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CASE REPORT

Herpetic meningoencephalitis associated with acute anticonvulsants intoxication

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Abstract

Objective: To report a case of meningoencephalitis caused by herpes virus in a patient with acute intoxication by anticonvulsants and to review the literature with respect to the disease. **Methods:** The evaluation of a patient with herpes meningoencephalitis is described using data from his medical record along with a literature review of scientific articles and guidelines with respect to the condition. **Closing remarks:** The reported case and referred publications highlight and discuss the severity of herpes meningoencephalitis, importance of diagnostic suspicion based on the clinical history and physical examination, relevance of complementary tests, and effectiveness of early acyclovir treatment.

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INTRODUCTION

Encephalitis is defined as an inflammation of the brain parenchyma associated with clinical evidence of brain dysfunction. It is related to both noninfectious conditions, such as acute disseminated encephalomyelitis (ADEM), and infectious conditions, usually diffuse and viral. Herpes simplex virus type 1 (HSV-1) is one of the leading causes of encephalitis in immunocompetent individuals.[1,2]

The inflammatory process is not just limited to the brain; it also involves the meninges. Thus, the term viral meningoencephalitis is used to describe the infectious process that affects the brain, meninges, and spinal cord.[2]

A diagnosis of meningoencephalitis can be suspected if there is fever associated with headache, sensorial changes, and signs of brain dysfunction. The latter sign can be divided into four categories: cognitive dysfunction (amnesia, dysarthria, and disorientation), behavioral changes (disorientation, hallucinations, psychosis, personality changes, and agitation), focal neurological abnormalities (anomic aphasia, dysphasia, and hemiparesis), and seizures.[2]

Treatment with acyclovir must be started empirically whenever the patient presents with prolonged focal crises, abnormal neurological examination, or a reduced level of consciousness.[1]

CASE REPORT

S. C. A. (age: 1 year and 8 months) was transferred from the city of Três Lagoas and had a history of rhinitis and nasal obstruction for 3 days and fever for 24 h. Initial medication comprised *Cimegripe*® (a combination of paracetamol, clorphenamine, and phenylephrine). Three hours after being medicated, he exhibited sleepiness, sialorrhea, unresponsiveness, and changes in the respiratory pattern. He was taken to an emergency clinic, where he had a febrile seizure and was further medicated with diazepam, phenytoin, phenobarbital, metamizole, epinephrine, terbutaline, and hydrocortisone; the doses administered were not informed at transfer. Orotracheal intubation was performed due to reduced consciousness and ventilation difficulties. No history of comorbid conditions, previous hospital admissions, or continuous medication use was recorded. Furthermore, adequate neuropsychomotor development was observed, and no family history of epilepsy was recorded. Vaccination was on schedule.

He was admitted intubated to the ICU, with a greenish secretion in the endotracheal cannula but no meningeal signs. Ceftriaxone was already initiated in the city of origin. A chest radiograph showed no changes. A complete blood count showed 8.8 g/dL hemoglobin, 12,040 total leukocytes/µL, 7 bands cells, and 317,000 platelets/µL. A maintenance dose of phenobarbital was administered. The patient was extubated uneventfully and maintained a good respiratory pattern but had periods of sleepiness, which until then had been justified by the anticonvulsive and sedative medication. In the following 24 h, his level of consciousness was reduced (Glasgow 7), and he presented with left hemiparesis and focal left-hand seizures. The patient was then intubated again and underwent urgent tomography examination, which showed no changes. Acyclovir, vancomycin, and dexamethasone were initiated. The seizures persisted; thus, a loading dose of phenytoin was administered, and continuous midazolam, phenobarbital (5 mg/kg/day), and phenytoin (7 mg/kg/day) were used as maintenance doses.

An electroencephalogram was obtained but did not indicate any changes. Serum levels of anticonvulsants were measured for assessing possible intoxication. Phenytoin level was found to be 27.3 µg/mL (toxic level: above 20 µg/mL). Phenobarbital level was found to be 53 µg/mL (toxic level: above 40 µg/mL). Once the intoxication was confirmed, phenytoin was gradually reduced and then suspended, and phenobarbital was reduced to 4 mg/kg/day.

It was decided that a lumbar puncture be performed, and the cerebrospinal fluid (CSF) analysis showed 32 leukocytes/µL, 100 erythrocytes/µL, 97% lymphomononuclear cells, glucose 90 mg/dL, and proteins 29 mg/dL, evidencing an increased cell count with a predominance of lymphomononuclear cells, which led to the diagnostic hypothesis of viral meningoencephalitis. Magnetic resonance examination showed signs of meningoencephalitis, with foci of alteration to the right; the foci were bilateral in the thalamus. Serology tests later confirmed IgM positivity for both herpes and Epstein-Barr virus (EBV). The family was questioned and confirmed a history of primary herpes infection (gingivostomatitis at 9 months). The EBV infection probably caused immunosuppression, which reactivated the herpes virus. A polymerase chain reaction (PCR) for herpes was performed in CSF, with a positive result.

The patient was extubated again 11 days later but displayed weakened head and trunk posture, left-side hypotonia, impaired speech and swallowing, and inability to keep standing. Focal seizures persisted in the left arm but improved after oxcarbazepine was initiated. Trunk and neck control was eventually restored, but the speech impairment persisted. The patient was discharged to the ward with a nasoenteral tube with a forecast of evolution to an oral diet (with speech therapy).

DISCUSSION

HSV is the most common sporadic virus associated with meningoencephalitis, with an approximate incidence of 1 to 3 cases per million. Ninety-five percent of deaths are caused by HSV-1, which is reactivated in immunocompetent patients.[3]

HSV infection occurs through the respiratory tract and ascends through the trigeminal nerve, reaching the central nervous system (CNS). It may either be a primary infection or a reactivation of the virus in immunocompromised patients. A third possibility is genetic polymorphism, in which changes in interferon production favor infection and hematogenous dissemination of the virus.[4]

The clinical picture usually shows a sudden onset. The initial symptoms are usually headache and fever, followed by changes in consciousness or behavior, focal neurological impairment or seizures, amnesia, ataxia, or emotional lability. Fever is present in over 90% of cases. In the neonatal period, vesicular skin lesions appear along with conjunctivitis, CNS changes, either hypothermia or hyperthermia, and nonspecific symptoms. In the acute phase, it cannot be distinguished from encephalites caused by other viruses, such as flavivirus, togavirus, and EBV.[1,4,5]

The most sensitive diagnostic imaging examination is nuclear magnetic resonance, which can detect changes after 2 or 3 days of symptom initiation. In herpes simplex infection, the characteristic lesion surrounds the limbic system bilaterally and asymmetrically, including the medial part of the temporal lobe, insular cortex, inferior lateral part of the frontal lobe, and cingulate gyrus. Typically, it spares the basal ganglia.[3,4]

Electroencephalography shows nonspecific findings in most cases, but periodic temporal epileptiform discharges and status epilepticus may be observed.[1]

CSF analysis shows nonspecific changes, such as lymphocytic pleocytosis, presence of erythrocytes, and elevated proteins, but the results may be normal at first. The detection of viral DNA by PCR is highly sensitive and specific. It is essential for the diagnosis, becomes positive 24 h after symptom initiation, and persists for the first week of treatment. It replaces the previously used brain biopsy.[1,4] The definitive diagnosis of the case described herein was reached with a PCR test of CSF.

Differential diagnosis includes other viral encephalitis (EBV, cytomegalovirus, varicella-zoster, JC virus, enterovirus, and influenza) and other infections, such as subdural empyema, neurosyphilis, and brain abscesses as well as tumors, autoimmune diseases, and ADEM.[4]

Treatment is administered using acyclovir, a nucleoside analog that inhibits viral DNA polymerase, and should be initiated after the first clinical suspicion because its effectiveness is reduced as the condition progresses. Ideally, it should be initiated within the first 24 h and maintained for 14–21 days.[1,4-6] A shorter treatment time is associated with reactivation and CNS lesions.[4]

If the condition is untreated, the prognosis is bleak, with high mortality (70%) and morbidity rates. If treated, mortality is reduced to 19%-36%. Most cases result in long-term consequences, including anomic aphasia (most frequently), neuropsychiatric changes, mental retardation, and seizures. A two-day delay in initiating the treatment is associated to a worse prognosis.[1,4,6,7]

Other contributing factors for a worse prognosis are age over 60 years, a Glasgow score of 6 or less, and neurological symptoms present for over 4 days.[4]

Phenytoin is metabolized in the liver and excreted in the urine. This is a limited process with considerable individual variation, which explains why small dose increments may account for large increases in serum phenytoin levels in some patients.[7]

The therapeutic target of phenytoin is a serum level of 10 µg/mL. Values above 20 µg/mL are considered toxic and may cause nystagmus and ataxia in an early phase, and later, dysarthria, sleepiness, and seizures. High phenytoin levels can also cause generic symptoms, such as nausea and vomiting. Treatment of the intoxication is supportive. Gastric lavage and activated charcoal are controversial. There is no known antidote.[7,8]

Phenytoin intoxication is underdiagnosed because it mimics other neurological conditions. There are few references in the literature, particularly for acute iatrogenic cases, because most cases are chronic and caused by self-medication.[7,8] In our present case, phenytoin intoxication caused some diagnostic confusion because it shows neurological symptoms that mimic encephalitis.

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