

# ACUTE HEMORRHAGIC LEUKOENCEPHALITIS MIMICKING HERPES SIMPLEX ENCEPHALITIS

## Case report

Henrique Milhomem Martins<sup>1</sup>, Antônio Lúcio Teixeira-Jr<sup>2</sup>,  
Marco Aurélio Lana-Peixoto<sup>3</sup>

**ABSTRACT** - Acute hemorrhagic leukoencephalitis (AHLE) is a more severe form of acute disseminated encephalomyelitis (ADEM) characterized by a fulminant clinical course and the presence of hemorrhagic necrosis of the white matter. We report the case of a 57-year-old woman who developed delirium following a respiratory infection. Magnetic resonance imaging of the brain disclosed signal abnormalities in the frontal and temporal lobes, usually found in herpes simplex encephalitis (HSE). Gram stain, India ink and acid-fast bacilli staining were all negative in CSF as was a polymerase chain reaction (PCR) for herpes simplex virus. A diagnosis of AHLE was made and the patient was treated with IV methylprednisolone 1g/day for 5 days. Despite treatment, the patient developed several neurological sequelae compatible with the severity of her illness.

**KEY WORDS:** acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, herpes simplex virus encephalitis.

### **Leucoencefalite hemorrágica aguda mimetizando encefalite herpética: relato de caso**

**RESUMO** - Leucoencefalite hemorrágica aguda (AHLE) é forma grave da encefalomielite disseminada aguda, caracterizada por curso clínico fulminante e necrose hemorrágica da substância branca. Relatamos o caso de uma paciente de 57 anos de idade que desenvolveu estado confusional agudo uma semana após infecção respiratória. Ressonância magnética do encéfalo mostrou alterações de sinal bilateralmente em lobos frontal e temporal sugestivas de encefalite herpética. O estudo microbiológico do líquor foi negativo, assim como a reação de cadeia da polimerase (PCR) para o vírus herpes simplex. Diagnosticou-se AHLE e a paciente foi tratada com metilprednisolona 1g/dia durante 5 dias. Apesar do tratamento, a paciente apresentou sequelas neurológicas compatíveis com a gravidade de seu quadro clínico.

**PALAVRAS-CHAVE:** encefalomielite disseminada aguda, leucoencefalite hemorrágica aguda, encefalite herpética.

Acute disseminated encephalomyelitis (ADEM) is a rare inflammatory demyelinating disease of the central nervous system (CNS) affecting predominantly children and young adults<sup>1-3</sup>. It is usually preceded by an infectious illness, such as measles, mumps, rubella, and respiratory infections, including influenza A or B, *Mycoplasma pneumoniae*, *Legionella*, *Chlamydia* or *Streptococci*<sup>1,2,4</sup>. Vaccines mainly for rabies and smallpox have also been reported to precipitate ADEM. In fact, approximately 70% of patients report a precipitating infection or vaccination<sup>1,2</sup>. ADEM was originally believed to

represent a delayed but direct invasion of the CNS by a virus. Nevertheless, no virus or other infectious agent has been isolated from the CSF or brain in cases of ADEM. Furthermore, its pathology, characterized by perivascular inflammation and demyelination, is quite different from that of infectious encephalitis. ADEM is now believed to result from a transient autoimmune response towards myelin-oligodendrocyte antigens possibly via molecular mimicry, or by non-specific activation of autoreactive T cell clones<sup>1,2,5</sup>. Few patients can develop acute hemorrhagic leukoencephalitis (AHLE), a more

Minas Gerais Center for Investigation of Multiple Sclerosis (CIEM), Federal University of Minas Gerais Medical School, Belo Horizonte MG, Brazil and The Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS): <sup>1</sup>Resident in Neurology; <sup>2</sup>Neurologist; <sup>3</sup>Associate Professor of Neurology and Ophthalmology.

Received 8 May 2003, received in final form 5 September 2003. Accepted 4 October 2003.

Dr. Marco A. Lana-Peixoto - Rua Padre Rolim 769/1301 - 30130-090 Belo Horizonte MG - Brazil. E-mail: lanapma@uol.com.br

severe form of ADEM, which is characterized by hemorrhagic necrosis of the white matter and a fulminant clinical course<sup>6,7</sup>.

We report a case of AHLE that followed a respiratory infection and mimicked on clinical and initial imaging grounds herpes simplex encephalitis (HSE).

### CASE

A previously healthy 57-year-old black woman was admitted to the hospital for evaluation of an acute inhibited delirium associated with fever. One week prior to the onset of these symptoms, she had presented a flu-like episode that resolved spontaneously in few days. Her medical and family history was unremarkable. The initial laboratory work-up disclosed no abnormality. Computerized tomography (CT) of the head was unrevealing. Analysis of the cerebrospinal fluid (CSF) showed 1 lymphocyte/mm<sup>3</sup>; 2 RBC/mm<sup>3</sup>; protein concentration 34 mg/dl and glucose concentration 82 mg/dl. Chest x-rays showed a diffuse interstitial infiltrate. The patient was given ceftriaxone and clarithromycin as treatment of a presumptive atypical pneumonia.

Despite treatment the patient evolved with mental status deterioration and coma but no sign of respiratory failure. On the fourth day of disease, she was transferred to our hospital and put on mechanical ventilation in the intensive care unit. On examination she could react to pain stimulation bilaterally. Her pupils measured 3/3 mm, the light reflex and oculocephalic reflex were intact. The deep tendon reflexes were brisk and a left Babinski sign could be easily elicited. A new head CT scan was performed demonstrating bilateral poorly defined areas of fronto-temporal hypodensities (Fig 1). Repeated lumbar puncture disclosed CSF with 58 WBC (85% lymphocytes); 1 RBC; protein concentration 285 mg/dl and glucose concentration 62 mg/dl. Gram stain, India ink and acid-fast bacilli staining were all negative. Blood cell count, coagulogram, blood urea nitrogen and creatinine concentrations were all within normal range values. Serology for human immunodeficiency virus, syphilis and hepatitis B were negative.

A presumptive diagnosis of HSE was made and the patient was treated with acyclovir (30 mg/Kg/ day). On the second intensive care day, she developed decerebrate posturing bilaterally and was given IV mannitol and put on hyperventilation. As serum and CSF enzyme-linked immunoassay and CSF Polymerase Chain Reaction (PCR) for HSV 1 and 2 were negative, acyclovir was interrupted. Magnetic resonance imaging (MRI) of the brain was then performed revealing a T2-hyperintense sign in both frontal and temporal lobes as well as signs of hemorrhages (Fig 2).

The diagnosis of acute hemorrhagic leukoencephalitis (AHLE) was made and the patient was treated with IV methylprednisolone (1 g/day for five days). She recov-

ered consciousness but exhibited global aphasia and assymmetric tetraparesis, more severe in left side. She was discharged two months later following treatment of nosocomial pulmonary and urinary tract infections. On follow-up examination her neurological condition remains unchanged.

### DISCUSSION

The diagnosis of ADEM is based on history of acute onset focal neurological disturbances, frequently associated with mental changes following a febrile illness, usually an upper respiratory tract infection. Exclusion of a better explanation for the neurological symptoms is necessary. The main conditions to be considered in the differential diagnosis are other inflammatory disorders including vasculitis, ischemic vascular disease, tumors such as lymphoma and glioma, paraneoplastic disorders, infectious diseases and exposure to toxic agents<sup>1,8</sup>.

Our patient had no history or clinical evidence of any systemic disease except of an upper respiratory infection antedating the onset of neurological signs. It may be significant that atypical pneumonia was suspected in our patient as infection by *Mycoplasma pneumoniae* has already been described in association with ADEM and AHLE<sup>5,9,10</sup>.

Other disorders predominantly affecting the white-matter were ruled out on grounds of an

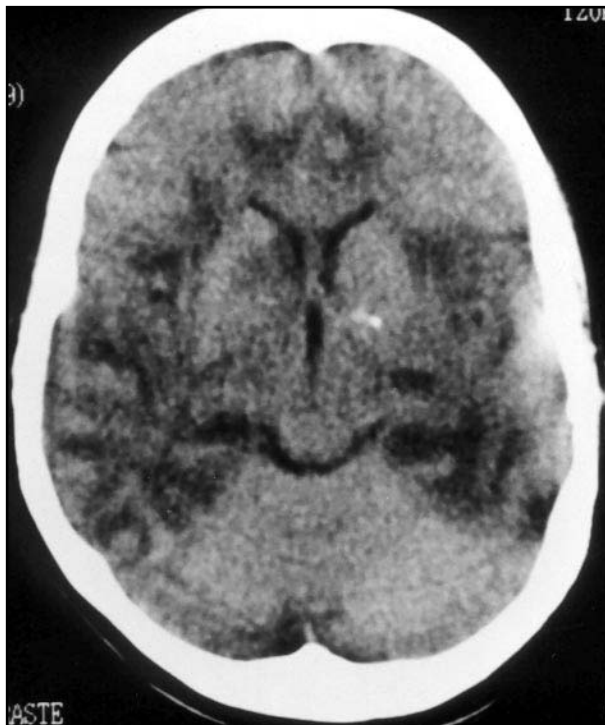


Fig 1. CT scan demonstrates bilateral areas of fronto-temporal hypodensities.

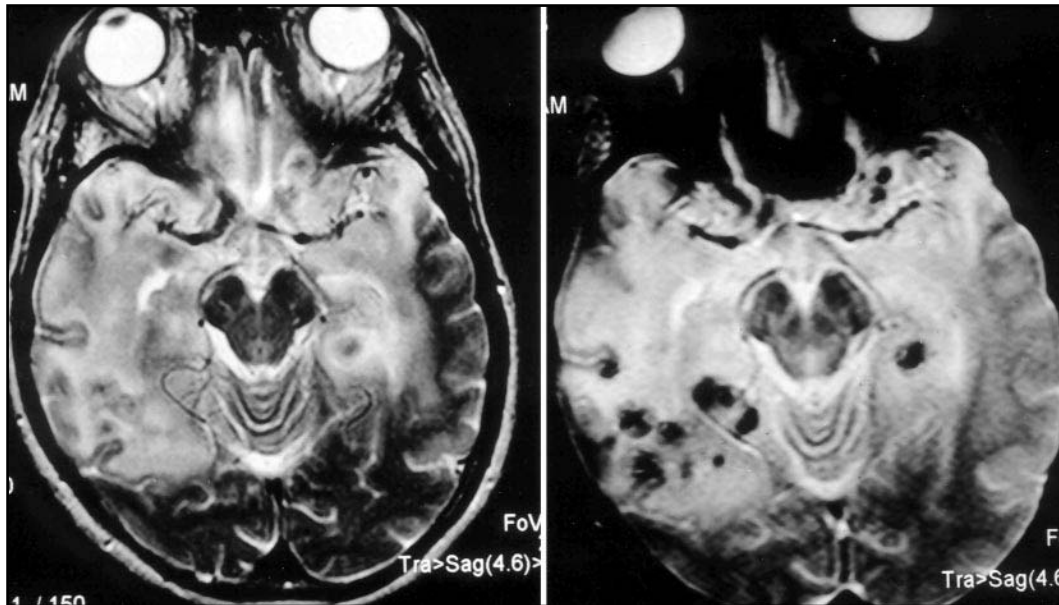


Fig 2. Axial T2-weighted MR image demonstrates areas of T2-hyperintense sign in both frontal and temporal lobes as well as signs of hemorrhages.

unremarkable past medical history. The diagnosis of multiple sclerosis, the most common among the demyelinating diseases, requires the presence of relapsing or progressive neurological disturbances with spatial dispersion<sup>11-13</sup>. More aggressive variants of multiple sclerosis, such as Schilder's disease and Baló's concentric sclerosis, usually take months or years but rarely weeks to develop.

A more difficult differential diagnosis to be ruled out in the current case was herpes simplex encephalitis (HSE). Clinical features, such as fever, delirium and the presence of focal neurological signs, cannot differentiate the two diseases. In fact, our patient presented many features commonly seen in HSE. The patient's age would preferentially point to HSE<sup>14</sup> as the majority of ADEM cases occur in children<sup>7</sup>. Typical neuroimaging findings in HSE include abnormalities in the orbitofrontal and temporal lobe areas associated with variable degrees of mass effect, edema and, occasionally, hemorrhage<sup>15</sup>. The T2-weighted images show signal hyperintensity in the orbitofrontal and temporal lobes<sup>15</sup>. Our patient presented similar changes on her head CT scan and MRI studies, although it is noteworthy that her first CT scan was normal (Fig 1 and 2). Interestingly, CT scans performed in an early stage of the HSE can also be normal. On the other hand, in ADEM CT scans are often normal early in the course of the illness, but over one-half of the patients develop white matter lucencies later on. MRI is more sensitive for diagnosing ADEM and demon-

strates areas of increased signal intensity on T2-weighted images, mainly in the white matter<sup>16</sup>. Some of these areas exhibit gadolinium-enhancement on T1-weighted images<sup>16</sup>. However, in some case reports of AHLE in the literature, MRI demonstrates a more diffuse compromise of the brain, affecting not only the white matter, but also extensive cortical areas like our patient<sup>17</sup>.

The patient's initial CSF examination failed to demonstrate any abnormality. A repeated lumbar puncture, however, disclosed CSF with marked pleocytosis, increased protein concentration and normal glucose concentration. This CSF profile may be seen in a number of conditions such as viral meningitis and encephalitis, as well as post-infectious encephalomyelitis. As the CSF PCR for herpes simplex virus was negative, the diagnosis of HSE was ruled out. It is well established that CSF PCR for herpes simplex virus has a high sensitivity (98%) and specificity (94%) being considered the method of choice for the diagnosis of HSE<sup>18,19</sup>. However, in some circumstances a negative PCR assay can not exclude the diagnosis of HSE as pointed out by some authors<sup>20,21</sup>. One reason for negative PCR might be an advanced stage of disease as CSF PCR becomes negative over time, especially in immunocompetent patients<sup>20</sup>. This seems unlikely in our case as the CSF for PCR analysis was collected in the fourth day following the onset of the neurological symptoms. Anyway, brain biopsy remains as the gold standard method for the definite diagnosis of HSE<sup>20,21</sup>.

In a Brazilian series of 61 patients with clinically suspected HSE, only 29.5% of them had the diagnosis of HSE confirmed by CSF PCR, while 29.5% received an alternative diagnosis, such as demyelinating diseases and other CNS infections (bacterial meningitis and neurocysticercosis)<sup>22</sup>. In the remaining patients, the diagnosis was undetermined. Only two patients had non-herpetic viral encephalitis. This low frequency of non-herpetic viral encephalitis in that series probably reflects a non systematic search for CNS viruses<sup>22</sup>. However, even in a larger Brazilian series of 383 patients with aseptic meningitis and encephalitis, the use of PCR protocols for the presence of 17 infectious agents, including enteroviruses, herpes simplex virus, varicella zoster virus, Epstein-Barr virus (EBV), cytomegalovirus, measles and mumps virus, yielded a positive result in just 12% of the patients<sup>23</sup>. Interestingly, as 32.6% of patients in this series were known to have HIV infection, a large number of CSF samples were positive for EBV, a virus whose role in pathogenesis of CNS disease still remains uncertain<sup>23</sup>. It is therefore not probable that the search for other viruses by PCR analysis of the patient's CSF would turn out more revealing.

ADEM and AHLE are the only two diseases of the white matter with a monophasic clinical course associated with a rapidly progressive demyelination. As both conditions share many features they are considered part of a spectrum of diseases rather than distinct entities<sup>6,7</sup>. The more severe and more acute clinical symptomatology discriminates AHLE from ADEM<sup>8,24</sup>. In addition, MRI may establish the diagnosis in the appropriate clinical setting<sup>17</sup>. Of note is the fact that until recently AHLE was misdiagnosed as a viral encephalitis<sup>17</sup>.

AHLE is a rare demyelinating disease first described by Hurst<sup>25</sup> in 1941. Although considered a form of viral encephalitis for many years it is now considered a severe variant of ADEM. Until 1991, approximately 70 cases had been reported in the literature<sup>5,26</sup>. Rust<sup>7</sup> believes that AHLE is still becoming less frequent with the development and dissemination of safer programs of immunization. Its clinical features are usually very characteristic with previous history of a respiratory tract infection one or a few weeks before the onset of the neurological symptoms<sup>26</sup>. Following this prodromal illness, neurological symptoms such as mental changes, signs of meningeal irritation and variable focal signs start abruptly in association with fever. Death from brain edema is common in the first

week<sup>26</sup>. Although there has been no established guidelines for treatment of AHLE, the use of various combinations of immunosuppressive agents, including corticosteroids, immunoglobulin, plasmapheresis and cyclofosamide have been proved beneficial for some patients<sup>5,27,28</sup>. Occasionally patients may be discharged with no neurological sequelae<sup>5,26</sup>. Recently two case reports<sup>17,24</sup> demonstrated that treatment with high-dose intravenous corticosteroid (e.g. methylprednisolone 1 g/day for 3 days<sup>24</sup>) was followed by full recovery. The authors suggest that patients with AHLE must be put on high-dose corticosteroid therapy as early as possible<sup>17,24</sup>. Unfortunately in spite of the use of this therapy our patient remains with severe neurological deficits.

The present case illustrates that AHLE must be considered in patients with clinical and imaging suspicion of HSE. Repeated CSF examination and imaging studies may provide evidences to establish the differential diagnosis and allow early and effective treatment.

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