

Case reports

Clinical, electrophysiological and brain imaging features during recurrent ictal cortical blindness associated with chronic liver failure

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Abstract

Transient neuroimaging features indicating primary cortical and secondary subcortical white matter cytotoxic oedema have been described in association with prolonged or intense seizures. We describe the unusual condition of recurrent ictal cortical blindness due to focal occipital status epilepticus, in the context of chronic hepatic failure. There was a close association between the onset and disappearance of clinical, electrophysiological and magnetic resonance imaging abnormalities.

Key words : Focal status epilepticus ; hepatic failure ; MRI ; cortical blindness.

Case report

In November 2003, a 55-year old woman was admitted to the Neurology department for progressive bilateral visual loss over a two-day period, together with continuous occipital headaches. She had end-stage liver disease due to hepatitis B, with portal hypertension and stage 1 to 2 hepatic encephalopathy (HE). Her treatment included lactulose, esomeprazole, furosemide, spironolactone, lamivudine and cetirizine. Body temperature was normal on admission. Blood pressure was 120/70 mmHg. Neurological examination revealed a confusional state with complete bilateral visual loss, except for bright light. The direct and consensual pupillary light reflexes were normal. As the ophthalmological examination was otherwise unremarkable, a diagnosis of cortical blindness was proposed. Laboratory investigations revealed signs of hepatic insufficiency. The blood ammonia concentration was 96 mg/dl (normal value below 125 mg/dl). Cerebrospinal fluid analysis was normal. Electroencephalography (EEG) demonstrated repeated episodes of focal occipital seizures starting with fast activity on right or left occipital derivations, prolonged by continuous slow spikes on both occipital electrodes (Fig. 1a). Brain magnetic resonance imaging (MRI), obtained three days after onset of symptoms, revealed areas of increased signal intensity on T2, FLAIR and diffu-

sion-weighted (DW) images within the cortex of the parieto-occipital regions, with an apparent diffusion coefficient (ADC) decreased to between 90 to 50% of the normal value (Fig. 2a). Antiepileptic treatment was initiated using gabapentin (2400 mg/day) and levetiracetam (2 g/day), since these drugs are not metabolised by the liver. Intravenous methylprednisolone (500 mg/day for 5 days) was administered at the same time, followed by an oral tapering regimen. Subsequently, the number of seizures, recorded under continuous EEG monitoring, decreased progressively and the background rhythm of the EEG increased from 5-6 to 7-8 cycles per second. Two weeks after admission, the patient was able to name objects on visual inspection. One month later, EEG failed to reveal any residual epileptiform activity. Early MRI follow-up examination demonstrated regression of the cortical oedema but the appearance of similar changes within the adjacent subcortical white matter areas (Fig. 2b).

In March 2004, the patient underwent orthotopic liver transplantation and was treated with tacrolimus (up to 7 mg/day). Anti-epileptic medication was withdrawn in the immediate post-operative period. One week later, the patient's status required readmission to the intensive care unit after several generalized tonic-clonic seizures. She then developed non convulsive status epilepticus with bilateral continuous generalized epileptiform discharges on EEG monitoring, which did not respond to intravenous phenytoin (500 mg/day) or valproate (1600 mg/day). Seizures were finally controlled by levetiracetam (2 g) and gabapentin (2100 mg). As serum levels of tacrolimus were toxic at 24.7 ng/ml (normal range between 5 and 14 ng/ml), the daily dose was reduced to 1 mg/day to limit its potential neurotoxic effects. This resulted in acute graft rejection, which required intravenous administration of methylprednisolone.

In September 2004, ophthalmological examination revealed a visual acuity of 9/10 and a right superior altitudinal visual field defect, considered to be of peripheral origin. EEG showed no

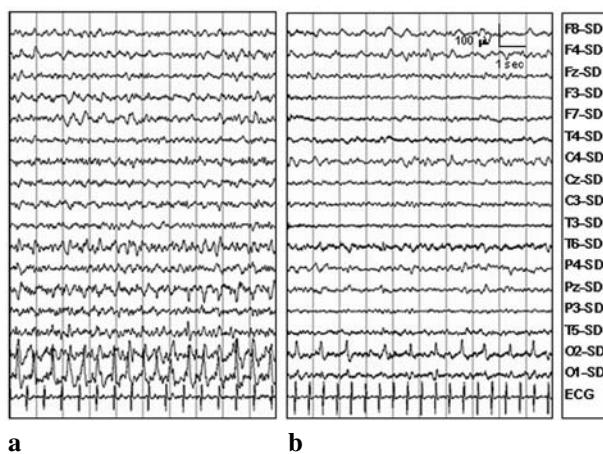


FIG. 1. — a. *1st December 2003*. EEG shows continuous slow spikes on both occipital derivations, intermixed with slow waves, more diffuse on the right hemisphere ; b. *21st December 2004*. EEG shows continuous slow spikes, at about 1 Hz, on the right occipital derivation, with predominant slow waves on the right hemisphere.

epileptiform activity, but a diffusely slow background rhythm at 6-7 cycles per second. Late follow-up MRI examination, performed 12 months after the first one, revealed an almost complete resolution of the imaging abnormalities, with only a small residual area of gliotic scar and loss in white matter volume in the right occipital lobe (Fig. 2c).

In December 2004, the patient presented again with headache and visual loss, predominantly in the left visual field. EEG showed continuous slow spike-and-waves and polyspike-and-waves on the right hemisphere, while background rhythm was still visible on the left hemisphere or continuous slow spikes on the right occipital area (Fig. 1b). This correlated with the reappearance of extensive cortical oedema in the right parietal and occipital lobes on MRI (Fig. 2d). The daily doses of gabapentin and levetiracetam were increased to 3600 mg and 3 g respectively. Topiramate was added to the treatment regimen at the daily dose of 25 mg. Unfortunately, the patient's status worsened because of chronic graft rejection and she died in February 2005 from hepatic insufficiency, internal haemorrhage, and septicaemia.

Discussion

We herein describe the unusual condition of recurrent ictal cortical blindness, associated with brain MRI abnormalities, in a patient suffering from chronic hepatic failure. Cortical blindness has sometimes been described as a negative or post-ictal manifestation of occipital lobe seizures, although positive ictal symptoms such as elementary visual hallucinations are by far more frequent (Blume *et al.*, 2005 ; Salanova *et al.*, 1992 ; Panayiotopoulos, 1999). The occipital cortex displays elective sensitivity to various metabolic

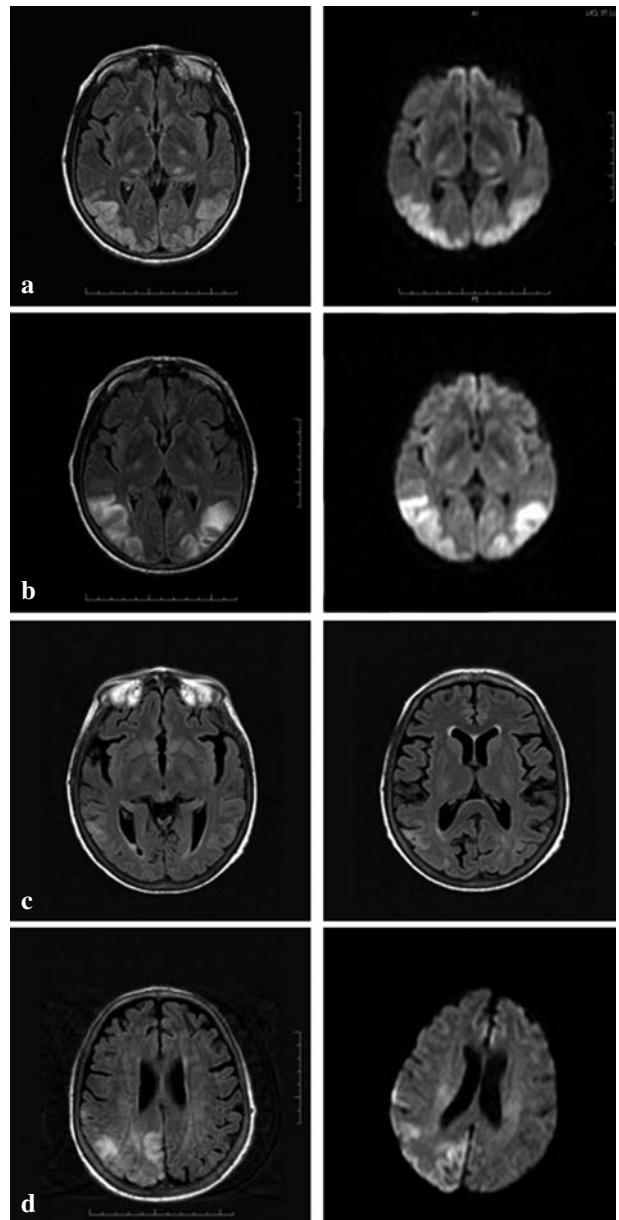


FIG. 2. — a. *1st December 2003*. FLAIR MR image shows symmetrical signal hyperintensity of the occipito-parietal cortical ribbon. Diffusion-weighted (DW) image shows increased signal in the areas of the FLAIR abnormality ; b. *10th December 2003*. Axial FLAIR image shows persistence of cortical oedema in the occipito-parietal regions, with extension to the subcortical white matter. Note the increased signal upon DW imaging ; c. *30th November 2004*. Axial FLAIR images show an almost complete resolution of the lesions, with only residual gliotic scar and atrophy in the right occipital lobe ; d. *30th December 2004*. Axial FLAIR image shows the recurrence of the cortical oedema in the right occipito-parietal region, with increased signal on DW image.

insults, such as hypoxia, hypotension, or hepatic failure. Ammar *et al.* (2003) reported on a case of permanent cortical blindness following grade 2 HE, with normal imaging and no seizure activity on EEG. Similarly, Miyata *et al.* (1988) reported transient cortical blindness in a patient with recurrent episodes of HE in whom imaging and EEG failed to reveal any abnormality. Hepatic insufficiency by

itself is rarely associated with seizures. In a retrospective study of 118 patients with HE, Ficker *et al.* (1997) documented only 18 patients (15%) with epileptiform activities on EEG, 12 of whom had clinical seizures. These patients had a poor prognosis. Our case differs from those previously reported, in that the cortical blindness in our patient resulted from focal occipital status epilepticus with documented EEG ictal discharges and MRI abnormalities.

Initial MRI examination demonstrated increased signal intensity restricted exclusively to the bilateral occipital cortical ribbons. Decreased ADC values reflecting cytotoxic oedema raised a differential diagnosis of oedema due to status epilepticus, ischaemia, or encephalitis. The latter diagnosis was excluded by cerebrospinal fluid analysis. The lesions did not respect a vascular territory, arguing against ischaemia of arterial origin. Cerebral venous thrombosis was also excluded by imaging. Although acute onset of headache, confusion, and visual loss constitutes the usual clinical triad of posterior reversible encephalopathy syndrome (PRES), this diagnosis was not retained because of the elective initial cortical involvement and the reduction in ADC values arguing against vasogenic oedema. Indeed, cytotoxic oedema is usually considered to be a secondary complication of severe vasogenic oedema in the common radiological forms of PRES (Kahana *et al.*, 2005; Lamy *et al.*, 2004; Kinoshita *et al.*, 2003; Provenzale *et al.*, 2001). Moreover, PRES has been associated with many conditions including uncontrolled hypertension, uraemia, and immunosuppressant therapy with calcineurin inhibitors in transplant recipients, but not with liver failure (Lamy *et al.*, 2004; Stott *et al.*, 2005).

In our patient, MRI performed two weeks after the start of symptoms, showed an almost complete regression of the cortical oedema with normalisation of the ADC values, but appearance of oedema in the white subcortical matter. This apparent normalisation was presumed to be due to intravoxel averaging of the ADC values from both sub-areas of vasogenic and cytotoxic oedema. Previous reports have documented that even though cortical involvement is prominent in focal status epilepticus, subcortical lesions may be observed days or even weeks after the start of status epilepticus (Cole, 2004; Cohen-Gadol *et al.*, 2004; Doherty *et al.*, 2004). The MRI lesions observed in our patient were, therefore, likely to be due to the periictal state. After treatment with antiepileptic drugs that are not metabolised by the liver, visual acuity gradually improved in our patient, concomitant with the disappearance of the epileptiform discharges recorded on EEG and the dramatic resolution of the abnormalities detected on MRI examination. However, MRI performed 5 and 12 months after the initial episode showed a residual area of gliotic

scar and secondary loss in white matter volume of the right occipital lobe. This probably reflects a mixed end-stage process combining demyelination and neuronal cell death, indicating that permanent ischaemic damage can follow a transient phase of cytotoxic oedema. The status epilepticus suffered by the patient one week following liver transplantation can be attributed to both the withdrawal of antiepileptic medication and to tacrolimus therapy. Indeed, calcineurin inhibitors are known to be responsible for leucoencephalopathy in organ transplant recipients, resulting in seizures (Singh *et al.*, 2000). Clinical and imaging abnormalities resolve within weeks after withdrawal of the offending medication (Singh *et al.*, 2000; Schuring *et al.*, 2003; Arikhan *et al.*, 2003). Unfortunately, brain MRI was not performed at that time in our patient.

Twelve months after the initial episode, our patient, suffering from liver failure due to chronic graft rejection, presented again with left visual field loss due to focal right occipital status epilepticus. Strikingly, this relapse coincided with the reappearance of unilateral cortical injury on MRI. To our knowledge, the recurrence of cortical oedema in the context of focal status epilepticus, with almost complete damage restitution in-between the clinical episodes, has not been documented previously.

In summary, we have described a case of a patient with a relapse of ictal cortical blindness on a background of chronic liver failure, coinciding with the appearance of occipito-parietal cortical oedema on brain MRI and of focal occipital status epilepticus on EEG. The initial episode of focal status epilepticus was efficiently treated by gabapentin and levetiracetam, and resulted in almost complete resolution of brain abnormalities seen on MRI. Nine months after undergoing liver transplantation, recurrence of focal status epilepticus resulted in the reappearance of clinical, EEG, and radiological manifestations.

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