Probable acute disseminated encephalomyelitis due to *Haemophilus influenzae* meningitis

Case report

Pedro Beleza* MD, Department of Neurology;
Manuel Ribeiro MD, Department of Neuroradiology;
João Pereira MD;
Carla Ferreira MD;
Maria José Jordão MD;
Fátima Almeida MD, Department of Neurology, São Marcos Hospital, Braga, Portugal.

Correspondence to first author at Serviço de Neurologia, Hospital São Marcos, Largo Carlos Amarante, Apartado 2242, 4701-965 Braga, Portugal.
E-mail: beleza.76@gmail.com

DOI: 10.1111/j.1469-8749.2008.02052.x
Published online 18th March 2008

We report the case of a 17-year-old male on long-term steroid therapy for minimal lesion glomerulopathy who, after an upper respiratory infection, presented with *Haemophilus influenzae* type b meningitis. Twenty-four hours later he developed depression of consciousness which progressed to coma and left hemiparesis. Brain magnetic resonance imaging (MRI) revealed multiple lesions (hyperintense on T2 and slightly hypointense on T1) involving mainly white matter suggestive of inflammation. MRI features were compatible with acute disseminated encephalomyelitis (ADEM), although a differential diagnosis included cerebritis or vasculitis, secondary to bacterial meningitis. The patient was treated with high-dose steroids which resulted in a gradual improvement followed by complete clinical recovery. We propose a diagnosis of ADEM was the best diagnosis because of the radiological features and response to steroids. The occurrence of ADEM associated with acute meningitis, however rare, represents an important diagnostic challenge for the clinician.

See end of paper for list of abbreviations.

Neurological complications of bacterial meningitis presenting with brain lesions include venous sinus thrombosis, arterial stroke, subdural empyema, vasculitis, abscesses, and acute disseminated encephalomyelitis (ADEM).[1] We report a case illustrating the difficulty in establishing a differential diagnosis between ADEM and cerebritis or vasculitis on the basis of the current, nonspecific neuroradiological criteria of ADEM. The association of ADEM with meningitis is rare; however, a high level of awareness is needed to reach a timely diagnosis and initiate appropriate treatment.

Case report

A 17-year-old male was admitted to the Emergency Department of the São Marcos Hospital, Braga, Portugal with a dull occipital progressive headache of rapid onset that began 6 hours earlier. This clinical picture occurred in the setting of an upper respiratory infection which had lasted for 1 week, and had been treated with acetaminophen. His medical history was remarkable for minimal lesion glomerulopathy, at that time in remission with prednisolone (10mg administered daily). The patient had been vaccinated against *Haemophilus influenzae* type b (Hib) at 2, 4, 6, and 18 months, in accordance with the national immunization programme. On examination in the emergency department he was found to have neck rigidity and hyperthermia (38.5°C). Blood tests showed leukocytosis (17.6×10^9/L), neutrophilia (0.85), and increased reactive C protein (75.52mg/L). Chest X-ray and brain computed tomography (CT) were normal. Cerebrospinal fluid (CSF) revealed 1120 cells/μL (78% neutrophils, 15% monocytes, 7% lymphocytes), 1.44g/L proteins, and 41mmol/L glucose; Hib was disclosed with a latex particle agglutination antigen test, but no bacteria were detected with Gram's stain.

We were, therefore, facing acute bacterial meningitis, probably caused by Hib, in an immunocompromised young male. Antibiotic therapy against Hib was initiated with cefotaxime (2g IV 4-hourly for 14d).

At 24 hours clinical worsening occurred with depression of consciousness and bilateral pyramidal syndrome which progressed further the following day to coma and left hemiparesis. Brain CT at that time showed multiple non-contrast-enhancing hypodensities, located on both hemispheres, involving white matter and right internal capsule.

In the light of acute bacterial meningitis complicated by multiple brain lesions, we considered the following differential diagnoses: cerebritis, multiple arterial or venous strokes in the context of vasculitis, and ADEM. Therefore, methylprednisolone (1g IV/d) was initiated and the antibiotic spectrum was widened by adding to the cefotaxime a high dose of ampicillin (2g IV 4-hourly for 21d) and gentamicin (100mg IV 8-hourly for 12d), with the aim of enhancing the coverage of Gram-negative bacteria. Within 24 hours the patient regained consciousness and exhibited left hemiparesis with no language impairment. After 48 hours he was apyretic and from then on underwent a gradual clinical improvement in neurological deficits.

The remaining infection (blood and CSF cultures, polymerase chain reaction–human immunodeficiency virus), biochemistry (glucose, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, 3,3′,5-tri-iodothyronine and thyroxine levels) and immunology (immunoglobulin [Ig] G, IgM, complement [C3, C4, and CH50], antinuclear antibodies, anticardiolipin antibodies, antineutrophil cytoplasmic antibodies, and double-stranded DNA) studies were negative. A CSF examination repeated on day 4 showed signs of recovery, with 114 cells/μL (60% neutrophils, 30% lymphocytes), 1.03g/L protein, 59mmol/L glucose, and negative culture tests. Brain MRI performed on day 6 revealed multiple T2 hyperintense and T1 slight hypointense lesions with little mass effect and involving the subcortical white matter, basal ganglia, and internal capsule bilaterally (Fig. 1). No disruption of the blood–brain barrier, restriction of diffusion, or abnormality in the major arterial vessels were present. These imaging findings were compatible with areas of inflammation. Afterwards, the patient showed a clinical recovery associated with improvement of laboratory indices with no further recurrences for a period of more than 1 year. On day 16 he was asymptomatic with a normal neurological examination; CSF showed 14 cells/μL (95% lymphocytes) and hypoglycorrachia (28mmol/L; 34% glycemia) with normal proteinorrachia (0.43g/L). MRI performed on day 18 showed a volume decrease of the lesions (Fig. 1 c,d) and by month 7 no new lesion was found.

Discussion

In the context of acute bacterial meningitis supported by clinical and laboratory data, the detection of Hib in CSF was based on a latex-particle agglutination antigen test because Gram's staining and a bacterial study were negative. This method has proved to be highly sensitive (95.7%) and specific (100%) for the diagnosis of Hib meningitis,[2] even in blood-stained CSF specimens.[3] On the basis of this knowledge, we provided antibiotic therapy directed against Hib, which is supported by other studies.[4]

Hib meningitis is a rare finding in adults, accounting for 1.8% of meningitis cases.[5] In our patient, Hib meningitis might well have resulted from the occurrence of a respiratory infection in an immunosuppressed patient related to prolonged steroid therapy. Predisposing factors have been found in 74% of adults with Hib meningitis[6] and include pneumonia, otitis, diabetes, and alcoholism.[7] In addition, prolonged steroid therapy provides a low risk of infections in general and not specifically meningitis or cerebritis.[8] However, it increases susceptibility to infections due to encapsulated bacteria, such as Hib.[9]

In the reported patient, meningitis had a surprising deteriorating course, despite continuing therapy: within 48 hours the patient had become comatose with multiple brain lesions on brain CT. The differential diagnosis included cerebritis, vasculitis, and ADEM. MRI was consistent with ADEM, because it showed multiple large, asymmetric, mainly white matter T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense lesions.[10] No MRI criterion has yet been identified that is specific to ADEM,[11] and T2 and FLAIR hyperintense lesions may also be seen in cerebritis.[12] Vasculitis was less likely to be involved because MRI did not show restricted diffusion and the angioMRI was normal; it would also be unlikely for vasculitic lesions to resolve completely after only a single course of steroids. The brain lesions were probably of an inflammatory nature because they were T2 hyperintense and T1 hypointense and resolved with little scarring.[10] Solely on the basis of MRI, it is not possible to distinguish ADEM with allergic inflammatory perivenous encephalitis from cerebritis with inflammatory lesions related to bacterial meningitis. This raises the issue of the specificity of the actual diagnosis of ADEM based on clinical–imagiological grounds. The diagnosis of ADEM has evolved significantly, mainly as a result of MRI. One proposed radiological classification of ADEM includes four patterns of cerebral involvement: (1) ADEM with small lesions (less than 5mm); (2) ADEM with large, confluent lesions; (3) ADEM with additional symmetric bithalamic involvement; and (4) acute haemorrhagic encephalomyelitis.[13] This heterogenity in neuroradiological criteria of ADEM has led to increasing recognition but has also led to a significant blurring of the definition of the disease. Studies reported in the literature consider different definitions of ADEM[11] and it is possible that not all these syndromes correspond to pathological ADEM.

In our patient, although histopathological studies were not performed, we considered ADEM as the most probable diagnosis on the basis of clinical and neuroimaging results. ADEM should be considered whenever there is a close temporal relation between an infection and the subacute, polysymptomatic onset of neurological deficits attributable to the central nervous system.[10] The suspicion of ADEM was driven by the depression of consciousness, the speed of onset of neurological deficits, and the distribution of the lesions predominantly located in the white matter. Accordingly, others have suggested that worsening encephalopathy and persistent fever in meningitis may indicate para-infectious ADEM.[14] It is crucial to perform a timely diagnosis because early use of high-dose steroids has been shown to improve the prognosis of ADEM.[15]

The main differential diagnosis was cerebritis. However we felt that cerebritis was less likely because the MRI did not show the typical distribution of the lesions. Cerebritis resulting from direct extension of meningeal infection, as might have been the case in our patient, should not show deep brain lesions.[12] Even in the setting of haematogeneous spread, the lesions

should be located at the grey–white matter junction.[12] Moreover, the lesions lacked mass effect and showed no restricted diffusion. The diagnosis of probable ADEM was corroborated by the dramatic and rapid clinical improvement associated with the laboratory and imagiological recovery seen after the initiation of methylprednisolone, with no further recurrences.

Although less frequently than viruses, some bacterial agents have been found to be related to ADEM. These include *Borrelia burgdorferi*,[16] *Chlamydia pneumoniae*,[17] *Legionella pneumophila*,[18] *Mycoplasma pneumoniae*,[19] *Rickettsia rickettsi*,[20] *Streptococcus,*[21] and *Pasteurella multocida*.[14] However, to our knowledge only two other case reports have described ADEM due to bacterial meningitis, and none was associated with Hib.[14,19]

Here we have shown, for the first time, to our knowledge, that ADEM can occur in association with acute Hib meningitis. In the setting of an acute bacterial meningitis, complicated with depression of consciousness and focal neurological deficits, the hypothesis of ADEM must be considered and should prompt further neurological investigation. Timely diagnosis and early treatment with high-dose corticoids may improve the prognosis of ADEM.

Accepted for publication 15th January 2008.

Acknowledgements

The authors would like to thank José Armando Leitão for linguistic advice.

References

1. Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006; **354:** 44–53.
2. Camargos PA, Almeida MS, Cardoso I, et al. Latex particle agglutination test in the diagnosis of Haemophilus influenzae type B, Streptococcus pneumoniae and Neisseria meningitidis A and C meningitis in infants and children. *J Clin Epidemiol* 1995; **48:** 1245–50.
3. Camargos PA, Almeida MS, Filho GL, Batista KW, Carvalho AG, Pereira CL. Blood stained cerebrospinal fluid responsible for false positive reactions of latex particle agglutination tests. *J Clin Pathol* 1994; **47:** 1116–17.
4. Das BK, Gurubacharya RL, Mohapatra TM, Mishra OP. Bacterial antigen detection test in meningitis. *Indian J Pediatr* 2003; **70:** 799–801.
5. Tang LM, Chen ST, Wu YR. Haemophilus influenzae meningitis in adults. *Diagn Microbiol Infect Dis* 1998; **32:** 27–32.
6. Bol P, Spanjaard L, van Alphen L, Zanen HC. Epidemiology of Haemophilus influenzae meningitis in patients more than 6 years of age. *J Infect* 1987; **15:** 81–94.
7. Spagnuolo PJ, Ellner JJ, Lerner PI, et al. Haemophilus influenzae meningitis: the spectrum of disease in adults. *Medicine (Baltimore)* 1982; **61:** 74–85.

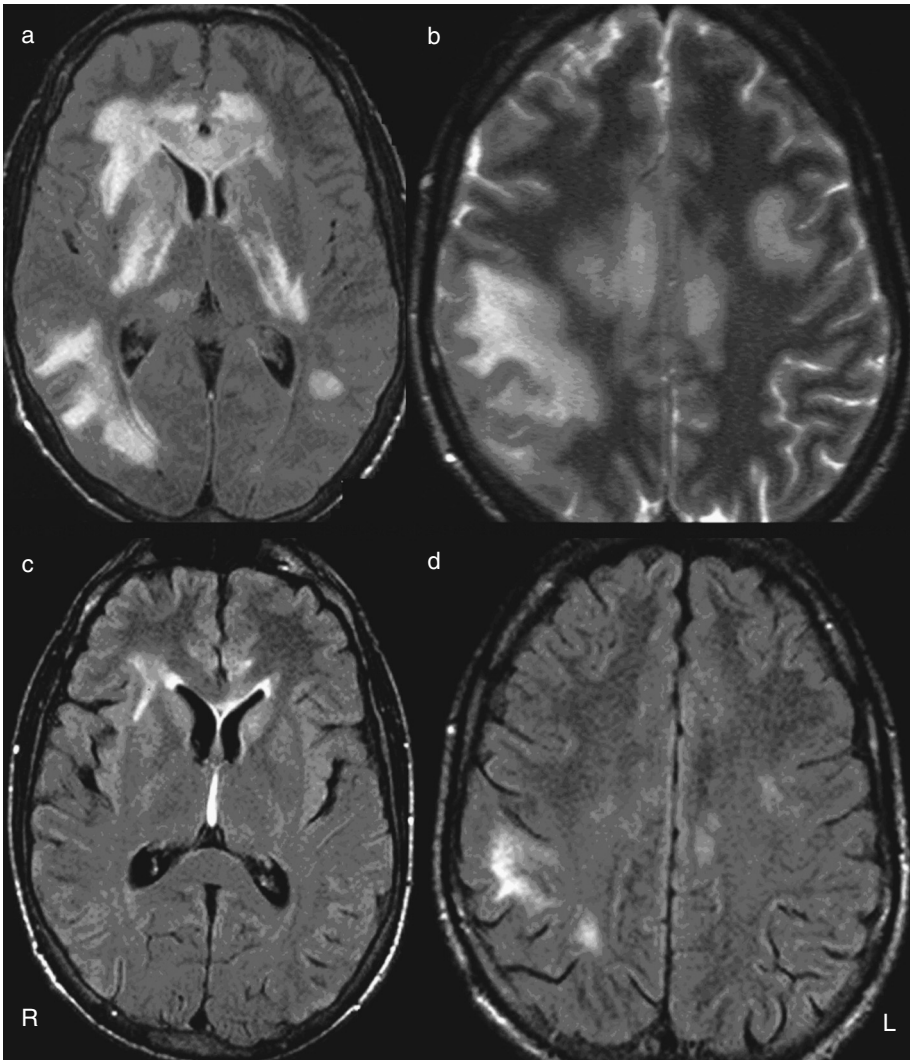

Figure 1: *(a, b) brain magnetic resonance images (MRIs) performed on day 6. Axial fluid-attenuated inversion recovery (FLAIR) and axial T2–TSE show bilateral asymmetric confluent hyperintensity involving subcortical white matter, corpus callosum, and deep grey matter. (c, d) MRIs performed on day 18. FLAIR shows a decrease in lesion load.*

8. Wilckens T, De Rijk R. Glucocorticoids and immune function: unknown dimensions and new frontiers. *Immunol Today* 1997; **18:** 418–24.
9. Vinuesa CG, de Lucas C, Cook MC. Clinical implications of the specialised B cell response to polysaccharide encapsulated pathogens. *Postgrad Med J* 2001; **77:** 562–69.
10. Menge T, Hemmer B, Nessler S, et al. Acute disseminated encephalomyelitis: an update. *Arch Neurol* 2005; **62:** 1673–80.
11. Tardieu M, Mikaeloff Y. What is acute disseminated encephalomyelitis (ADEM)? *Eur J Paediatr Neurol* 2004; **8:** 239–42.
12. Falcone S, Post MJ. Encephalitis, cerebritis, and brain abscess: pathophysiology and imaging findings. *Neuroimaging Clin N Am* 2000; **10:** 333–53.
13. Tenembaum S,Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. *Neurology* 2007; **68** (Suppl. 2)**:** S23–S36.
14. Proulx NL, Freedman MS, Chan JW, Toye B, Code CC. Acute disseminated encephalomyelitis associated with Pasteurella multocida meningitis. *Can J Neurol Sci* 2003; **30:** 155–58.
15. Shahar E, Andraus J, Savitzki D, Pilar G, Zelnik N. Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. *J Child Neurol* 2002; **17:** 810–14.
16. van Assen S, Bosma F, Staals LM, et al. Acute disseminated encephalomyelitis associated with Borrelia burgdorferi. *J Neurol* 2004; **251:** 626–29.
17. Heick A, Skriver E. Chlamydia pneumoniae-associated ADEM. *Eur J Neurol* 2000; **7:** 435–38.
18. Spieker S, Petersen D, Rolfs A, et al. Acute disseminated encephalomyelitis following Pontiac fever. *Eur Neurol* 1998; **40:** 169–72.
19. Riedel K, Kempf VA, Bechtold A, Klimmer M. Acute disseminated encephalomyelitis (ADEM) due to Mycoplasma pneumoniae infection in an adolescent. *Infection* 2001; **29:** 240–42.
20. Wei TY, Baumann RJ. Acute disseminated encephalomyelitis after Rocky Mountain spotted fever. *Pediatr Neurol* 1999; **21:** 503–05.
21. Dale RC, Church AJ, Cardoso F, et al. Poststreptococcal acute disseminated encephalomyelitis with basal ganglia involvement and auto-reactive antibasal ganglia antibodies. *Ann Neurol* 2001; **50:** 588–95.

List of abbreviations

ADEM	Acute disseminated encephalomyelitis
FLAIR	Fluid-attenuated inversion recovery
Hib	Haemophilus influenzae type b