storm has been proposed, such as the use of IL-6 receptor antagonist (Tocilizumab), administered in early stages of the disease, with good results in short- and long-term prognosis¹⁶. In this case, our patient was treated with corticosteroids and oseltamivir, and later immunoglobulin was added to the therapy, with a slow but favorable response. This management was similar to the one described in a 2006 article, which described the case of a 3-year-old boy without identified trigger, treated with immunoglobulin and methylprednisolone, who evolved with marked improvement of ataxia, spasticity, and dysarthria¹⁷. However, it should be noted that in a study published in 2015, the factors associated with prognosis in children with ANE were analyzed, concluding that the treatment modality did not affect the outcome of these patients (including methylprednisolone and immunoglobulin pulse therapy)¹⁸.

The prognosis of ANE is variable, recovery is slow, and it has been described that less than 10% of patients have a complete recovery, with a mortality rate of 30%, mainly associated with cerebral edema in some reports^{4,15}. The main factor associated with mortality described is the involvement of the brainstem¹⁵. Within the indicators of good prognosis, the following are reported: age under 4 years, mild hyperproteinorrhea, unilateral thalamus involvement, absence of brainstem involvement, complete recovery of neuroimaging lesions, and low-risk ANE severity scale score¹⁸. The presence of shock at admission, age over 4 years, and the identification of brainstem lesions in neuroimaging were significantly associated with poor neurological outcome¹⁸. Although our patient did not meet good prognosis criteria, his evolution was very favorable compared with what was reported in the literature. This could be due to the timely access of neuroimaging and specialists who were able to make an early diagnosis, initiating the therapeutic options available in the first days of the symptoms. However, there is a lack of evidence that allows us to clarify what other factors could have influenced the favorable evolution of our patient.

Conclusions

ANE is a rare pathology of clinical-radiological diagnosis. It is essential to suspect it early, to request the pertinent imaging tests in search of the associated characteristic findings, and to investigate related infectious causes. Its associated morbidity and mortality are very high, and there is no conclusive evidence regarding its treatment. Empirical antiviral therapy and immunomodulators may be proposed as valid treatment alternatives.

There is a need for more studies to guide diagnostic-therapeutic management, however, this case report could be used as an initial coping experience.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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