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Western equine encephalitis, a report of two cases in pediatric patients

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ABSTRACT

Western equine encephalitis (WEE) is vector-borne infection caused by an RNA virus of the genus *Alphavirus*, disseminated by mosquitoes that can cause WEE in humans. There are two cycles of transmission, a maintenance cycle and an occasional amplification with vector augmentation, where equines and humans are terminal hosts. In Argentina, no human cases had been reported since 1983.

Here we describe 2 pediatric patients with brain symptoms and serological diagnosis of WEE. Both samples of cerebrospinal fluid (CSF) showed pleocytosis, while the neuroimaging test showed alterations in the basal ganglia. The serological diagnosis was based on the detection of specific IgM in serum and CSF and neutralizing antibodies 14 days after symptom onset. The patients were managed with supportive treatment. One patient recovered his normal neurological status without seizures before discharge, while the other was discharged with right hemiparesis, which resolved after 2 months, and continued with anticonvulsants due to a pathological EEG.

Keywords: *arbovirus; Western equine encephalitis; meningoencephalitis.*

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INTRODUCTION

Western equine encephalitis (WEE) is an endemic, zoonotic, acute, mosquito-borne viral infection of the central nervous system (CNS) that incidentally affects humans and horses. It is in general asymptomatic and few cases progress to different degrees of meningoencephalitis. Here we describe 2 clinical cases who developed brain symptoms and were diagnosed with WEE.

CASE REPORT 1

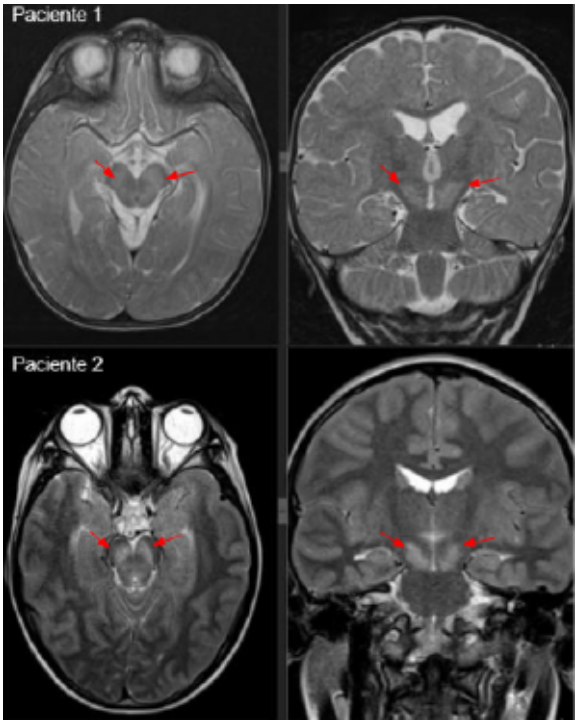
This was a 9-month-old healthy boy from a rural area in the province of Santa Fe. He presented with febrile syndrome for 4 days, so he was given antibiotic therapy for otitis media. After 48 hours, he had vomiting, food refusal, and altered sensorium, so he was admitted to the hospital. Upon admission, he was in poor condition, hyporeactive, with nuchal rigidity, bulging fontanelle, and moderate dehydration. Meningitis was suspected, so laboratory tests were performed (leukocytosis with neutrophilia, CRP 12 mg/L), together with blood cultures and a lumbar puncture, which was compatible with aseptic meningitis (*Table 1*). He was started on an empirical treatment with ceftriaxone and, due to the positive epidemiological result for WEE, cerebrospinal fluid (CSF) and serum samples were sent for examination. Twelve hours later, he developed intercurrent refractory generalized tonic-clonic seizures, so he was placed on mechanical ventilation (MV) for 36 hours. He received intravenous acyclovir and diphenylhydantoin, which stopped the seizures. He continued with fever for 72 hours. A magnetic resonance imaging (MRI) of the brain done on day 7 of the course of disease showed bilateral focal midbrain hyperintensity (*Figure 1*). The

Table 1. Laboratory parameters, magnetic resonance imaging, and serological tests of patients

	Patient 1	Patient 2
Lab tests upon admission	Htc 34%. Hb 11.40 g/dL. WBCs 32 000/mm^3 (73/20/6). Platelets 612 000/m^3. CRP 12.4 mg/L. Blood urea 11 mg/dL. Creatinine 0.55 mg/dL. AST 33 U/L. ALT 20 U/L.	Htc 34.6%. Hb 11.9 g/dL. WBCs 13 900/mm^3 (93/4.5/1.7). Platelets 223 000/mm^3. CRP < 6 mg/L.
Physicochemical characteristics of CSF	Colorless, mildly cloudy, clear aspect. Leukocytes 72/mm^3 (MMN 20% / PMN 80%). RBCs 14 000/mm^3. Proteins 0.13 g/L. Glucose 55 mg/dL (HGT 95 mg/dL).	Colorless, mildly cloudy aspect. Leukocytes 870/mm^3 (MMN 80% / PMN 20%). Scarce RBCs. Proteins 0.74 g/L. Glucose 81 mg/dL (HGT 120 mg/dL).
CSF culture for common germs	Negative.	Negative.
Viral PCR in CSF	Negative (enterovirus, herpes simplex virus 1 and 2).	Negative (enterovirus, herpes simplex virus 1 and 2, Epstein Barr, varicella zoster virus, cytomegalovirus).
Blood cultures upon admission	Negative.	Negative.
MRI of the brain	Spontaneous hyperintense bilateral focal images in T2 and FLAIR sequences of the midbrain.	Spontaneous hyperintense focal images in T2 and FLAIR sequences in the right parietal and occipital regions, basal ganglia specifically in lenticular nuclei with right and bilateral midbrain predominance.
Serum IgM WEE (MAT ELISA)	Positive.	Positive.
CSF IgM WEE (MAT ELISA)	Positive.	Positive.
Serum PCR WEE	Negative.	Negative.
CSF PCR WEE	Negative.	Negative.
Serum IgG seroconversion WEE	Positive.	Positive.

Htc: hematocrit; Hb: hemoglobin; WBCs: white blood cells; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; MMM: monomorphonuclear; PMN: polymorphonuclear; HGT: hemoglucotest; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; MRI: magnetic resonance imaging; IgM: immunoglobulin M; IgG: immunoglobulin G; WEE: Western equine encephalitis.

Figure 1. Magnetic resonance imaging of the brain



Axial and coronal sections in T2 sequences. Spontaneous hyperintense lesions observed at the level of the midbrain in patient 1; the same sections and sequences in patient 2 showed similar signal changes.

patient completed 10 days of ceftriaxone as partially treated bacterial meningitis and was subsequently discharged. He recovered his normal neurological status and had a normal electroencephalogram (EEG). The diagnosis of WEE was confirmed by positive IgM in CSF and serum samples, with positive neutralizing antibodies at day 14 of the course of disease. After 3 months, the anticonvulsant agent was discontinued and the patient did not have recurrent epileptic seizures or sequelae.

CASE REPORT 2

This was a 12-year-old healthy boy from a semi-urban area in the province of Buenos Aires. He consulted after 72 hours of holocranial headache, vomiting, fever, photophobia, and meningeal signs. Meningitis was suspected, so the following were done: computed tomography (CT) of the brain, lab tests (normal blood count and CRP < 6 mg/L), blood cultures, and lumbar puncture, which showed predominantly mononuclear pleocytosis (*Table 1*). Due to the positive epidemiological result for WEE, CSF and serum samples were requested. The patient was started on ceftriaxone + acyclovir. On day 5, he developed cogwheel rigidity in the right upper limb and altered sensorium, which progressed in 24 hours to focal tonic-clonic refractory seizures affecting the right lower limb and subsequent generalization. He required MV for 9 days due to extubation failures in relation to recurrent seizures, with a low-voltage and slowed EEG tracing. During the course of his condition, he developed urticarial rash and thrombocytopenia (70 000/mm^3), which resolved spontaneously. He continued with fever and ventilator-associated pneumonia for 14 days. The MRI of the brain showed hyperintensity in the cerebral cortex, midbrain, and basal ganglia with right lenticular predominance (*Figures 1 and 2*). The diagnosis of WEE was confirmed by positive IgM in CSF and serum samples, with positive neutralizing antibodies at day 21. He was discharged with mild right hemiparesis predominantly in the upper limb without recurrence of seizures. Hemiparesis resolved completely 2 months later. The EEG showed bilateral, synchronous

and asynchronous frontal, midline, and parietal spikes, with a low frequency of presentation; the patient is currently receiving treatment with levetiracetam.

DISCUSSION

WEE is caused by Western equine encephalitis virus, an arbovirus that belongs to the genus *Alphavirus*. It is transmitted in an enzootic cycle that takes place among mosquitoes, birds, and other vertebrates. Both equines and humans are considered terminal hosts, since they do not develop sufficient viral load to infect vectors and maintain the cycle.[1]

Equine cases usually precede human cases by several weeks; their surveillance is used to assess the risk of epidemic transmission. However, the low frequency of laboratory-confirmed diagnoses in animals, vaccination, and underreporting of cases hinder their accuracy as a predictive marker.[1]

In Argentina, the *Aedes albifasciatus* mosquito is the main vector involved.[2] It is prevalent in rural and suburban areas, and its population increases during periods of rainfall. It shares aquatic habitats with birds that amplify the virus in nature.

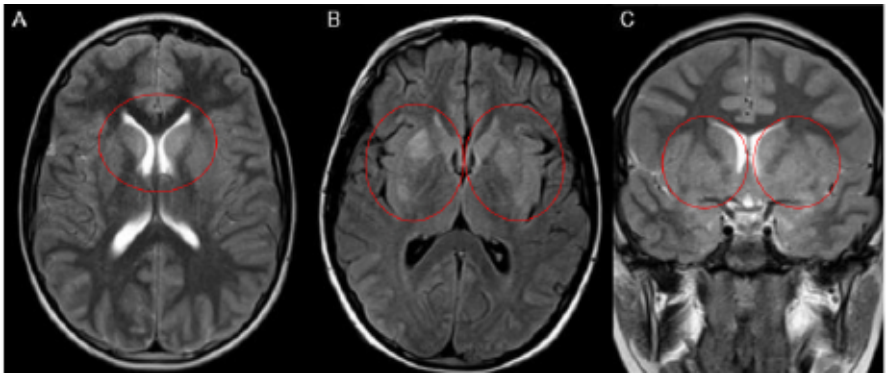
In Argentina, equine outbreaks have not been associated with WEE in humans, except in 1972–1973 (2 cases), 1982–1983 (5 cases), and at present, with an alert issued on 11-25-2023 until early April 2024 (epidemiological week 14) that included 471 suspected cases, 100 confirmed cases, and 10 deaths reported to the National Health Surveillance System. Confirmed cases were located in Buenos Aires, the City of Buenos Aires, Córdoba, Santa Fe, Entre Ríos, Santiago del Estero, La Pampa, and Río Negro, with a median age of 57.1 years (maximum: 81 years and minimum: 4 months); 87% were male and 13%, female.[3]

Most infections are asymptomatic or non-specific, but may progress to neuroinvasive disease (encephalitis, meningitis, myelitis, or seizures) at a case/infection ratio of 1:58 in children aged 1–4 years and 1:1150 in adults. In addition to age, other risk factors are male sex, rural place of residence, and agricultural occupation.[4]

After an incubation period of 2 to 10 days, the disease usually begins abruptly with fever, headache, malaise, nausea, and vomiting. Gradually, signs of CNS involvement appear with meningeal manifestation and evolution to encephalitis, altered sensorium, and seizures/persistent seizures, with likely spasticity or flaccid paralysis. Infants generally have a more rapid course with loss of appetite, irritability, and drowsiness.[1]

Both cases described here began as aseptic meningitis, which rapidly progressed to encephalitis and persistent seizures. Parkinsonism (bradykinesia, resting tremor, rigidity, and extrapyramidal signs) and involuntary movements correlate to basal ganglia involvement and, although these are not specific, they suggest arboviral diseases (Eastern equine encephalitis [EEE], WEE, West Nile encephalitis,

Figure 2. Magnetic resonance imaging of the brain



A *axial section and* **C** *coronal section in T2 sequences show spontaneous hyperintense focal lesions in basal ganglia in patient 1.* **B***: the axial section in FLAIR sequence shows the same lesions plus signal changes at the right parietal and occipital levels in patient 2.*

Saint Louis encephalitis).

A severe presentation, complications, and long-term sequelae have been more frequently described in infants.[5] However, in our experience, the clinical presentation was more severe in the 12-year-old patient, who had motor sequelae at discharge.

Both patients had midbrain lesions; the second patient also showed lesions at the cortical level and in the basal ganglia, with greater clinical neurological involvement. This is consistent with the neuroimaging described in arbovirus infections, where hyperintense lesions are usually observed in T2 and FLAIR sequences, located in the basal ganglia, the midbrain, and the cortex.[6] In severe cases, lesion progression has been observed, with restriction in diffusion sequences, indicative of cerebral edema. No specific information was found in the bibliography regarding WEE in MRIs of the brain.

In relation to lab tests, leukocyte counts may be normal. CSF usually shows normal CSF glucose levels, normal or slightly increased protein levels, and pleocytosis between 10 and 300/mm^3 with mononuclear predominance.[1] The CSF of case 1 was predominantly polymorphonuclear, with normal CSF glucose and protein levels, which could be due to the early sample collection compared to the onset of neurological symptoms. Patient 2 presented greater pleocytosis with a mononuclear predominance. Although in EEE a leukocyte count > 500/mm^3 in CSF is associated with a worse prognosis,[7] we found no data in this regard in relation to WEE.

Molecular biology tests are usually negative at the time of clinical suspicion due to the rapid negativization of viral load, so the diagnosis is made based on serological tests. The development of specific antibodies occurs within the first week of infection. Detection of specific IgM by capture ELISA (MAT-ELISA) in CSF and serum samples confirms the diagnosis.[8] Positive IgM in CSF indicates intrathecal production, but not an isolated serum IgM value due to potential false positive results. The presence of neutralizing antibodies at day 14 excludes any possible cross-reaction with other arboviruses.

In both patients, serum and CSF samples for PCR and antibody measurement were collected on days 3 and 4 of the course of disease; the PCRs were negative, with serological confirmation.

At present, there is no specific treatment for WEE; therapy is supportive. Small molecule inhibitors of neurotropic alphaviruses are being investigated in phase 1 studies.[9]

The mortality rate is low (3–7%). According to the bibliography, 15–30% of patients have neurological sequelae,[10] including quadriplegia, spasticity, intracerebral calcifications, developmental delay, and seizures.

No vaccines have been authorized for human use.[11] Therefore, prevention, aimed at avoiding mosquito bites, together with environmental hygiene measures are critical.

We emphasize that, in the presence of patients with acute febrile syndrome and neurological symptoms in areas with WEE outbreaks, it is important to alert the healthcare team for proper detection and timely treatment. ■

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