obscure the onset, and delay the diagnosis of, toxoplasmosis.

The aim of this study was to assess whether HIV-infected patients with cerebral toxoplasmosis can have demyelinating lesions that could be responsible for neurological dysfunction. Demyelination was investigated by evaluating cerebrospinal fluid (CSF) levels of myelin basic protein (MBP), which represent a sensitive marker of active myelin breakdown, in both HIV-seronegative and HIV-seropositive individuals [4,5]. We studied 16 AIDS patients with cerebral toxoplasmosis diagnosed on the basis of clinical presentation, computed tomography (CT) or magnetic resonance imaging (MRI) scans, *Toxoplasma* serology and response to treatment. Fourteen HIV-seropositive individuals without evidence of neurological involvement and nine HIV-seronegative individuals with other non-demyelinating diseases were included as controls. MBP concentration in CSF was performed by a competitive double-antibody radioimmunoassay (Diagnostic System Laboratories, Webster, Texas, USA), as previously described [4]. Values greater than 4 ng/ml were considered elevated, in accordance with the manufacturer's instructions. As shown in Fig. 1, raised levels of MBP were found in CSF of seven out of 16 (43.7%) patients with cerebral toxoplasmosis, while levels were within the normal range in the other nine patients (56.2%). Furthermore, in four of the seven individuals with CSF MBP elevation MRI showed multiple foci of demyelination in the periventricular whitematter of both cerebral hemispheres in addition to the characteristic contrast-enhancing lesions. No evidence of MBP elevation was observed in CSF of the controls.

Our results indicate that HIV-infected patients with cerebral toxoplasmosis may develop a demyelinating process, as determined by the findings of elevated MBP levels in CSF. MBP release may depend on the acute myelin breakdown due to necrotizing lesions of *Toxoplasma gondii*. However, since MBP elevation in CSF has been found in only 44% of patients, we believe that additional factors not directly related to toxoplasmosis may contribute to the development of demyelination. In this respect, the role of HIV and other neurotropic viruses or indirect immunological mechanisms associated with cytokine involvement should be taken into consideration.

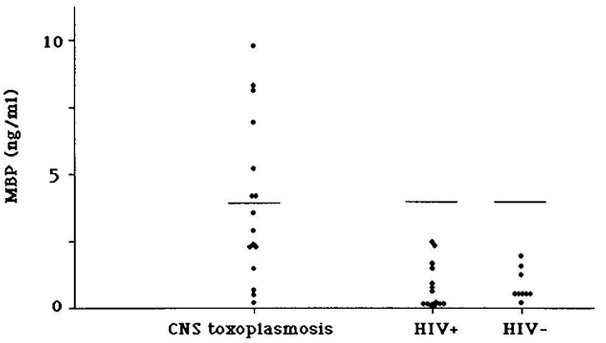

Fig. 1. Cerebrospinal fluid of myelin basic protein (MBP) concentrations in patients with central nervous system (CNS) toxoplasmosis and control subjects.

The neurological consequences and the pathological implications of HIV-related demyelination that occur in cerebral toxoplasmosis remain to be established. Nevertheless, since white matter involvement can present itself before, during and/or after CNS toxoplasmosis, the detection of active myelin breakdown by assessment of CSF MBP should be performed systematically in HIV-infected individuals with progressive neurological impairment.

C.M. Mastroianni, G.M. Liuzzi*, V. Vullo, S. Delia and P. Riccio*, *Istituto di Malattie Infettive, Università 'La Sapienza', Rome, *Dipartimento di Biochimica e Biologia Molecolare, Bari, Italy.*

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Retinal microvascular abnormalities in patients with AIDS-related complex or lymphadenopathy syndrome

Ocular microangiopathic syndrome is a common finding in patients with AIDS. The most frequent manifestation of retinal microvascular abnormalities in patients with HIV-1 are cotton-wool spots [1]. Other microvascular abnormalities include retinal haemorrhages, ectasia of conjunctival vessels, and conjunctival blood-flow sludging [2,3]. In 43.3% of patients with AIDS, and 8.8% of patients with AIDS-related complex (ARC), ophthalmoscopically visible microvascular lesions were observed [4]. Retinal HIV-1-related microvascular abnormalities are similar to those seen in diabetes mellitus, or systemic lupus erythematosus.

Fundus fluoresceinangiography in AIDS patients shows microaneurysms, teleangiectasis, focal areas of non-

perfusion with capillary drop-out and focal leakage [5]. However, fundus fluoresceinangiography was not performed in patients with ARC or lymphadenopathy syndrome (LAS). Therefore, we performed fluoresceinangiographic studies of the eye in patients with LAS or ARC.

Fundus fluoresceinangiography was performed using a scanning laser ophthalmoscope (Rodenstock Inc., Munich, Germany) under standard conditions in four homosexual men. Three patients were staged LAS (Walter Reed stage 3), and one patient ARC (Walter Reed stage 4). Absolute CD4+ lymphocyte count was determined by FACScan (Becton-Dickinson, Heidelberg, Germany), and plasma fibrinogen levels by the method according to Clauss [6]. No microvascular abnormalities were observed on indirect ophthalmoscopy after dilating pupils in any of the patients (eight eyes). Fluoresceinangiography demonstrated retinal microaneurysms in the area around the four major branches of the central retinal artery in all eight eyes. In one patient additional microaneurysms were seen in the posterior pole (Table 1). No focal areas of non-perfusion with capillary drop-out and focal leakage were observed in the four patients. These fluoresceinangiographic findings were similar to those in very early diabetic retinopathy [7].

Table 1. Clinical staging, absolute CD4+ lymphocyte count ($\times 10^6$/l), plasma fibrinogen concentration and results of fundus fluoresceinangiography.

Patient	Clinical staging*	Absolute CD4+ count	Fibrinogen (mg/dl)	Fluorescein-angiography
1	LAS/3	390	244	PM
3	LAS/3	300	278	PM
2	LAS/3	250	298	PM
4	ARC/4	200	331	CPM

*AIDS-related complex (ARC) or lymphadenopathy syndrome (LAS)/Walter Reed stage. PM, peripheral microaneurysms; CPM, central and peripheral microaneurysms.

Our results show that retinal microvascular abnormalities can occur in HIV-1-infected patients without cotton-wool spots and haemorrhages. Microaneurysms can be visible in patients with symptomatic HIV-1 infection staged LAS or ARC. Elevated fibrinogen levels were reported for patients with HIV-1 infection and cotton-wool spots [3]. Fibrinogen levels were within normal limits in all four patients (normal values for healthy control, 150–350 mg/dl), but there was a trend towards elevated levels with progression of HIV-1 infection.

HIV-1-infected individuals are at increased risk of cerebrovascular accidents, most often due to occlusion of small vessels [8]. Post-mortem series also suggest cerebral vascular abnormalities [8]. HMPAO-SPECT (Siemens Inc., Münich, Germany) studies suggest cerebral blood flow abnormalities in patients with HIV infection and AIDS [10–12]. Close associations between ocular microvascular abnormalities and cerebral hypoperfusion or cognitive dysfunction were reported [13,14], while HMPAO-SPECT (Siemens Inc.) studies suggest a reduced cerebral blood flow in early stages of HIV-1 infection [11]. Our results may be in accordance with this finding because they suggest that retinal microvascular abnormalities in HIV-1-infected patients are not restricted to patients in more advanced stages of HIV-1 infection or full-blown AIDS.

Retinal or cerebral microvascular abnormalities in patients with HIV-1 infection might be more common than previously expected. HIV-1-related microangiopathic alterations should be added to a list of indirect factors that might contribute to the pathogenesis of neurologic and neuro-ophthalmic abnormalities in patients with HIV-1 infection [15]. In addition, the analogy between HIV-1-related microangiopathic syndrome and diabetic retinopathy requires further consideration. The underlying conditions resulting in HIV-1-related microangiopathic syndrome need to be elucidated.

S.A. Geier*†, K. Holler*, J. Nasemann*, J.R. Bogner†, A. Scheider*, V. Klauss*, U. Kronawitter† and F.D. Goebel†, **University Eye Clinic Munich, †Medizinische Poliklinik, University of Munich, 8000 Munich 2, Germany.*

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Three-year follow-up of asymptomatic HIV-infected men receiving combination zidovudine and acyclovir

Combination of other antiviral drugs with zidovudine (ZDV) has been proposed to improve clinical efficacy and delay viral resistance. Acyclovir (ACV) and ZDV have been evaluated in a number of studies [1–7]. ACV is of particular interest because of its activity against some herpesviruses, which may cause disease in HIV-infected individuals and could theoretically act as cofactors for disease progression [8]. Although several investigators have not found that this combination (compared to ZDV alone) resulted in a greater improvement in laboratory parameters such as p24 antigen [2,5], this combination may still reduce the frequency of certain opportunistic infections or improve long-term prognosis. One recent study of patients with AIDS or AIDS-related complex (ARC) concluded that addition of high-dose ACV cotherapy to ZDV resulted in significant improvement in survival with minimal increase in toxicity [6]. Since most studies of ZDV and ACV were in individuals with AIDS or ARC, additional data are needed for asymptomatic HIV-infected individuals who may require therapy for many years.

Twenty asymptomatic, HIV-positive homosexual men received ZDV and ACV in an open-labeled pilot study, as described in our initial report of the first 24 weeks [9]. We now present data from 3 years of follow-up. This study evaluated safety and tolerance of two regimens, given in five divided doses per day: 500 mg ZDV plus 2000 mg ACV daily (500 ZDV/2000 ACV), and 500 mg ZDV plus 4000 mg ACV daily (500 ZDV/4000 ACV). Moderate side-effects or laboratory abnormalities resulted in 40% dose reduction. Therapy was discontinued for more severe clinical or laboratory abnormalities.

Of the 10 men receiving 500 ZDV/2000 ACV, one was diagnosed with non-Hodgkin's lymphoma (week 7), and another with Kaposi's sarcoma (week 144). All other men remained free of AIDS and completed the study. One man required dose reduction (week 63) because of myalgias and an increased creatine kinase (CK = 1387 U/l).

Of the 10 men receiving 500 ZDV/4000 ACV, one was diagnosed with candida esophagitis at approximately week 8 and another (on reduced doses) developed *Pneumocystis carinii* pneumonia (week 63). Four others withdrew from the study (at weeks 10, 10, 36 and 129), because of symptoms such as nausea, malaise and fatigue. Dose reduction was required for five men suffering from nausea or anorexia (two men), myalgias with an elevated CK (663 U/l) (one man), anemia (hemoglobin, 11.6 g/dl) (one man) and neutropenia (0.93×10^9) (one man). These last two men were subsequently returned to full doses without further hematologic toxicity.

Table 1 shows hematologic parameters for 15 men who remained in the study and without AIDS for 52 weeks, 14 men followed for 104 weeks, and 12 men who completed the study. If results for a specific week were missing, the value was interpolated based on preceding and subsequent weeks. The greatest changes were noted for red blood cell count (RBC) and mean corpuscular volume (MCV); changes were most pronounced during the first 26 weeks.

Table 1. Mean hematologic values among asymptomatic HIV-infected men completing at least 52 weeks of combination therapy with zidovudine and acyclovir.

		Week				
Laboratory test	Baseline (n = 15)	10 (n = 15)	26 (n = 15)	52 (n = 15)	104 (n = 14)	Conclusion (n = 12)
Red blood count ($\times 10^{12}$)	5.07	4.30	4.13	4.09	4.02	4.04
Serum hemoglobin (g/dl)	14.8	14.1	14.8	14.8	14.8	14.6
Mean corpuscular volume (fl)	87	96	106	105	106	105
Neutrophils ($\times 10^9$)	3.19	2.47	2.84	2.67	2.85	3.17
Total lymphocytes ($\times 10^9$)	2.06	1.99	1.94	2.00	2.24	2.11
CD4+ count ($\times 10^6$)	538	505	557	610	522	497
Monocyte ($\times 10^9$)	0.42	0.37	0.43	0.41	0.40	0.40
Platelets ($\times 10^6$)	276 400	293 355	292 630	278 095	274 606	283 500