Case reports

BILATERAL BLINDNESS AFTER STARTING HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT IN A PATIENT WITH HIV INFECTION AND CRYPTOCOCCAL MENINGITIS

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Key-words : cryptococcal meningitis, blindness, HIV infection

ABSTRACT

A 26-year-old HIV-seropositive Caucasian man with cryptococcal meningitis developed permanent bilateral blindness shortly after starting highly active antiretroviral treatment. The blindness may have been a consequence of an immune reactivation inflammatory syndrome caused by this treatment.

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INTRODUCTION

Ocular complications are commonly observed in 50-70% of AIDS-patients (1). Causes include cytomegalovirus (CMV) infection, herpes simplex/zoster infection, HIV-related microvasculopathy, syphilis, mycobacterium tuberculosis infection, cryptococcal meningitis, and toxic or allergic drug reactions (1).

Before the use of highly active antiretroviral treatment (HAART), 25% of patients with cryptococcal meningitis developed a neuro-ophthalmic complication (2), but the incidence of such complications since the availability of HAART remains unknown. We describe an HIV-seropositive patient with cryptococcal meningitis, who developed temporary unilateral deafness, diabetes insipidus and permanent bilateral blindness during HAART.

CASE REPORT

In May 2002, a 26-year-old Caucasian man was hospitalised because of worsening headache and vomiting over a period of a few weeks. He was diagnosed as being HIV seropositive, with a CD4+ lymphocyte count of 12/µl, and a viral load of >750000 copies/ml. Indian ink staining of the cerebrospinal fluid revealed Cryptococcus neoformans. Intracranial pressure was not measured. A computed tomography (CT) scan of the brain showed no focal lesions and no oedema, but

fundoscopy revealed bilateral papiloedema with haemorrhages. Visual acuity was normal.

Treatment with amphotericine B 0.5 mg/kg/d IV, and methylprednisolone 80 mg/d IV was started, together with lopinavir/ritonavir (400 mg/100 mg twice daily), lamivudine (150 mg twice daily) and zidovudine (300 mg twice daily). Fluconazole 600 mg daily was added a few days later. Initially his clinical condition improved but after 2 weeks of amphotericine therapy the nausea and vomiting reappeared. Intracranial pressure, measured by lumbar puncture was 45 mmHg (normal : < 21 mmHg), but a CT-scan of the brain was normal. The amphotericine B was switched to fluconazole. Six weeks after admission he was discharged on oral fluconazole 400 mg daily, lopinavir/ritonavir (400/100 mg twice daily), lamivudine (150 mg twice daily), zidovudine (300 mg twice daily), methylprednisolone 16 mg daily and acetazolamid 500 mg twice daily. At that time, his CD4 lymphocyte count was 28/µl and his HIV viral load < 400 copies/ml.

Two weeks later, he was re-admitted with vomiting, anorexia, weight loss and bilateral progressive visual loss. After he had been discharged from the hospital he had been fully compliant with his medication. One week before admission the methylprednisolone had been decreased to 8 mg daily. Indian ink examination of the CSF showed the presence of C. neoformans, but cultures remained negative. The intracranial pressure was normal. Fluconazole 600 mg per day was given intravenously. One week after the onset of his visual complaints, he experienced complete loss of vision. Fundoscopy showed bilateral papilloedema. Magnetic resonance imaging (MRI) of the brain revealed an effusion around the optic nerves. Surgical decompression of the right optic nerve was performed. Microscopic examination of the fluid obtained during surgery revealed C. neoformans but a fungal culture of the fluid remained negative. Although surgery was performed promptly, his vision did not improve. Therapy was switched to amphotericin B (1mg/kg/d IV) with flucytosine (100 mg/kg/d per os). He developed left-sided deafness and neuralgic pain in his left ear, polyuria and polydipsia. Symptomatic treatment with amitriptyline (50mg/d) alleviated the pain. Diabetes insipidus was diagnosed and treated with desmopressin (10µg twice daily by endonasal spray). During maintenance fluconazol treatment the deafness disappeared but he remained blind (no light perception). In December 2003 he was in good general health, with a CD4 count of 366/µl and a viral load <50 copies/ml, but the bilateral blindness remained.

DISCUSSION

This patient with cryptococcal meningitis developed bilateral blindness, unilateral deafness and diabetes insipidus while on antifungal and antiretroviral treatment. Deafness (3) and diabetes insipidus (4) are observed only exceptionally during cryptococcal meningitis, whereas visual problems are encountered frequently (1).

Meningitis caused by C. neoformans can impair vision through several mechanisms: by direct spread of inflammation to the optic nerves, or by compressive optic neuropathy secondary to a raised intracranial pressure (5-9). The first mechanism will give a rapid visual loss, within 12 hours, and the second a more progressive loss (8,9). A nerve sheath fenestration can resolve papilloedema (10), and if the intracranial pressure is high, immediate drainage of the cerebrospinal fluid can reverse the blindness (5,8).

In our patient it is possible that the blindness was caused by a HAART-induced immune reconstitution disease. Microscopic examination of the fluid surrounding the optical nerve revealed C. neoformans but a fungal culture of the fluid remained negative, indicating that there was no longer any active C. neoformans infection. It is possible that an inflammatory reaction, as a consequence of immune reactivation after initiation of the antiretroviral treatment, caused the permanent damage to the optic nerves. The fact that the patient's CD4+ lymphocyte count remained low at the time he lost his vision does not exclude some form of immune reconstitution. Indeed, immune reconstitution disease usually occurs during the first 12 weeks of HAART, and sometimes before there is a significant increase in CD4+ lymphocyte count (11).

Immune reconstitution disease has been observed in patients with cryptococcal infections treated with HAART (12,13). Manifestations include paradoxical exacerbations of meningitis, necrotizing lymphadenitis and necrotizing pneumonitis (14). In Mulago hospital Kampala, Uganda, the ophthalmologists of this hospital recently observed several patients with cryptococcal meningitis who developed blindness during the

first weeks of HAART, despite an effective antifungal treatment (J. Otiti-Sengeri, personnel communication).

We certainly need clinical trials to determine when it is most optimal to start HAART in patients with HIV and cryptococcal meningitis. However this case report suggests that when such patients present with signs of intracranial hypertension, the initiation of HAART should probably be delayed until normalisation of the intracranial pressure and disappearance of the papilloedema.

ABSTRACT

Een 26-jarige HIV positieve blanke man met een cryptococcen meningitis ontwikkelde een permanente bilaterale blindheid na het opstarten van "highly active antiretroviral treatment". Deze blindheid zou kunnen ontstaan zijn door een immuunreactivatie met inflammatoir syndroom veroorzaakt door deze behandeling.

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