

Epilepsy secondary to encephalitis due to Epstein Barr virus

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Abstract

Case presentation. This case is about a 44 years old woman with a history of occipital headache, incoherent speech and confused thinking. She initially presented ten points on the Glasgow scale and left hemiparesis. Cranial CT scan reported cerebral edema with right thalamic hypodense lesion and progressive neurological deterioration. The electroencephalogram showed unilateral right hemispheric deceleration. The cerebrospinal fluid study showed hyperproteinuria and a predominantly lymphocyte count of 450 cells with preserved glycorrachia, without the presence of bacteria. **Treatment.** was managed with invasive ventilatory support and antibiotic and antiviral treatment at meningeal doses, in addition to anticonvulsants. Control tomographic findings showed hydrocephalus; a Becker type ventricular shunt was placed. IgM serology was positive for Epstein Barr virus and the viral genome was identified in the cerebrospinal fluid by polymerase chain reaction test. The control brain tomography showed persistent ventriculomegaly and cerebral edema, which led to the diagnosis of encephalitis of viral etiology complicated by epilepsy secondary to a demyelinating structural lesion of the right cerebral hemisphere. **Outcome.** Therapeutic intervention with intravenous immunoglobulin was performed with improvement of the general condition, it was possible to remove the ventricular shunt and pulmonary ventilation ten and 19 days after admission, respectively. The patient is currently in physical therapy with persistence of left hemiparesis, gait disturbances, dysarthria, and controlled convulsive episodes during the last six months.

Keywords

Epilepsy, Brain, Inflammation, Encephalitis.

Resumen

Presentación del caso. Se trata de una mujer de 44 años de edad, con historia de cefalea occipital, lenguaje incoherente y pensamiento confuso. Inicialmente presentaba diez puntos en la escala de Glasgow y una hemiparesia izquierda. La tomografía computarizada de cráneo, reportó edema cerebral con lesión hipodensa talámica derecha y deterioro neurológico progresivo. El electroencefalograma evidenció desaceleración unilateral hemisférica derecha. El estudio del líquido cefalorraquídeo describió hiperproteinorrea y un recuento a predominio linfocitario de 450 células con glucorraquia conservada, sin presencia de bacterias. **Intervención terapéutica.** se manejó con soporte ventilatorio invasivo y con tratamiento antibiótico y antiviral a dosis meníngeas, además de anticonvulsivantes. Los hallazgos tomográficos de control reportaron una hidrocefalia; se colocó una derivación ventricular tipo Becker. La serología IgM resultó positiva para virus de Epstein Barr y se identificó el genoma viral en el líquido cefalorraquídeo, a través de la prueba de reacción en cadena de polimerasa. La tomografía cerebral de control, evidenció la persistencia de la ventriculomegalia y de edema cerebral, lo que generó el diagnóstico de una encefalitis de etiología viral complicada con epilepsia secundaria por una lesión estructural desmielinizante del hemisferio cerebral derecho. **Evolución clínica.** La intervención terapéutica con inmunoglobulina intravenosa generó una mejoría del estado general. Fue posible retirar la derivación ventricular y la ventilación pulmonar diez y 19 días después del ingreso, respectivamente. La paciente se encuentra actualmente en fisioterapia con persistencia de hemiparesia izquierda, alteraciones de la marcha, disartria y episodios convulsivos controlados durante los últimos seis meses.

Palabras clave

Epilepsia, cerebro, inflamación, encefalitis.

Introduction

Encephalitis is an inflammation of the brain parenchyma¹. It can occur due to infectious or autoimmune causes². It is characterized by symptoms such as fever, headache, and behavioral or personality alterations; it

evolves within 24 to 72 hours with changes in the level of conscious awareness and a stiff neck and may trigger seizures and permanent neurological damage with focal neurological deficits, neurological disability³, and may cause death if not diagnosed in a timely assessment^{1,4}.

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Epilepsia secundaria a encefalitis por el virus de Epstein Barr

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Conflict of interests:

The authors declare there are no conflict of interests.

Worldwide, 1.7 to 12.6 cases per 100 000 populations per year were reported to be diagnosed⁴. In the United States of America (USA), an estimated prevalence rate of 13.7/100 000 was identified, describing that the incidence of viral encephalitis probably increased due to improved detection of the disorders and more widespread diagnostic capabilities and stating that viral causes are very common⁵. In low-income countries, regional reports have recorded a low incidence of viral encephalitis, presenting mainly as recurrent outbreaks⁶.

Infection is the most common cause, mainly due to viral pathogens^{2,3}, which account for about 70 % of confirmed cases of encephalitis⁴. The frequency of viral causes varies according to geographic location, seasonal changes, the patient's immune status, as well as the viral genetic mutations over time^{2,4}.

In the USA, the most common causes of viral encephalitis are herpes simplex virus (HSV), West Nile virus and enteroviruses⁴. Varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpes virus types 6 and 7, measles virus, mumps virus, rubella virus, St. Louis virus, Eastern equine virus, Western equine virus, dengue virus, rabies virus⁵ and recently SARS-CoV-2⁷ have been described as the leading agents associated with encephalitis.

In recent years, there has been progress in understanding the clinical and pathobiology of viral encephalitis. However, despite increasing evidence of an underlying inflammatory process, the root cause remains unknown, and targeted therapeutic strategies remain uncertain due to the absence of controlled studies⁸.

Although the clinical characteristics of infectious encephalitis are based on neurological symptomatology^{9,10}, they occur mainly due to inflammation of the brain, even though the exact mechanism that develops them is not understood, among which neurotropic infections that provoke a release of cytokines and lead to cytotoxicity, inflammation, and damage are described. Increased permeability of the blood-brain barrier and perivascular lymphocytic infiltration that can lead to further breakdown of the barrier appear¹¹⁻¹³.

In connection with viral encephalitis, the secondary development of autoantibodies directed to neuronal surface synaptic antigens involves diverse mechanisms¹⁴. These antigens are often located in the limbic system of the brain, and several *in vitro* and *in vivo* models demonstrate the direct pathogenicity of the antibodies¹⁵. However, molecular interactions of antibodies with

viral antigens can lead to complement deposition, antigen internalization, and direct modulation of antigenic target function. Therefore, the precise potential therapeutic intervention differs significantly, depending on the target antigen. However, at present, there is more clarity from immunogenetic associations and B-cell studies¹⁶.

Although, given the fact that fever, focal neurological deficits, and cerebrospinal fluid lymphocytosis remain as diagnostic criteria for encephalitis, from any cause, cases are likely to be underestimated².

Diagnostic confirmation is made by polymerase chain reaction test applied to cerebrospinal fluid, with the detection of various viral agents; however, this test is not available in all countries¹⁷.

Case presentation

It is about a 44 years old woman who consulted with a history of recurrent occipital headache, mild to moderate intensity, radiating to the frontal region, with episodes of vomiting, incoherent speech, and confused thinking.

The patient's history included cytomegalovirus viral encephalitis four years before the consultation. She also stated that two months before, she received diphtheria and tetanus conjugate vaccination with no immediate reaction to the immunization; in addition, she had multiple viral processes in the last two months. There was also a history of two previous pregnancies, both ending in cesarean delivery. She did not present any comorbidity.

In the physical evaluation, the patient presented deficient general condition, hemodynamically stable, with cardiopulmonary status without alterations, and presented with countless projectile vomiting. Initially, she had ten points on the Glasgow scale. The ocular fundus showed discrete bilateral edema of the papilla. In the physical evaluation, she presented blood pressure of 102/54 mmHg, heart rate of 102 beats per minute, and respiratory rate of 28 per minute; pupils were reported as isochoric with decelerated response to light, and there were no signs of cranial nerve involvement. The patient manifested left hemiparesis with a moderate diminished in muscle strength and generalized hyporeflexia, and the Babinski's sign was positive on the left side.

Laboratory tests showed leukocytosis at the expense of segmental, renal, and hepatic function were not altered, and red blood cell and platelet counts were within normal limits (Table 1).

Table 1. Para-clinical at admission

Variables	Values
Hemoglobin	12.3 g/dL
Mean corpuscular volume	89 fL
Mean corpuscular hemoglobin	32
Leukocytes	15990
Neutrophils	89 %
Lymphocytes	10 %
Platelets	320 000
Creatinine	1.02 mg/dL
Urea Nitrogen	20 mg/dL
Total Bilirubin	1 mg/dL
Direct Bilirubin	0.4 mg/dL
Indirect Bilirubin	0.6 mg/dL
Aspartate aminotransferase	32 UI L
Alanine aminotransferase	34 UI L
Cerebrospinal fluid	Lymphocytic cells 450 Protein 59 mg/dL Glucose 98 mg/dL pH 7.2
C-Reactive Protein	125 mg
Protrombin time	14.5 s control 13.8 sec
Partial thromboplastin time	34 s control 36.2 sec

Brain computed tomography performed in the first hours of admission reported cerebral edema with a hypodense lesion in the right thalamus. After 18 hours of hospital permanence, the patient performance evolved with further neurological deterioration; a total of seven points on the Glasgow scale was reported. In addition, there were rales in the right lung base without radiological evidence of a lower respiratory infection, despite the fact that there was clinical suspicion of bronchospiratory pneumonia. At the same time, the patient presented with focal convulsive episodes and motor manifestations in the left hemibody.

The electroencephalogram manifested unilateral right hemispheric deceleration, and mechanical ventilation was started. Lumbar puncture was performed 20 hours after admission; the cerebrospinal fluid study described hyperproteinorrhachia and a predominantly lymphocyte count of 450 cells with preserved glycorrachia, with no presence of bacteria. All viral serologies for neurotropic agents included were found negative on admission, including the HIV test.

Treatment

Based on the suspected neurological infection, intravenous treatment with ceftriaxone, 2 g every 12 hours, vancomycin, 1 g every 12 hours, and acyclovir, 600 mg every eight hours, were indicated.

Control tomographic findings performed on the fifth day of admission reported hydrocephalus. A Becker-type ventricular derivation was implanted immediately. Given the persistence of the neurological manifestations, focal convulsive episodes, and motor manifestations in the left hemisphere that did not subside, treatment was supplemented with phenytoin sodium, 100 mg every eight hours, levetiracetam, one gram every 12 hours, and valproic acid 500 mg every eight hours, all by oral administration.

Outcome

The patient's clinical condition remained with poor response to stimuli and poor interaction with the environment. After seven days of hospital confinement, a control brain CT scan showed the presence of cerebral edema with ventricular dilatation and alteration of the white matter in the right hemisphere. In addition, IgM serology was positive for the Epstein-Barr virus and negative for the rest of the neurotropic viruses. Subsequently, a polymerase chain reaction test was performed, which identified the presence of a viral genome in cerebrospinal fluid for Epstein-Barr.

The patient relapsed with focal motor seizures in the left hemibody when sedation was interrupted; therefore, sedation was discontinued only after 14 days. At the same time, a new simple brain tomography control was performed, showing the persistence of ventriculomegaly and cerebral edema (Figure 1). Mechanical ventilation continued due to the coma vigil condition. In addition, due to the clinical imaging findings, a diagnosis of viral encephalitis complicated by epilepsy secondary to a demyelinating structural lesion of the right cerebral hemisphere was established, and specific management with immunotherapy initiated due to the refractoriness to antivirals.

Five doses of intravenous immunoglobulin treatment were administered and resulted in neurological improvement, evident clinical progress, cessation of motor crises in the left hemisphere, as well as more interaction with the team attending her, compliance with verbal instructions and reaction to stimuli with non-verbal language response. The Becker ventricular derivation was removed 18 days

after its placement, and mechanical ventilation, 19 days after hospital admission. This patient is currently in physical therapy with a stationary evolution since she persisted with evidence of moderate left hemiparesis, gait disturbances, dysarthric language, with controlled seizure episodes during the last six months.

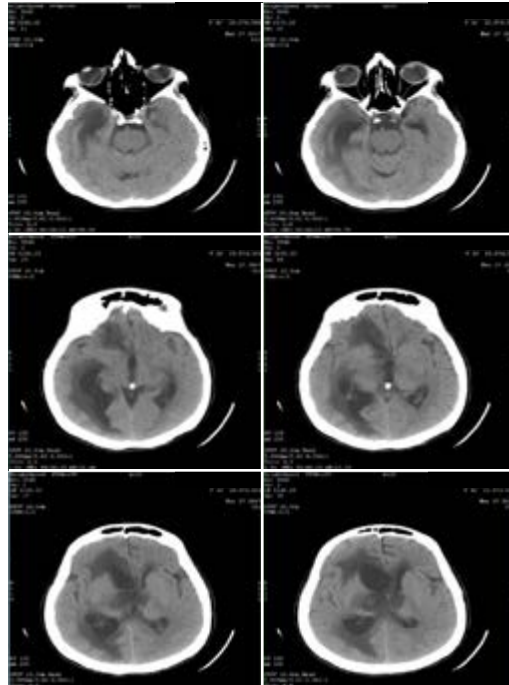


Figure 1. Cranial tomography performed on the patient.

Clinical diagnosis

This case represented a diagnostic challenge due to the clinical manifestations and paraclinical findings that generated the diagnostic suspicion of viral encephalitis complicated with structural epilepsy secondary to an intense right hemispheric demyelination. Confirmation of Epstein-Barr virus infection by serological virus identification tests, such as polymerase chain reaction, emphasized the viral etiology of encephalitis.

Discussion

The diagnostic criteria for encephalitis are based on altered mental state lasting more than 24 hours, with no identified alternative cause, and at least two of the following alterations: quantified fever above 38° C in the last 72 hours before or after presentation, seizure activity unrelated to pre-existing seizure disorders, new focal neurological signs, cerebrospinal fluid pleocytosis with new neuroimaging findings suggestive of encephalitis, and abnormal

findings on electroencephalography compatible with encephalitis with other causes having been ruled out¹⁶. The present case described a patient with seizures, defined as unilateral deceleration of the right hemisphere, considered a common manifestation in viral encephalitis¹⁸. In addition, a course with progressive neurological deterioration, decreased muscle strength, altered consciousness, and bilateral papillary edema were described.

It is worth noting that approximately one-quarter of patients with confirmed encephalitis will have some symptoms suggestive of an infection outside the central nervous system¹⁶. The case presented showed neurological changes that progressed to neurological impairment; this may be observed in similar cases where neurological impairment provoked the need to use mechanical ventilation on the patient¹⁹. Within the clinical exercise, multiple causes of autoimmunity against collagen, metabolic, endocrinologic, oncologic causes, and congenital metabolic defects were ruled out since the patient's age did not support such association and even more, because there were no functional or clinical alterations that would suggest them. Vasculitic causes, immunosuppression, and other primary demyelinating diseases of the central nervous system were also ruled out.

It is clear that an electroencephalogram can be helpful to study encephalitis and evidence of encephalopathy. It would be unusual in primary psychiatric diagnoses or subclinical seizures. Viral encephalitis may be an underlying cause of non-convulsive status epilepticus in some settings. There are electroencephalographic patterns characteristic of viral encephalitis, particularly, the appearance of extreme delta brush, as a pathognomonic sign of encephalitis due to NMDAR12-type¹² antibodies formed by molecular mimicry. Anticonvulsant management needs to be performed and maintained over time, as demonstrated by scientific evidence¹⁸.

Cerebral edema with a hypodense lesion in the right thalamus identified by brain computed tomography in the first hours of admission is consistent with viral encephalitis¹⁷. Due to the wide range of pathologies with altered mental status, a high index of suspicion is required; furthermore, most patients with encephalitis will not have a severely depressed Glasgow Coma Scale score on initial admission, and may even do well on basic cognitive tests such as the mini-mental test, and many often lack fever or CSF pleocytosis¹⁹.

Regarding the etiology of encephalitis, some studies highlight that the presence of a virus or antigen may suggest a trigger for this entity. The search for the virus or antigen requires continuous efforts, from looking for the presence of Epstein-Barr virus to ruling out HIV and herpes simplex¹⁹. In this case, the decision to perform the polymerase chain reaction test to detect the viral genome in cerebrospinal fluid, given the positive IgM serology for Epstein-Barr virus, confirmed the presence of the etiologic agent.

Treatment of encephalitis aims to reduce the severity and frequency of sequelae and to improve long-term functional outcomes as measured by motor and cognitive performance. In the case of viral encephalitis, additionally to treatment of the underlying process, it is often necessary to consider management of seizures, movement disorders, behavior, pain, sleep disturbances, and mood disorders. Case reports and series of uncontrolled patients have been reported, in whom the effects of long-term immunotherapy for viral encephalitis have failed to generate any response to antivirals¹⁸. The findings of these publications show a positive experience with long-term corticosteroids. Moreover, intravenous immunoglobulins and plasmapheresis¹⁸ have been used as strategies to limit the excessive immune response that becomes harmful. In the present case, management with immunoglobulin, as described, substantially improved the clinical progression. Describing new therapies such as hemispherectomy is fundamental because of the sequels that could produce. Surgery has also been reported as a therapeutic option in refractory cases²⁰.

Most patients with viral encephalitis recover without sequelae. Those who remain symptomatic have difficulty concentrating, speech and behavioral disorders, and or memory loss. In rare cases, patients may persist in a vegetative state. Following viral encephalitis, patients may develop seizures, severe mental retardation, and diverse modes of paralysis¹⁸.

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