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Anticardiolipin antibodies in HIV infection: association with cerebral perfusion defects as detected by ^{99m}Tc-HMPAO SPECT

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SUMMARY

Anticardiolipin antibodies (ACA) belong to a heterogeneous group of antibodies directed against negatively charged phospholipids. In patients with rheumatic disorders, their presence has been correlated to the occurrence of thromboembolic complications, thrombocytopenia, abortions and other disease manifestations. Several studies have revealed the detection of mostly high-titre ACA in a significant proportion of HIV-infected patients without any known clinical relationship. In our study, ACA were detected in 17/34 HIV-infected patients, and their presence was significantly associated with the detection of cerebral perfusion abnormalities by ^{99m}Tc-HMPAO SPECT. SPECT scans were classified as normal or as focal or diffuse defects in uptake. Most patients (13/16) with cerebral perfusion defects had elevated ACA titres in contrast to 4/18 patients with normal SPECT findings ($P = 0{\cdot}002$). Focal uptake defects were always associated with the presence of ACA. No correlation to clinical features or other laboratory parameters was evident. Our results suggest a possible implication of autoimmune mechanisms in the pathogenesis of cerebral perfusion abnormalities detected by SPECT scanning in HIV-infected patients. However, further studies are needed to evaluate the clinical significance and to develop possible therapeutic consequences.

Keywords HIV-1 anticardiolipin antibodies cerebral blood flow HMPAO SPECT

INTRODUCTION

Central nervous system (CNS) disease is frequently encountered in patients with HIV infection, leading to a variety of clinical disorders. Although opportunistic infections and neoplasms, particularly CNS lymphoma, may emerge in these immunocompromised patients, the brain itself represents a primary target for infection with HIV, resulting in subacute encephalopathy or dementia in most patients with end-stage disease.

However, the detection of HIV-1 DNA and infectious virus in cerebrospinal fluid (CSF) not only in patients with advanced disease but also in asymptomatic HIV-positives [1], the presence of intrathecally synthesized anti-HIV immunoglobulins [2], the isolation of HIV from brain, spinal cord and nerves [3], as well as the detection of electrophysiologic abnormalities in asymptomatic HIV carriers [4] suggest that CNS involvement may occur early in the course of disease without the development of overt neuropsychiatric symptoms.

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CNS infection is histologically characterized by the presence of multinucleated giant cells, reactive astrocytosis, microglial nodules, vacuolar myelopathy and vascular infarcts [5]. HIV may be detected in monocytes, macrophages, microglial and endothelial cells [6]. In asymptomatic patients, perivascular inflammatory infiltrates and demyelination have been described [17].

As antiretroviral therapy may ameliorate cognitive dysfunction in HIV encephalopathy and reduces the incidence of multinucleated giant cells significantly [8], early diagnosis of potential CNS involvement in order to allow therapeutic intervention seems desirable. Structural neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) is useful for the evaluation of parenchymal changes or the diagnosis of secondary CNS disease like toxoplasmosis or lymphoma. However, they show unspecific or even normal findings in HIV encephalopathy, especially early in the course of disease [9].

Functional neuroimaging using SPECT (single-photon emission computed tomography) or PET (positron emission tomography) techniques may detect brain abnormalities before structural damage occurs. The domain of SPECT scanning is to

provide information on regional brain perfusion, closely linked to cerebral metabolism.

A high incidence of cerebral perfusion abnormalities detected by SPECT in HIV-infected patients has been reported by several investigators [10,11]. Interestingly, perfusion defects were not only observed in patients with advanced disease, but in a substantial proportion of asymptomatic patients. No correlation to other markers of disease was observed.

As direct viral infection of CNS seems to be restricted to only few cells, the pathogenic mechanisms leading to CNS involvement even early in the course of disease are still controversial.

HIV not only leads to depletion of $CD4^+$ T cells, but also induces polyclonal activation of B cells. The detection of serological autoimmune phenomena like immune complexes, hypergammaglobulinaemia, low titre antinuclear antibodies or antibodies to cardiolipin (ACA) has been related to B cell dysfunction. Although ACA can be detected in both sera and CSF [12] in a significant proportion of HIV-infected patients, their prevalence could not be correlated to disease progression or other serological markers in previous studies [13,14].

The present study reveals a significant correlation of the presence of ACA with cerebral perfusion defects detected by ^{99m}Tc-HMPAO SPECT in HIV-infected patients, suggesting that autoimmune mechanisms may be implicated in the pathogenesis of cerebral perfusion defects related to HIV disease.

PATIENTS AND METHODS

Patients

Thirty-four patients with documented HIV infection (by Western blot) of various disease stages were enrolled in the study and submitted to SPECT scanning of cerebral perfusion. None of the patients presented with signs of dementia or severe neurological dysfunction. Patients with opportunistic infections, ongoing drug abuse (i.v. drugs or cocaine) or hypertension were excluded. Informed consent to the study was obtained from all patients. In most patients (29/34), SPECT evaluation was performed before initiation of antiretroviral treatment.

When symptoms suggestive of neuropsychiatric disease were evident, patients were evaluated by a neurological or psychiatric consultant. In selected patients, MRI or CT scanning ($n = 9$) or CSF analysis ($n = 5$) was performed. CT scans were obtained in three patients with a Siemens DR3 computer tomograph, using standard techniques and contrast enhancement. MRI scans were performed in six patients with a Siemens Magnetom, 1·5 T, using standard spin-echo techniques (transverse slices, 5 mm thick, with axial orientation). For routine evaluation, proton density (time to recovery/time to echo (TR/TE) = 3000/25) and T2-weighted images (TR/TE = 3000/90) were obtained in all six patients.

Patients were physically examined and routine blood examinations for haematology, chemistry and immunology were performed. Routine immunological assays included the analysis of lymphocyte subpopulations by two-colour flow cytometry of whole-blood preparations, the determination of β_2-microglobulin (by radioimmunoassay), neopterin in urine (by high performance liquid chromatography (HPLC)), immune complexes (by C1q-binding assay and polyethylene glycol precipitation followed by laser-nephelometric determination of the immunoglobulin component), p24 antigen (by ELISA) and the determination of serum IgG, IgA, IgM levels by laser nephelometry. For the detection of IgG anticardiolipin antibodies, a quantitative ELISA was used, employing a sandwich ELISA technique (Cheshire Diagnostics Limited, Chester, UK).

The normal range of ACA ($\leqslant$ 20 GPL units) was defined as within 2 s.d. of the mean level detected in 164 healthy blood donor controls. One GPL unit (IgG-ACA international standards) is defined as the cardiolipin binding activity of 1 μg/μl of an affinity-purified IgG-ACA preparation validated against International Workshop Standards. Patients were routinely screened for infections with *Toxoplasma gondii* and *Treponema pallidum*.

Twenty-nine patients were male, five were female. Mean age was 33·1 + 8·6 years (±s.d.), ranging from 21 to 57 years. In 22 of the 29 male subjects, HIV infection was either homo- or bisexually acquired, in seven patients heterosexual transmission was assumed. Five patients were former i.v. drug users, but had a drug-free interval of at least 3 years.

According to the CDC classification (1987) of HIV disease, nine patients with CDC class II disease, eight patients with CDC III and 17 patients with CDC IV were enrolled in the study.

HMPAO-SPECT

SPECT scanning was performed as described elsewhere [15]. In brief, ^{99m}Tc-HMPAO (hexamethylopropylene amine oxime; Amersham Buchler, Germany) was prepared according to the manufacturer's recommendations. Patients were placed in a supine position in a quiet room with dimmed lights and were allowed to relax for 15 min before i.v. administration of 555–740 MBq of ^{99m}Tc-HMPAO. The effective dose equivalent was 0·018 mSv/MBq. Patients were therefore exposed to approximately 10–13·3 mSv during the procedure. SPECT data acquisition started 30 min after injection. A rotating gamma camera (Siemens Orbiter with neurofocal imaging system; Siemens, Erlangen, Germany) with a 64 × 64 matrix and a 360° step-and-shoot acquisition was used.

Reconstruction of transaxial slices was performed by filtered back-projection. Oblique (along the orbitomeatal line), sagittal and coronal slices were created from transaxial slices. Slice thickness was 6·25 mm. Spatial resolution was 12 mm (full width at half maximum (FWHM)) in the horizontal plane. SPECT slices were evaluated by an investigator without knowledge of the clinical data.

Visual qualitative grading was performed by two independent observers. Homogeneous brain perfusion without focal uptake defects or visible asymmetry was considered normal. Focal uptake defects in at least two consecutive slices in two reconstructions were evaluated as follows. A predefined table of 256 rainbow colours on the computer screen was used, which condensed (with a constant upper and lower threshold) into 16 discrete colour steps on hard copy (from dark blue to white), each representing a 6·25% difference in the percentage of maximum pixel counts. A visible contrast of at least two colour steps compared with the contralateral hemisphere was considered a perfusion defect on the side with the lower colour intensity. If there were more than two focal uptake defects in at least two consecutive slices, SPECT scans were classified as showing diffuse uptake defects.

Statistical analysis

Contigency analysis including Fisher's exact test and Student's *t*-test was performed to evaluate the data on a significance level of $P \leqslant 0{\cdot}05$, using a commercially available software package.

RESULTS

SPECT results

According to the criteria described above, a normal brain perfusion pattern was noted in 18 patients. The remaining 16 patients showed an abnormal brain perfusion pattern, with focal uptake defects in eight and diffuse uptake defects in the remaining eight patients. Representative examples for normal SPECT scans or SPECT scans with focal or diffuse uptake defects are shown in Figs 1, 2 and 3.

Patients' characteristics

Patients were grouped into those with and those without cerebral perfusion defects (Table 1). No significant differences were observed with respect to sex, age, transmission route, stage of disease according to the CDC classification of 1987 or concomitant anti-retroviral treatment. Most patients (26/34 or 76·5%) did not present with any symptoms or complaints suggestive of CNS disease. However, in nine patients neuropsychiatric symptoms (headache in six patients, paresthesias of both legs in two patients and acute psychosis in another patient) prompted us to initiate further evaluation with CT or MRI in all nine patients and CSF analysis in five patients. Five of these patients had both normal SPECT and MRI/CT scans. Two patients had focal defects in SPECT and focal lesions in the periventricular white matter in the MRI scan. In another patient, who had a normal SPECT scan, MRI showed an inhomogenicity in the left basal ganglia. The last patient showed diffuse uptake defects in the SPECT scan, but had normal findings on CT. CSF analysis revealed oligoclonal IgG in three samples.

SPECT findings and laboratory parameters

ACA (normal $\leqslant 20$ GPL units) were detected in 17 patients with titres ranging from 24 to 161 GPL.

A significant correlation was found between the presence of ACA and cerebral perfusion defects as determined by SPECT scanning. Patients with ACA ($n = 17$) showed cerebral perfusion abnormalities in 76·5% (13/17), only 23·5% of patients with ACA had a normal brain perfusion pattern. In contrast, ACA-negative patients ($n = 17$) had a normal brain perfusion pattern in 82·4% (14/17) ($P = 0{\cdot}002$). All patients ($n = 8$) with focal uptake defects had elevated ACA levels (8/8), whereas patients with diffuse uptake defects had positive ACA in 62·5% (5/8). Among the patients with a normal cerebral perfusion pattern, 4/18 were ACA-positive. However, as demonstrated in Fig. 4, three of these four patients had only slightly elevated ACA levels ($\leqslant 25$ GPL units). The mean level of ACA in patients with cerebral perfusion defects was significantly higher (58 ± 47 GPL) than in patients with a normal brain perfusion ($14{\cdot}3 \pm 15{\cdot}1$ GPL) ($P = 0{\cdot}0007$). No association was observed between the presence of ACA and CD4 cell counts, β_2-microglobulin, positive treponemal antibodies (in 7/32 patients tested), p24 antigenaemia, serum IgG levels or thrombocytopenia.

β_2-microglubulin (normal values age-dependent, $\leqslant 2{\cdot}0$ mg/*l* for patients <40 years; $\leqslant 2{\cdot}5$ mg/*l* for patients $\geqslant 40$ years)

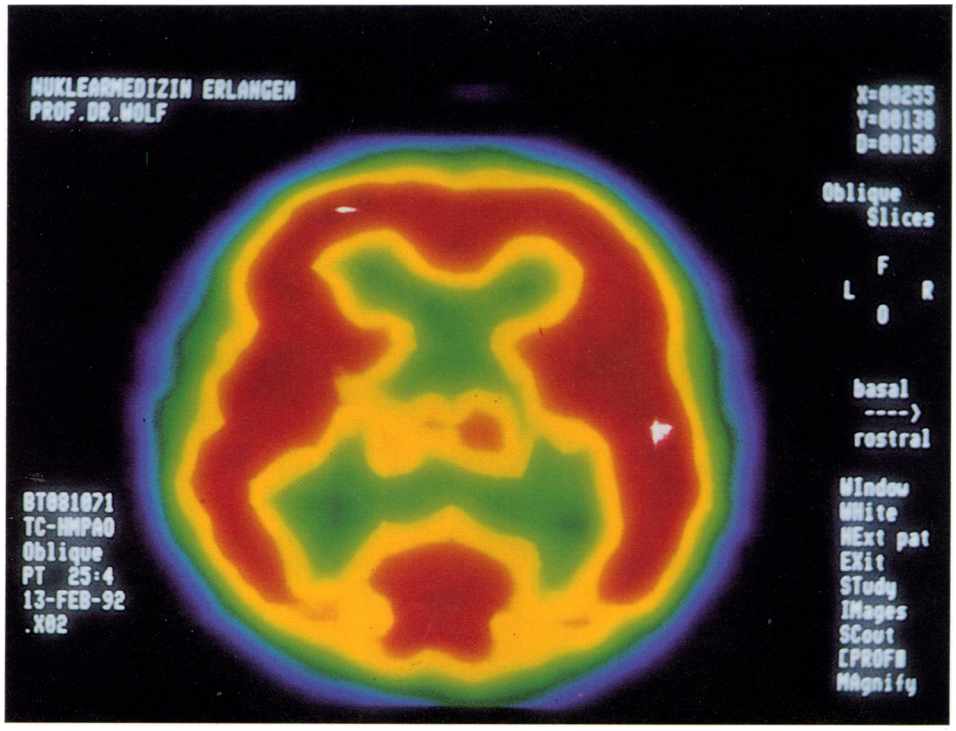

Fig. 1. SPECT scanning of a 21-year-old homosexual man showing a normal brain perfusion pattern. Anticardiolipin antibodies (ACA) were within the normal range ($\leqslant 20$ GPL).

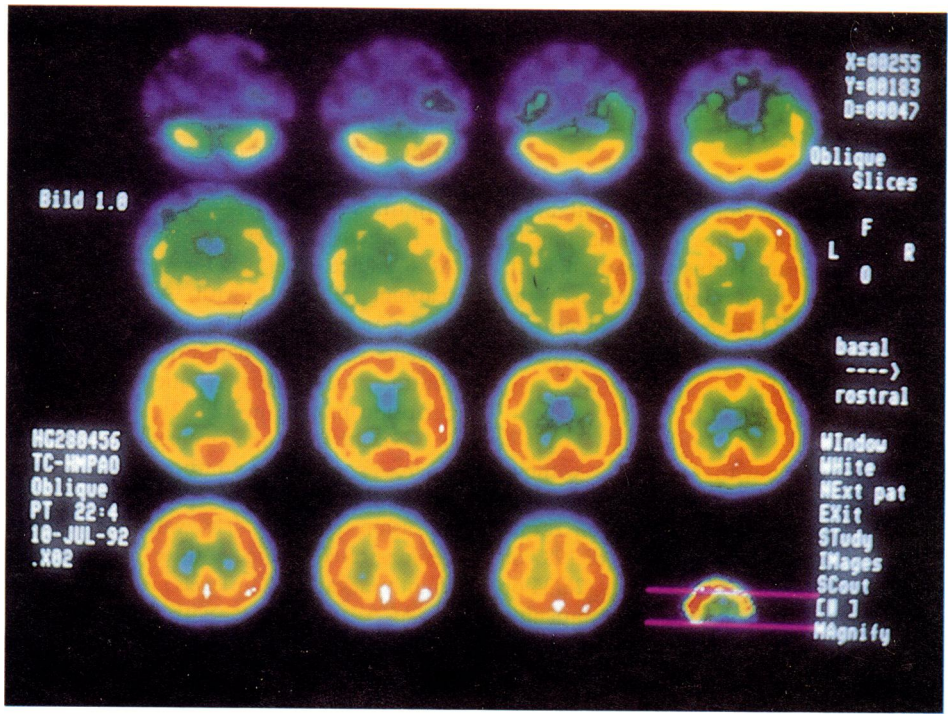

Fig. 2. Focal uptake defects were detected in a 36-year-old homosexual man with significantly elevated anticardiolipin antibodies (ACA) (56 GPL).

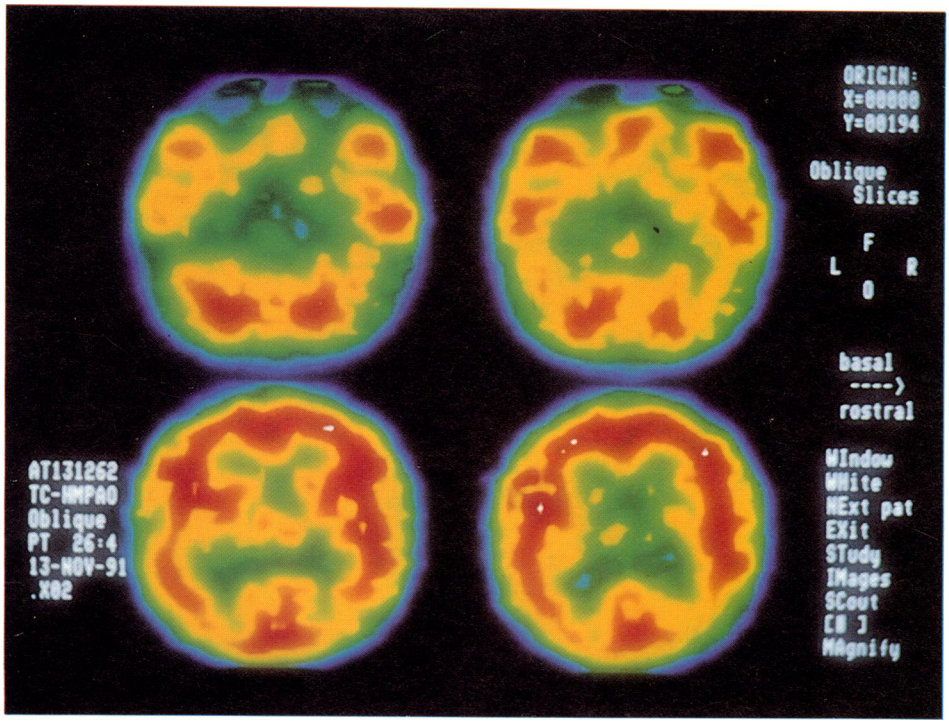

Fig. 3. SPECT scanning shows diffuse uptake defects in this 30-year-old homosexual man; an elevated anticardiolipin antibody (ACA) titre was measured (42 GPL).

Table 1. Characteristics of patients with and without cerebral perfusion defects as detected by SPECT scanning

	Abnormal SPECT ($n = 16$)	Normal SPECT ($n = 18$)	
Sex			
Male	$n = 15$	$n = 14$	NS
Female	$n = 1$	$n = 4$	
Stage of disease			
CDC II	$n = 4$	$n = 5$	NS
CDC III	$n = 4$	$n = 4$	
CDC IV	$n = 8$	$n = 9$	
Anti-retrovirals			
With AZT	$n = 1$	$n = 4$	NS
Without AZT	$n = 15$	$n = 14$	
Transmission			
Homo/bisexual	$n = 9$	$n = 13$	NS
Heterosexual	$n = 4$	$n = 3$	
Former i.v. drug user	$n = 3$	$n = 2$	
Age			
Mean (years)	$34{\cdot}3 \pm 7{\cdot}2$	$31{\cdot}9 \pm 10{\cdot}1$	NS
Range (years)	25–50	21–57	

NS, Not significant; AZT, zidovudine.

was elevated in 28/34 patients (82·4%). Increased levels of neopterin in urine (normal, $\leqslant 120\,\mu$mol/mol creatinine) were measured in 13/21 patients (61·9%).

Elevated levels of circulating immune complexes were found as determined by the C1q-binding assay (normal, $\leqslant 40\,\mu$g/dl) in only 3/30 patients. After polyethylene glycol (PEG) precipitation, IgG-containing immune complexes (normal $\leqslant 8$ mg/dl) were detected in 13/23 patients (56·5%), IgA-containing immune complexes (normal $\leqslant 2$ mg/dl) in 11/23 patients (47·8%), and IgM-containing immune complexes (normal $\leqslant 3$ mg/dl) in 12/23 patients (52·2%).

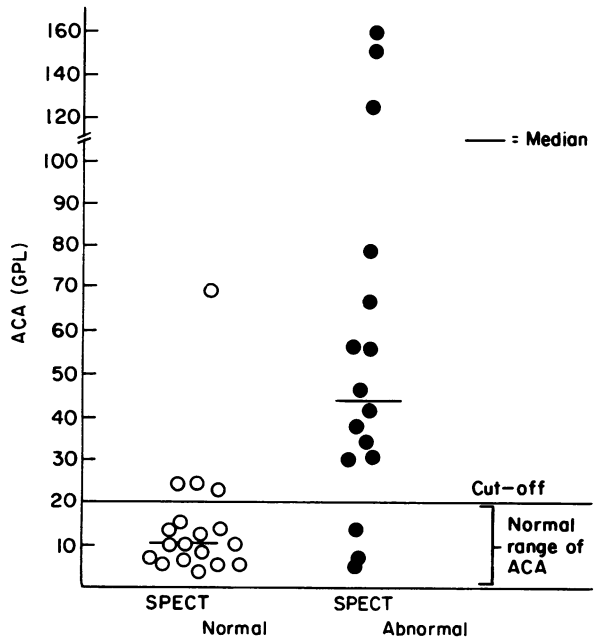

Fig. 4. In most patients with abnormal brain perfusion, elevated anticardiolipin antibodies (ACA) were detected. In contrast, only 4/18 patients with normal SPECT findings had ACA > 20 GPL.

Increased levels of serum IgG (normal 800–1800 mg/dl), IgA (normal 90–350 mg/dl) and IgM (normal 60–280 mg/dl) were measured in 18/34, in 14/34 and in 8/34 patients, respectively.

No significant correlation between SPECT results and levels of β_2-microglobulin, neopterin, circulating immune complexes or serum IgG, IgA and IgM was detected (Table 2).

Patients had a mean CD4 cell count of $312 \pm 252/\mu$l, ranging from 10 to $959/\mu$l. Mean CD4 cell counts were comparable in patients with and without cerebral perfusion defects. No significant differences were observed with regard to absolute B and CD8 cell counts between the two groups (Table 2).

In 8/31 patients (25·8%), p24 antigen was detectable. Thrombocytopenia ($\leqslant 140\,000/\mu$l) was evident in 7/34 patients (20·6%). Four of the seven patients with thrombocytopenia were ACA-positive with platelet counts ranging from 100 000 to 118 000/μl (not significant). Abortions or thromboembolic complications were not observed in our patients.

No association between the presence of p24 antigen or thrombocytopenia and cerebral perfusion abnormalities was noted (Table 2).

DISCUSSION

Neurological dysfunction is a frequent complication during the course of HIV disease. Of AIDS patients, 40–60% present with typical neurologic deficits [16], and more than 90% show characteristic neurologic changes [17]. As HIV-1 DNA, infectious virus and intrathecally synthesized anti-HIV antibodies have been detected not only in patients with advanced disease but also in asymptomatic individuals early in the course of disease [1], CNS involvement seems to occur in all stages of disease, not necessarily being accompanied by overt neuropsychiatric symptoms. Although CT or MRI are useful techniques in ruling out structural brain processes, they mostly reveal normal findings in asymptomatic subjects and mild to moderate cerebral atrophy in patients with advanced disease [9]. Functional neuroimaging techniques like SPECT or PET are potentially more promising in detecting subtle alterations in brain perfusion and metabolism before structural damage is evident.

SPECT scanning has been used to detect brain perfusion abnormalities in patients with acute stroke, transient ischaemic attacks (TIA), brain metastasis or in patients with systemic lupus erythematosus (SLE) [15]. In contrast to PET, SPECT is widely available, easy to perform and inexpensive.

Previous studies have shown pathologic SPECT scans in a substantial proportion of patients with HIV infection or AIDS. Pohl *et al.* [18] performed SPECT scanning using IMP (iodine 123-N-isopropyl-*p*-iodoamphetamine-hydro-acetate) in 12 patients with AIDS dementia complex, and detected brain perfusion abnormalities in all of them. Pathologic uptake patterns in IMP-SPECT in 30/33 patients with HIV-related encephalopathy were also described by Masdeu *et al.* [19].

However, Schielke *et al.* [20] reported abnormal ^{99m}Tc-

Table 2. Correlation of SPECT results with laboratory parameters

	Abnormal SPECT ($n = 16$)	Normal SPECT ($n = 18$)	
CD4 cell count			
Mean ± s.d.	322 ± 268	303 ± 237	NS
Range	10–959	15–652	
CD8 cell count			
Mean ± s.d.	1047·6 ± 538·4	736·2 ± 477·8	NS
Range	321–2422	236–1995	
B cell count			
Mean ± s.d.	167·1 ± 99·9	129·5 ± 77·9	NS
Range	20–409	29–282	
Anticardiolipin antibodies			
No. of patients	$n = 13$	$n = 4$	$P = 0{\cdot}002$
Mean level ± s.d.	58 ± 47 GPL	14·3 ± 15·1 GPL	$P = 0{\cdot}0007$
Range	2·7–161 GPL	2·4–70 GPL	
β_2-microglobulin			
Mean ± s.d. (mg/*l*)	3·4 ± 1·2	3·0 ± 1·1	NS
Range (mg/*l*)	1·9–7	1·8–5·6	
Neopterin (in urine)			
Mean ± s.d. (μmol/mol creatinine)	164·5 ± 66·2 ($n = 11$)	146 ± 57·4 ($n = 10$)	NS
Serum IgG			
Mean ± s.d. (mg/dl)	2284 ± 754	1927 ± 468	NS
Serum IgA			
Mean ± s.d. (mg/dl)	431·3 ± 320	384 ± 181	NS
Serum IgM			
Mean ± s.d. (mg/dl)	221 ± 109	205·7 ± 107·5	NS
PEG-immune complexes			
IgG	8/11	5/12	NS
IgA	6/11	5/12	NS
IgM	7/11	5/12	NS
C1q-immune complexes			
No. of patients	2/14	1/16	NS
Thrombocytopenia			
$\leqslant 140\,000/\mu l$	4/16	3/18	NS
p24 antigen			
Positive in	4/14	4/17	NS

NS, Not significant; PEG, polyethylene glycol.

HMPAO SPECT results in 14/20 patients without clinical signs of cognitive impairment. Similar results were presented by Tran Dinh *et al.* [11], who observed cerebral perfusion abnormalities in 88% of clinically asymptomatic HIV-infected patients.

As most of these patients showed normal CT or MRI findings, perfusion defects do not seem to correspond to structural lesions, but are supposed to reflect hypoperfusion, due either to cerebrovascular or to metabolic changes.

In our study, pathologic SPECT scans were detected in 16/34 patients, with eight patients showing focal uptake defects and diffuse uptake defects in the remaining eight patients. Twenty-six patients presented without clinical symptoms suggestive of neuropsychiatric involvement. SPECT scans were normal in 5/6 patients complaining of mild headache and in another patient presenting with acute psychosis as initial manifestation of HIV disease. Corresponding to other studies [10,11], abnormal SPECT scans were diagnosed in patients of all disease stages, regardless of standard laboratory disease markers.

Although brain perfusion abnormalities as identified by SPECT techniques are detected in a significant proportion of HIV-infected patients, little is known about their causal relationship or their implication in pathogenesis of CNS disease.

Neuropathologic studies demonstrate multinucleated giant cells, reactive astrocytosis, thickening of small vessel walls and

perivascular infiltrates as characteristic features of CNS involvement in AIDS patients [5]. Autopsy studies published by Rhodes [21] showed cerebral vasculitis in 8% and perivascular inflammation in 32% of 100 patients. Mizusawa *et al.* [22] demonstrated ischaemic infarctions in 29% of 83 AIDS patients, but most of them did not have any clinical symptoms of decreased cerebral blood flow during lifetime. By strict histologic criteria, the infection may be limited to only a few cells even in patients with global dementia. Therefore, indirect mechanisms of injury may play a role in the development of CNS changes.

Geier *et al.* [23] reported a close correlation between the presence of retinal microangiopathy and cerebral perfusion defects in HIV-infected patients, strengthening the view that microvascular disturbances might contribute to CNS disease.

HIV not only leads to depletion of $CD4^+$ T cells during the course of disease, but induces polyclonal B cell activation with marked hypergammaglobulinaemia, circulating immune complexes and ACA. In patients with autoimmune disorders such as SLE, the presence of ACA is closely related to the occurrence of venous and arterial thromboses, thrombocytopenia, abortions, chorea and a variety of other clinical disorders [24]. The observed vasculopathy in these conditions is regarded as either thrombotic or vasculitic, and appears to reflect the interaction of antiphospholipid antibodies with negatively charged phospholipids on endothelial cell surfaces. Increased levels of ACA have been reported in HIV-infected individuals [13,14]. However, the presence of ACA could not be correlated with clinical features as observed in rheumatic diseases, nor were associations with clinical or laboratory disease parameters of HIV disease evident. Furthermore, evidence of an association to habitual abortion or thromboembolism as known in autoimmune conditions is lacking in HIV disease [14,25].

In our study, increased levels of IgG-ACA were detected in 50% of the patients. Interestingly, most patients with cerebral perfusion defects had significantly elevated ACA titres, in contrast to patients with a normal cerebral perfusion pattern.

To our knowledge, this is the first study demonstrating a significant correlation between pathologic SPECT findings and the presence of ACA in HIV-infected patients. In agreement with other investigators, neither ACA nor SPECT results were associated with stages of disease, β_2-microglobulin, CD4 cell counts or medication. As SPECT scanning was mostly performed before initiation of anti-retroviral treatment, only few patients with zidovudine treatment were included in the study.

The clinical significance of serological autoimmune phenomena in HIV-infected patients is controversial. As the CNS is rich in phospholipids, systemic or local production of antiphospholipid antibodies might interfere with CNS function. Several mechanisms have been proposed for ACA-induced thrombosis, including interference with protein C and antithrombin III activity, platelet function or inhibition of prostacylin [26].

Clinical conditions such as autoimmune thrombocytopenia, polyneuritis, Guillain–Barré or polymyositis in patients with HIV infection provide evidence that serological autoimmune phenomena may be of clinical significance. The detection of ACA in CSF of asymptomatic HIV patients may also suggest a possible relationship of autoantibodies of CNS involvement [12].

Neither ACA nor SPECT findings could be correlated with levels of circulating immune complexes. However, circulating immune complexes as determined by PEG precipitation were detected in a substantial proportion of patients.

In conclusion, the present study shows that brain perfusion abnormalities are frequently detected in HIV-infected patients, and are significantly associated with the presence of anticardiolipin antibodies. Further studies are needed to evaluate whether not only HIV itself but also autoimmune mechanisms arising during the course of disease may contribute to its clinical features.

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