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Dengue encephalitis in pediatrics: case series in a hospital in Tucumán, Argentina

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ABSTRACT

Dengue is a vector-borne viral disease with a broad spectrum of clinical manifestations. Nervous system involvement is one of its severe forms. This is mainly due to three mechanisms: metabolic alterations, autoimmune reactions, and direct invasion of the virus. Encephalitis is one of the most frequent and usually presents with fever, decreased level of consciousness, convulsions, headache, focal neurological deficits, behavioral alterations, nausea, and vomiting.

Three cases of pediatric patients with serological confirmation of dengue and clinical compatibility with encephalitis are presented.

Keywords: *encephalitis; dengue; pediatrics.*

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INTRODUCTION

Dengue is an infectious disease of viral origin and vector-borne transmission with acute presentation and variable intensity ranging from asymptomatic to severe forms with shock, hemorrhage, and organ damage.[1]

Dengue virus is an RNA virus belonging to the *Flaviviridae* family. Its genome encodes ten proteins: three structural and seven non-structural proteins involved in RNA replication (among these is NS1, an antigen used for early-stage diagnosis).[2] There are four serotypes (DENV 1-4). DENV1, DENV2, and DENV3 circulate in Argentina. Up to the epidemiological week 22 of 2024 (the period in which our patients presented), 521,746 cases of dengue fever were reported (a total of 93,135 were children under 15).[3]

Transmission occurs through the bite of infected female mosquitoes of the genus *Aedes aegypti*. The *A. albopictus* mosquito also acts as a vector, and its presence has been documented in Misiones and Corrientes.[4]

In 2009, the World Health Organization classified the disease according to its clinical presentation; this classification is still used today. It distinguishes three categories: dengue without warning signs, dengue with warning signs, and severe dengue.[5]

The latter includes capillary leak syndrome, hemorrhage, and severe organ damage (hepatitis, myocarditis, and nervous system involvement).[6]

The spectrum of neurological manifestations includes encephalopathies, encephalitis, meningitis, myositis, myelitis, and immune-mediated syndromes (acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, and Guillain-Barré syndrome).[7] In our service, from February to May 2024, there were five cases of dengue encephalitis, of which we will report the three most representative.

CASE 1

A 7-year-old boy started with fever, asthenia, and poor appetite. On the third day of evolution, he consulted to the emergency department because he presented convulsive *status epilepticus* that subsided with anticonvulsants. In the Immediate postictal period, he evolved with altered awareness, disorientation, lack of sphincter control, irritability, psychomotor excitation, and visual hallucinations. Laboratory tests (normal hemogram, liver, and renal function) and normal brain computed axial tomography (CAT) were performed. Cerebrospinal fluid (CSF) with normal physicochemical, culture of common germs, and virological negative. Due to the epidemiological situation, serum NS1 antigen was requested and was positive. It was assumed to be dengue encephalitis. He continued with irritability, altered awareness, and episodes of psychomotor excitation without new seizures. He received treatment with levomepromazine and lorazepam. Electroencephalogram (EEG), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) showed normal results. Samples were sent for typing, and DENV2 was isolated using serum PCR. PCR for dengue in CSF was negative. On the sixth day of illness, he presented the last febrile peak. On the ninth day, there was clinical improvement, interacting with the environment normally. Anticonvulsants and psychotropic drugs were suspended. He was discharged without medication.

CASE 2

A 7-year-old girl was consulted for fever. Laboratory tests showed positive NS1 antigen in serum. Two days later, she presented abdominal pain and erythematous rash followed by a generalized tonic-clonic seizure that subsided with lorazepam. She evolved with visual hallucinations, continuing with seizures; she was impregnated with diphenylhydantoin, and a brain CT scan was performed, with normal results. On the fifth day, the fever subsided, with worsening of psychiatric symptoms (irritability, altered awareness, and psychomotor excitation), so he was medicated with levomepromazine. It was assumed to be probable dengue encephalitis, and a serum sample was sent for PCR (DENV1). Fundus examination showed bilateral papillary edema and linear hemorrhages, EEG with slow waves focused on the left parietal region. The anticonvulsant was adjusted, and brain CT was repeated, with normal results. Lumbar puncture was performed with normal CSF, negative culture, and negative PCR for dengue. Ten days later, she presented improvement, no seizures or hallucinations, and normalized eye fundus. MRI and angio-MRI of the brain were normal. She was discharged after two weeks on levetiracetam.

CASE 3

A 9-year-old boy initially consulted at a local hospital for acute fever and generalized tonic-clonic seizure. He received benzodiazepines and antipyretics and was referred to this hospital. He was admitted in convulsive *status epilepticus*, so

he was impregnated with diphenylhydantoin. The laboratory was performed (leukocytosis), and a positive NS1 antigen was found in the serum. In the immediate postictal period, psychomotor excitation and disorientation appeared. The brain CT was normal, the CSF had normal cytochemistry, and the culture of common germs was negative. The patient evolved in the first 48 hours with marked irritability, bradypsychia, episodes of temporospatial disorientation, not recognizing her caregivers, visual hallucinations, and insomnia. After 72 hours, the neurological and psychiatric symptoms subsided. Fundus examination and EEG were normal, and anticonvulsants were suspended. CSF PCR: DENV1 positive. The patient was discharged on the seventh day without any treatment.

DISCUSSION

The dengue virus initially infects immune cells (macrophages, dendritic cells, and Langerhans cells), which migrate to the lymph nodes. There, it replicates, generating viremia and releasing NS1 proteins that activate the cytokine storm responsible for the systemic inflammatory response. Central nervous system (CNS) involvement is mainly due to three mechanisms: direct virus invasion, autoimmune reactions, and metabolic alterations.[8] Recently, viral particles in CSF have been demonstrated, suggesting damage to the blood-brain barrier, highly suggestive of neurotropism.[9]

The most recent classification of neurological manifestations of dengue distinguishes the following categories: CNS and ocular involvement (encephalopathy, encephalitis, ischemic/hemorrhagic stroke, maculopathies, optic neuropathy, vitreous and subconjunctival hemorrhage), peripheral nervous system manifestations (cranial nerve involvement, myositis, neuritis) and post-dengue immune-mediated syndromes (transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barré syndrome).[10]

Encephalopathy and encephalitis are the most frequent neurological complications. Their incidence is estimated to be between 0.5% and 6.2% of cases worldwide, most associated with DENV2 and DENV3. We present the cases of three patients with dengue encephalitis who were hospitalized between February and May 2024. PCR performed serotype identification in serum in all three patients (DENV1 in two patients, DENV2 in one patient).

Encephalitis usually presents within three to seven days of the onset of illness, with fever, decreased level of consciousness, convulsions, headache, focal neurological deficits, behavioral disturbances, nausea, and vomiting.[11] The usual symptoms of dengue (rash, muscle aches, and bleeding) are present in less than 50% of patients with encephalitis. In our experience, the most frequent clinical manifestations were fever, convulsions, and behavioral disturbance. All three patients presented psychiatric symptoms: hallucinations and psychomotor excitement, rarely reported in the literature (*Table 1*).

Dengue encephalitis is diagnosed with compatible clinical manifestations and confirmation of systemic dengue infection (NS1 or IgM in serum). CSF is usually normal in 75% of cases, and the sensitivity of CSF PCR for viral detection is low, so a negative result does not rule out the diagnosis.[12] In all our patients, infection was confirmed by serum NS1, with subsequent identification of serotypes by PCR. CSF PCR was performed in all three patients; it was positive in only one of the cases (DENV1) (*Table 2*).

Neuroimaging findings are usually nonspecific, so they do not exclude the diagnosis. In brain CT, focal parenchymal hyperdensity corresponding to microhemorrhages and hypodensities in the thalamus and basal ganglia may be observed. In MRI, T2 hyperintensity in the basal ganglia,

Table 1. Dengue encephalitis: clinical manifestations in patients hospitalized during the period February-May 2024

Clinical manifestations	N.° of patients (n = 3)
Seizures	3
Hallucinations	3
Irritability	3
Sensorium depression	3
Fever	3
Pathological fundus	1
Exanthema	1
Abdominal pain	1

Table 2. Dengue encephalitis: diagnostic methods in patients hospitalized during the period February-May 2024

Methods	Positive results (n = 3))
Ag NS1+ serum (ELISA technique))	3
IgM/IgG (ELISA technique)	0
Serum PCR	2 (DENV1) 1 (DENV2)
Cerebrospinal fluid PCR	1 (DENV1)

Ag NS1+: NS1 antigen. IgM: immunoglobulin M. IgG: immunoglobulin G. PCR: polymerase chain reaction.

thalamus, temporal lobes, hippocampus, cerebellum, and white matter may be observed, and restriction in diffusion sequences may be observed.[13] In our patients, neuroimaging was normal.

One of the patients presented papillary edema and fundus hemorrhages with pathologic EEG, rarely reported in the literature.

The treatment of these patients consists of symptomatic and supportive treatment, correction of hydroelectrolyte disorders, anticonvulsant medication, and neuroleptics as needed. There is no evidence to support the use of systemic corticosteroids or antivirals to treat this entity.

CONCLUSIONS

The reported patients had a favorable evolution, with resolution of symptoms after seven days, behaving as acute viral encephalitis; they received only symptomatic treatment. They presented with normal CSF and normal neuroimaging. In only one case, the virus was detected by PCR in CSF, but all had diagnostic confirmation in serum.

Dengue has become epidemic and endemic in South America, which is conducive to the appearance of encephalitis caused by this virus. This entity should be considered part of the usual differential diagnosis within the pathologies of the nervous system. ■

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