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Cerebral vasculitis mimicking migraine with aura in a patient with Crohn's disease

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Abstract

Introduction : Whereas extraintestinal manifestations of inflammatory bowel disease in general are quite common, cerebral vasculitis is considered a very rare condition. We present a case of Crohn's disease-associated vasculitis mimicking migraine with aura.

Case Description : A 28-year-old woman with Crohn's disease and known migraine with aura had suffered from daily migraine attacks with recurrent focal neurological deficits for 6 weeks. Cerebral magnetic resonance imaging showed multiple acute, subacute, and chronic ischemic lesions in different vascular territories. Magnetic resonance and computed tomography angiography demonstrated vessel changes consistent with cerebral vasculitis. Laboratory investigations revealed systemic inflammation and lymphomonocytic pleocytosis of cerebrospinal fluid, supporting the diagnosis of Crohn's disease-associated vasculitis. Symptoms and inflammatory parameters quickly normalized after high-dose prednisolone treatment. During immunosuppressive therapy, migraine reccurred only once in 11 months.

Discussion : Cerebral vasculitis is a very rare but severe complication in Crohn's disease and should be excluded in case of comorbidity with migraine with aura. In our patient, migraine with aura may have been the only symptom of cerebral vasculitis for several years.

Key words : Vasculitis, central nervous system ; migraine disorders ; migraine with aura ; cerebral infarction ; crohn disease.

Introduction

Crohn's disease (CD) constitutes the most important chronic inflammatory bowel disease (IBD) along with ulcerative colitis. In developed countries, the incidence of CD is estimated to range from 5 to 10 per 100,000 per year, with a reported prevalence of 50 to 200 per 100,000 (Carter M. J., *et al.*, 2004). Whereas extraintestinal manifestations of IBD in general are quite common, neurological involvement occurs less frequently. In an overview of 638 IBD patients, only 19 (3%) showed neurological complications not related to malabsorption or iatrogenic cause (Carter M. J., *et al.*, 2004). Cerebrovascular disease is even less frequent, with one study reporting cerebrovascular complications in only 9 of 7199 (0.12%) patients with IBD (Carter M. J., *et al.*, 2004). Besides hypercoagulability due to various factors, cerebral vasculitis is recognized as a very rare cause of cerebral ischemia in patients with CD (Lossos A., *et al.*, 1995). Up to now, however, only a few cases of CD-associated cerebral vasculitis have been published (Talbot R. W., *et al.*, 1986 ; Adamek R. J., *et al.* 1993 ; Lossos A., *et al.*, 1995 ; Gobbele R., *et al.*, 2000 ; Ghezzi A., et Zaffaroni M., 2001). Vasculitis-associated autoantibodies have been found only inconstantly in these patients (Adamek R. J., *et al.* 1993 ; Brohee P., *et al.*, 1997 ; Gobbele R., *et al.*, 2000 ; Krapf H., *et al.*, 2000 ; Schluter A., *et al.*, 2004). There have been only few controlled studies on the treatment of cerebral vasculitis and no controlled studies on the treatment of CD-associated cerebral vasculitis at all (Ferro J. M., 1998). Usually, high-dose steroids combined with or switched to cyclophosphamide are recommended (Ferro J. M., 1998). However, there are striking differences in current treatment regimens, and optimal duration of therapy is not known.

Case description

A 28-year-old woman, who had suffered from migraine with aura at a frequency of 3-4 attacks per month since the age of 17 and had been seen irregularly by a neurologist during the last years, presented with daily migraine attacks for 6 weeks. Oral metamizole was used for the treatment of her acute migraine attacks, but had lost effectiveness over the last weeks. Symptoms fulfilled the International

Headache Society (IHS) diagnostic criteria for migraine with aura (International Headache Society, 2004). The patient experienced typical migraine attacks associated with photophobia, phonophobia, and nausea. Migraine headache usually was either preceded or accompanied by a homonymous scintillating scotoma, mostly followed by unilateral sensory symptoms and infrequently also by short-lasting motor deficits. Neither headache nor aura characteristics had changed over the last 6 weeks, although the frequency of migraine attacks had risen dramatically.

The patient had been diagnosed with CD at the age of 16 years on the basis of a gut biopsy. Due to exacerbation of gastrointestinal symptoms, immunosuppressive therapy with azathioprine was started 6 months before admission, but was changed to prednisolone because of increasing liver enzymes 2 months later. The prednisolone dose was gradually reduced from 80 to 20 mg per day. The further medical history of the patient was unremarkable except for smoking (12 pack/year) and aspirin allergy.

On admission, the patient complained of an acute migraine with aura attack. Hypoesthesia of the left forearm and lower leg, minor ataxia of the left arm, and gait instability were present at this time.

Cerebral magnetic resonance imaging (MRI) showed multiple acute, subacute, and chronic ischemic lesions in different vascular territories, one small haemorrhage close to an acute ischemic lesion, and multiple supratentorial T2-hyperintense white matter lesions (WML) with partial gadolinium enhancement (Fig. 1). Magnetic resonance angiography (MRA) revealed an irregular configuration in the petrous segment of the left distal internal carotid artery (dICA) and one branch of the right middle cerebral artery (MCA). Computed tomography angiography (CTA) one day later additionally detected a short-segment stenosis of the right MCA main stem (Fig. 2). In line with these findings, transcranial Doppler ultrasound (TCD) showed increasing peak flow velocities of the right MCA main stem (110 cm/s, day 1 ; 165 cm/s, day 4). Cardiac diagnostics including transoesophageal echocardiography and 24-hour electrocardiography were unremarkable.

Laboratory investigations revealed systemic inflammation, as indicated by leukocytosis (12.7×10^9/l, normal range $4.0\text{-}9.0 \times 10^9$/l), elevated erythrocyte sedimentation rate (29 mm/h, normal < 10 mm/h), C-reactive protein (2.3 mg/dl, normal < 0.5 mg/dl), and fibrinogen (766 mg/dl, normal range 200-450 mg/dl). Cerebrospinal fluid (CSF) analysis showed lymphomonocytic pleocytosis (70 cells/µl, normal range 0-4 cells/µl) with marginal blood–brain barrier disturbance (albumin quotient 8.1×10^{-3}, normal $< 8 \times 10^{-3}$). There were identical oligoclonal IgG bands in CSF and serum. No evidence of acute or chronic infection was found by microbiological and extensive serological testing in serum and CSF. PCR for herpesviruses was negative in CSF. Serological vasculitis screening was unremarkable, whereas coagulation diagnostics revealed a heterozygous prothrombin G20210A mutation.

Catheter angiography and brain biopsy were refused by the patient. We diagnosed cerebral vasculitis on the basis of the clinical findings, the MRI, and the CSF findings.

Following high-dose intravenous prednisolone (1000 mg per day) and heparin anticoagulation, the headache and the neurological deficits quickly resolved. The patient fully recovered within one day. Systemic inflammation parameters normalized within a few days. After one week, intravenous prednisolone was replaced with oral therapy (90 mg per day) and long-term immunosuppressive therapy with mercaptopurine was started. Anticoagulation was replaced with clopidogrel after completion of cardiac diagnostics.

At follow-up 6 months later, cerebral MRI showed transition from most acute and subacute ischemic lesions to chronic infarction, but no disease activity was observed, and MRA did not reveal any vascular changes (Figs. 2 and 3). Peak flow velocities in TCD also had normalized. During immunosuppressive therapy, migraine recurred only once in 11 months.

Discussion

The patient's symptoms consisted of daily migraine attacks, which differed from her usual migraine with aura episodes only in their high frequency and the poor effectiveness of metamizole. Clinical presentation of cerebral vasculitis is highly variable and may involve headache and focal neurological deficits as well as encephalopathy, psychiatric disorders, loss of consciousness, and seizures (Ferro J. M., 1998). Evidence of multiple ischemic lesions of various ages and different vascular territories combined with dynamic arterial changes and non-specific T2-hyperintense WML, as well as documentation of systemic inflammation and lymphomonocytic pleocytosis in CSF, are characteristic for cerebral vasculitis (Ferro J. M., 1998). In the clinical context, with exacerbation of CD only 6 months before admission, symptom onset during gradual prednisolone reduction, and rapid clinical improvement during high-dose prednisolone treatment, CD-associated cerebral vasculitis seems the most likely diagnosis, even though confirmation by brain biopsy

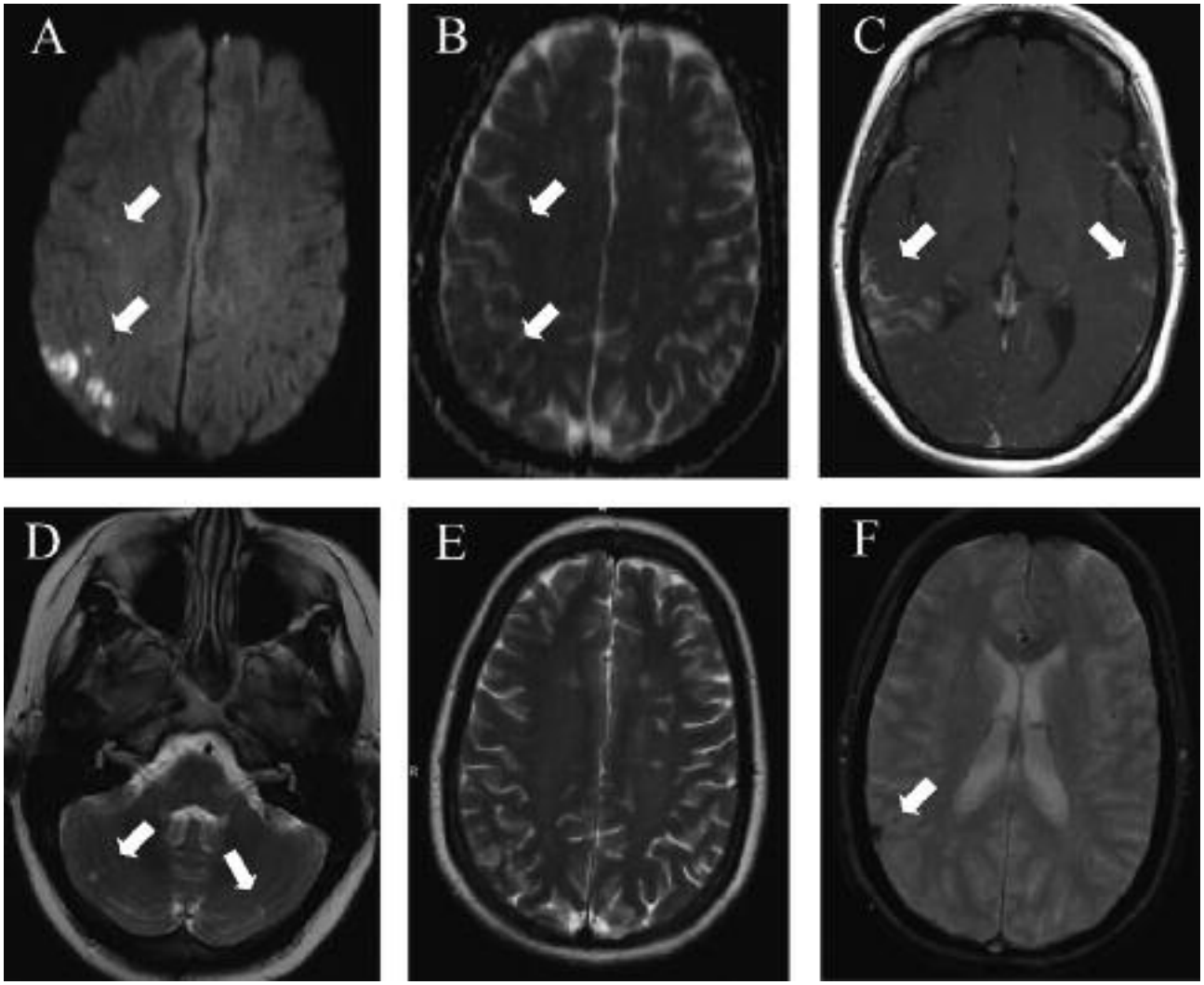

FIG. 1. — Hyperintensities in the right parietal and frontal lobes on axial diffusion-weighted (b = 1000) MRI (arrows, A) with corresponding hypointensities on the apparent diffusion coefficient map (arrows, B) indicating acute cerebral ischemia. Abnormal gadolinium enhancement in the right temporoparietal region and left temporal lobe on axial T1-weighted sequence (arrows, C) suggestive of blood-brain barrier disruption in subacute ischemia. Cerebellar signal changes indicating chronic ischemia (arrows, D) and multiple supratentorial WML (E) on axial T2-weighted sequence. Hypointensity (arrow, F) suggestive of cerebral haemorrhage on axial T2*-weighted sequence.

is lacking. The absence of vasculitis-associated autoantibodies in the patient is in line with diagnosis of CD-associated vasculitis (Gobbele R., *et al.*, 2000 ; Krapf H., *et al.*, 2000 ; Schluter A., *et al.*, 2004).

Thromboembolic infarction has to be mentioned as a possible differential diagnosis, as an increased risk for thromboembolic events, especially in active IBD, is well documented and may result in cerebral infarction and venous sinus thrombosis (Talbot R. W., *et al.*, 1986 ; Miehsler W., *et al.*, 2004 ; Solem C. A., *et al.*, 2004). In a recent study, IBD was associated with a 3.6-fold increased risk for thromboembolic complications (Miehsler W., *et al.*, 2004). Hypercoagulability due to various factors has been described, including thrombocytosis, elevation of factor V, factor VIII, and fibrinogen, deficiency of antithrombin III, and antiphospholipid antibody syndrome (Lake A. M., *et al.*, 1978 ; Mevorach D., *et al.*, 1996). Prothrombin G20210A mutation is known to further increase the thrombotic risk in IBD (Talbot R. W., *et al.*, 1986). However, there was no evidence of cardiac or paradoxical embolism in the patient, and thromboembolic infarction would not have caused CSF pleocytosis without marked blood-brain barrier disturbance.

Migrainous stroke also has to be considered as a differential diagnosis. Migraine with aura is considered to be an independent risk factor for ischemic stroke in women (Kurth T., *et al.*, 2006). Patients suffering from migraine with aura recently were shown

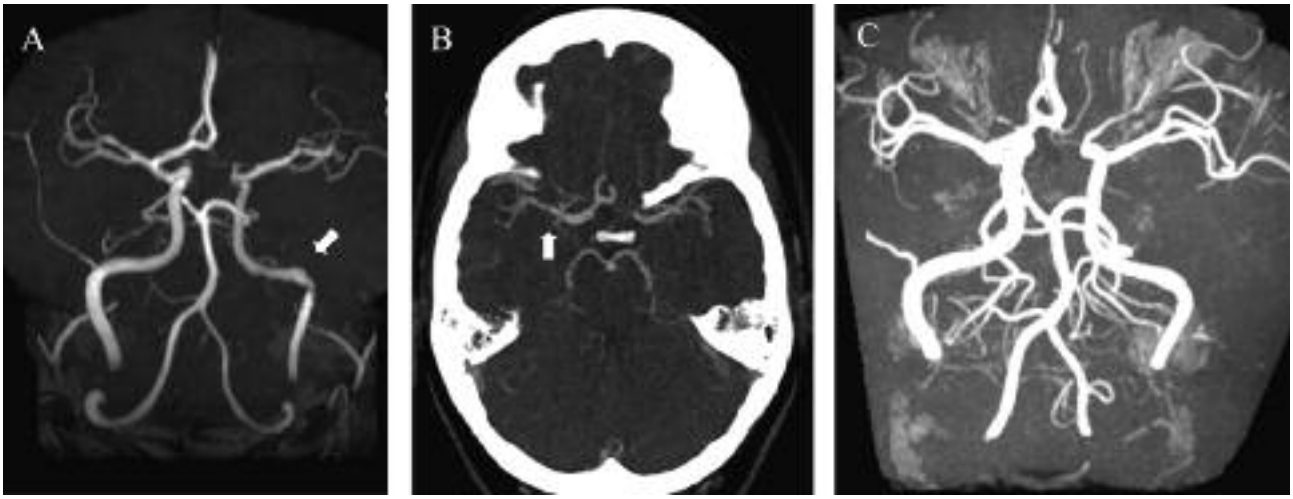

FIG. 2. — 3D time-of-flight MRA demonstrating irregular configuration of left petrous segment dICA (arrow, A) on the day of admission. CTA showing short-segment stenosis of the right MCA main stem one day later (arrow, B). MRA without any vascular changes at 6-month follow-up (C).

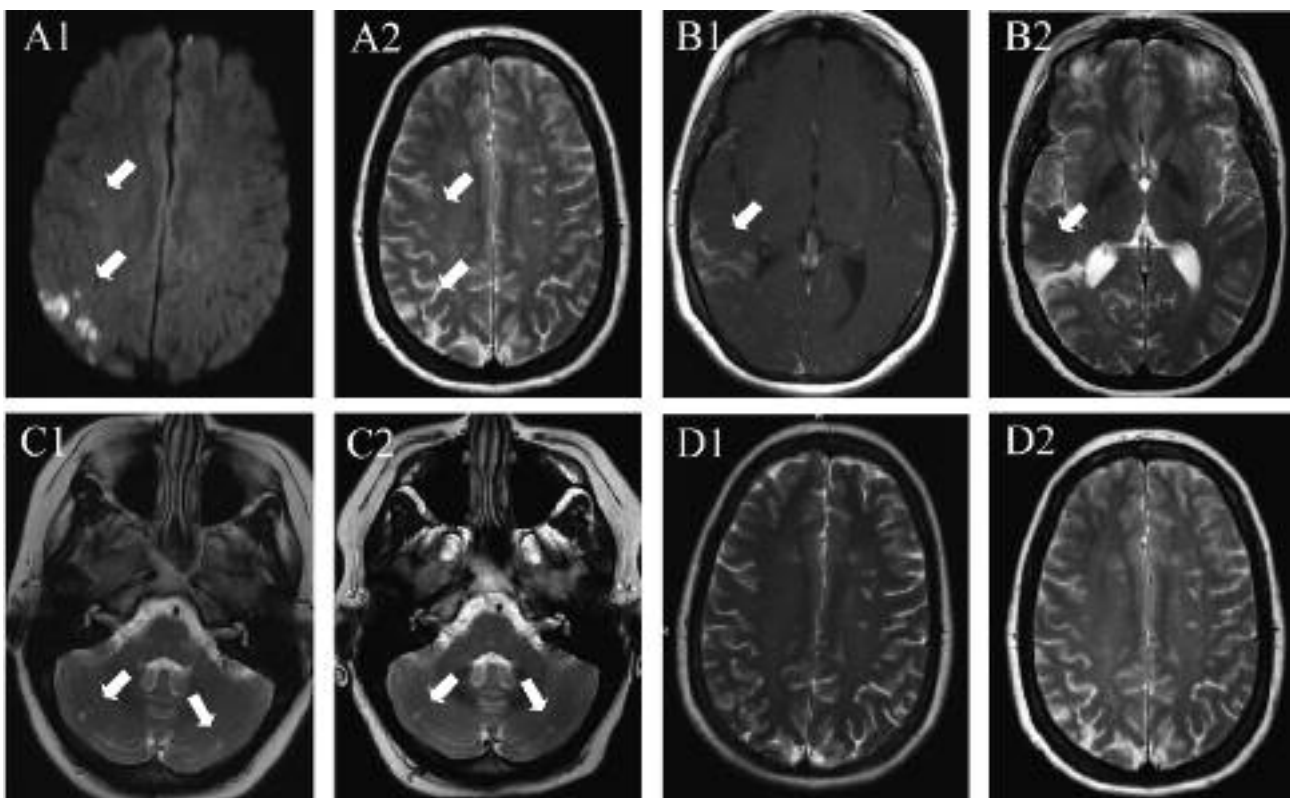

FIG. 3. — Transition of acute cerebral ischemia in the right parietal and frontal lobes as shown by axial diffusion-weighted (b = 1000) MRI (arrows, A1) and of subacute cerebral ischemia in the right temporoparietal region as demonstrated by axial T1-weighted sequence (arrows, B1) to chronic infarction patterns in follow-up axial T2-weighted MRI after 6 months (arrows, A2 and B2). Cerebellar signal changes indicating chronic ischemia (arrows, C1) and supratentorial WML (D1) as shown on axial T2-weighted sequence remaining unchanged in follow-up axial T2-weighted MRI after 6 months (C2 and D2).

to have a 13.7-fold increased risk for silent infarcts in the posterior circulation territory, and, among women, migraine also was associated with a 2.1-fold increased risk for deep white matter lesions in the same study (Kruit M. C., *et al.*, 2004). Therefore, both the cerebellar signal changes indicating chronic ischemia and the multiple supratentorial WML in our patient may have been linked to the diagnosis of migraine with aura. Moreover, as intravenous cortisone is commonly used in status migrainosus, rapid clinical improvement during prednisolone may have been simply related to therapeutic termination of migraine. The inflammatory CSF changes in our patient, however, cannot be explained by migraine. As inflammation is increasingly accepted to play a role in the pathogenesis of migraine (Waeber C., Moskowitz M. A., 2005), however, cerebral vasculitis may have triggered migraine attacks by inflammatory pathways. Interestingly, migraine developed only one year after diagnosis of CD in the patient and migraine activity decreased dramatically during immunosuppressive therapy. Therefore, migraine with aura may have been the only symptom of CD-associated cerebral vasculitis in the patient for several years. However, it remains unclear, whether the recurrent neurological deficits in our patient reflect aura symptoms solely, or can be partially attributed to cerebral ischemia in terms of transient ischemic attacks.

In conclusion, cerebral vasculitis is a very rare but severe complication in CD and should be excluded in case of comorbidity with migraine with aura, even if other typical symptoms of cerebral vasculitis are lacking.

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