Fig. 1. T₂-weighted MRI in the axial (a) and sagittal (b) plains, and a turbo-FLAIR-weighted MRI in the axial plain (c) demonstrate a coloboma of the left optic nerve (white arrow) in a patient with typical Moyamoya arteriopathy affecting the anterior and posterior cerebral circulation, as visualized on digital subtraction angiography (d) and magnetic resonance tomography (a, c; black arrows).

We present the case of a now 42-year-old woman with a history of unilateral amblyopia, due to an optic nerve coloboma (fig. 1a–c), and mental retardation since infancy, who developed a severe gait disorder over the last decade due to multiple ischemic cerebral lesions. Diagnostic evaluation established, by means of digital subtraction angiography, a diagnosis of Moyamoya arteriopathy affecting both the anterior and posterior circulation as the cause of relapsing brain ischemia (fig. 1d).

Optic nerve coloboma has been associated with mental retardation in a series of distinct syndromes [5–7]. To our knowledge, this is the first report of congenital optic nerve coloboma associated with mental retardation that is also accompanied by a progressive ischemic encephalopathy due to Moyamoya arteriopathy. It describes one more association of Moyamoya syndrome with other diseases.

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Rapidly Progressive Cerebrovascular Stenosis and Recurrent Strokes Followed by Improvement in HIV Vasculopathy

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Human immunodeficiency virus (HIV) infection is associated with an increased incidence of stroke [1–3]. Infected children and rarely adults have been reported to develop cerebral vasculopathy with aneurysms [4, 5]. We report here an AIDS patient with no other obvious risk factor for strokes, with rapidly progressive vascular stenosis and recurrent cerebral infarcts, who showed vascular and neurological improvement on highly active anti-retroviral therapy (HAART).

Case Report

A 33-year-old man with a HIV+ status for the past 1.5 years, noncompliant with medications, was admitted with confusion for 1 week. He was alert, but did not know the date or time. He understood simple 1-step commands, but had difficulty in word finding and he had a right central facial weakness. A cranial MRI scan revealed a left thalamic infarct (fig. 1a). Antinuclear, antineutrophil cytoplasmic, rheumatoid factor, anti-DNA, anti-Jo, and hepatitis B and C antibodies were absent. The erythrocyte sedimentation rate was normal and C-reactive protein was mild-

ly elevated (8 mg/l; $n < 0.4$). Serum cholesterol, LDL, HDL, triglyceride levels, proteins C and S and a transesophageal echocardiogram were normal. The CD4+ lymphocyte cell count was 3 cells/ μ l (normal = 600–1,500) and HIV RNA load was >228,000 copies/ml. Cerebrospinal fluid (CSF) analysis did not reveal any abnormalities. CSF cryptococcal antigen, treponemal and Toxoplasma antibodies were absent.

One month later, he was readmitted with disorientation and confusion. HIV RNA load was >100,000 copies/ml, suggesting poor compliance with HAART. On examination, he was disoriented and had left central facial paresis. Upon MRI examination, a new infarction in the right caudate and internal capsule was noted (fig. 1b). A magnetic resonance angiogram (MRA) showed bilateral stenosis of the anterior, middle and posterior cerebral arteries, both proximally and in distal smaller branches (fig. 1c, f). A repeated MRA scan, 4 months later, showed significant progression, with high-grade stenosis of the anterior, middle and posterior cerebral arteries and occlusion of the right vertebral artery (fig. 1d, g). On questioning the family, it was noted that about 3 months after the second stroke the patient moved in with his mother, who monitored his medication, and only then did he become totally compliant with HAART. HIV RNA load then remained low for the next 6 months (138–380 copies/ml). About 2 months after second stroke, the patient had been started on prednisone (60 mg/day). Cyclophosphamide (50 mg/day) was also added for a few weeks with a diagnosis of presumed cerebral vasculitis. One month later, the patient developed complications of hyperglycemia, lethargy and fever. Cyclophosphamide was discontinued and prednisone was reduced to 30 mg/day.

The patient has been doing well for the past 6 months on low-dose prednisone and regular HAART, with no new complaints or neurological abnormalities, and is fully alert, oriented and ambulatory. The CD4+ lymphocyte cell count is 13 cell/ μ l and HIV RNA load is 319 copies/ml. A final MRI/MRA study, 9 months after the onset of symptoms, did not show any new infarcts and showed improved vascular flow in the right vertebral, left anterior cerebral, posterior cerebral and distal right middle cerebral artery branches (fig. 1e, h).

Fig. 1. MRI at various times after symptom onset. **a** At onset, diffusion-weighted MRI shows left thalamic infarct. **b** One month later, diffusion-weighted MRI shows right caudate and corona radiata infarct. **c–h** MRA done at varying times after first stroke: 1 month (**c, f**), 4 months (**d, g**) and 9 months (**e, h**). Progressive high-grade multifocal stenosis (**c, d**) and improvement in vascular flow (**e**) in: (1) A1 segment of bilateral anterior cerebral arteries (thin black arrows); (2) bilateral posterior cerebral arteries (arrowheads); (3) right vertebral artery (thin white arrows) and distal branches of right middle cerebral artery (*). Beaded multifocal stenoses of distal MCA branches can be seen (**c**; thick black arrow). Vertebrobasilar MRA shows progression of stenosis in posterior cerebral arteries (**f, g**; black arrows) and improvement (**h**; black arrows), and progression to occlusion in right vertebral artery (**f, g**; white arrows) and partial restoration of flow (**h**; white arrows).

Discussion

In autopsy series of AIDS patients, researchers have found a 4–29% prevalence of cerebral infarction [2]. Most of these infarcts are associated with cardioembolic causes, coagulopathies or non-HIV central nervous system infections such as cytomegalovirus, tuberculosis, *Cryptococcus*, varicella zoster, hepatitis B or C [3]. When these causes are excluded, strokes in an HIV-infected individual have been linked to a less well-defined entity, HIV vasculopathy [6]. In children with AIDS, vasculopathy has been reported to present with multiple cerebrovascular aneurysms [4, 6]. Adults develop large vessel (primarily aortic) aneurysmal disease [6]. Pathologically, these cases show subintimal fibrosis, damage to internal elastic lamina and adventitial inflammatory infiltrate [6]. The etiopathogenesis of such changes, whether directly related to HIV infection or immune-mediated vasculitic changes, is unclear. In some studies, HIV glycoprotein 41 has been demonstrated in mononuclear cells of the intima of intracranial vessels [7], while others have not found HIV in affected vessels [8].

Our patient was unique because we could document, on sequential MRA studies, the rapid progression of severe cerebrovascular stenosis and its subsequent improvement, and correlate this with his therapy, HIV RNA load and clinical status. Over 3 months, the MRA documented his very rapid progression of high-grade cerebral vascular stenosis (without associated aneurysmal dilatation), while he had a very high HIV viral load. Since his infarcts occurred when he was noncompliant with HAART (with uncontrolled viral proliferation and a very high HIV viral RNA load [>100,000 to >228,000 copies/ml]), we speculate that cerebral arteriopathy was related to HIV infection of the cerebral vessels. On follow up, his HIV RNA load remained low (<400 copies/ml), and he remained neurologically normal without new cerebral lesions. After 6 months of adequate HAART, a MRA study confirmed improved vascular flow in multiple cerebral arteries, suggesting that the progression of arteriopathy was arrested after adequate anti-retroviral therapy. We considered the alternative diagnosis of immune-mediated vasculitis unlikely because recurrent infarcts occurred in the setting of severe immunosuppression (CD4+ count, 3 cells/ μ l), negative antibody tests and the absence of headaches or abnormal CSF findings. Furthermore, MRA studies showed that the vascular stenoses improved significantly, even while steroids were being markedly decreased. Also, rapid clinical improvement on HAART, the absence of typical brain MRI findings and negative laboratory tests made other opportunistic non-HIV infections of the central nervous system unlikely.

A larger number of AIDS patients with cryptogenic strokes and autopsy studies are needed to understand better the pathogenesis of HIV vasculopathy. Our patient suggests that untreated or poorly treated AIDS with a high viral load may be associated with rapidly progressing cerebrovascular stenosis and infarcts. Prompt initiation of HAART, with close monitoring of the decreased HIV RNA viral load, may be of benefit in ameliorating the arteriopathy associated with HIV.

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