Int J Leg Med (1993) 105:339–350

International Journal of
Legal Medicine

Case reports

Neuropathological studies in the brains of AIDS patients with opportunistic diseases

Eva Neuen-Jacob[1], Christian Figge[1], Gabriele Arendt[2], Bernd Wendtland[2], Bernhard Jacob[3], and Wolfgang Wechsler[1]

Departments of Neuropathology[1], Neurology[2], and Legal Medicine[3], Heinrich-Heine-University, Moorenstrasse 5, W-4000 Düsseldorf 1, Germany

Received November 3, 1992 / Received in revised form February 1, 1993

Summary. The brains of 70 fatal cases with AIDS were studied by means of immunohistochemistry and in-situ hybridization in a consecutive autopsy series (1985 – July 1992). In addition, the neuropathological changes were correlated with the neurological and neuroimaging findings. Opportunistic infections included toxoplasmosis (15 cases), cytomegalovirus (CMV)-encephalitis (6), progressive multifocal leucoencephalopathy (2) and fungal infections (3). Malignant lymphomas were found in 7 patients; 6 involved primarily the CNS, one was metastatic. In 14 cases the neuropathological changes were consistent with HIV encephalitis and HIV leucoencephalopathy. Non-specific lesions occurred in 31 cases. The clinical diagnosis in patients with opportunistic diseases ($n = 27$) diverged in 15 cases (55%) from the underlying pathology. Toxoplasma gondii, CMV and JC viruses were identified by immunohistochemistry and in-situ hybridization on serial paraffin sections. In addition, antibodies against lymphocyte subsets, tissue macrophages, the glial fibrillary acid protein (GFAP) and myelin basic protein were used to characterize the phenotype of cells and to highlight the degree of gliosis and demyelination. Our results show that the distribution and degree of morphological changes might be helpful for the differential diagnosis antemortem. Since neurological complications may represent the first or sole manifestation of AIDS and risk factors for AIDS are often not known, it should be taken into account that CNS manifestations of AIDS may contribute to a sudden and unexpected death or accident. Opportunistic diseases should be considered as a possible differential diagnosis in cases mimicking the clinical picture of apoplexia or dementia. Furthermore, CNS lesions may be detected postmortem in patients who were not known to suffer from Neuro-Aids during life, indicating that CNS involvement is more widespread than assumed.

This work was supported by the Heinz-Ansmann-Stiftung für AIDS-Forschung, Düsseldorf

Correspondence to: E. Neuen-Jacob

Key words: AIDS – Neuropathology – Immunohistochemistry – In-situ hybridization – Opportunistic diseases

Zusammenfassung. Die Gehirne von 70 verstorbenen AIDS-Patienten wurden mit Hilfe von Immunhistochemie und in-situ-Hybridisierung in einer systematischen Autopsie-Serie (1985–Juli 1992) untersucht. Die neuropathologischen Befunde wurden mit den neurologischen und neuroradiologischen Untersuchungsergebnissen korreliert. Opportunistische Infektionen umfaßten Toxoplasmose (15 Fälle), Cytomegalievirus (CMV)-Encephalitis (6), progressive multifokale Leukoencephalopathie (2) und Pilzinfektionen (3). Maligne Lymphome fanden sich bei 7 Patienten; 6 davon waren primäre ZNS-Lymphome, eines eine metastatische Absiedelung. In 14 Fällen waren die Befunde vereinbar mit einer HIV-Encephalitis bzw. HIV-Leukoencephalopathie. In 31 Fällen fanden sich unspezifische Veränderungen. Bei den Patienten mit opportunistischen Infektionen zeigte sich in 15 Fällen (55%) keine Übereinstimmung zwischen klinischer und pathologischer Diagnose. An Paraffin-Serienschnitten wurden Toxoplasmen, CMV und JC-Virus mit Immunhistochemie und in-situ-Hybridisierung identifiziert. Mit Hilfe von Antikörpern gegen Lymphozyten-Subtypen, Gewebsmakrophagen, saures Gliafaserprotein und basisches Myelin-protein wurden die Phänotypen der Zellen charakterisiert und das Ausmaß von Gliose und Demyelinisierung quantifiziert. Unsere Ergebnisse zeigen, daß Ausmaß und Verteilung der morphologischen Veränderungen bereits zu Lebzeiten der Patienten hilfreich für die Differentialdiagnose sein können. Da neurologische Komplikationen die erste oder einzige Manifestation von AIDS darstellen können und Risikofaktoren häufig nicht bekannt sind, kann eine ZNS-Beteiligung bei AIDS Mitursache eines plötzlichen, unerwarteten Todes oder Unfalls sein. Opportunistische Erkrankungen sollten bei klinischem Bild eines Apoplex oder einer Demenz differentialdiagnostisch ausgeschlossen werden. Darüberhinaus können ZNS-Läsionen post-

mortal bei Patienten gefunden werden, bei denen keine neurologische Beteiligung zu Lebzeiten bekannt war. Eine ZNS-Beteiligung im Rahmen von AIDS scheint somit verbreiteter zu sein als bisher angenommen.

Schlüsselwörter: AIDS – Neuropathologie – Immunhistochemie – In-situ-Hybridisierung – Opportunistische Erkrankungen

Introduction

Neurological symptoms due to central nervous system (CNS) involvement are common complications in patients with the acquired immune deficiency syndrome (AIDS), and may be present at the first onset of the disease (Berger et al. 1987; Lantos et al. 1989).

CNS manifestations encompass malignant B-cell lymphomas as well as various opportunistic infections caused by *Toxoplasma gondii, Aspergillus, Candida albicans Cryptococcus, Mycobacteria, Cytomegalovirus, Papovavirus* or *Herpes virus,* including combined infections with various opportunistic agents (Anders et al. 1986; Gill et al. 1985; Kuchelmeister et al. 1991; Laskin et al. 1987; Levy RM et al. 1985; Navia et al. 1986a; Sharer and Kapila 1985; Snider et al. 1983; So et al. 1986; Woods and Goldsmith 1990).

In contrast to these opportunistic diseases as a consequence of the immune deficiency, brain lesions assumed to be directly induced by the human immune deficiency virus (HIV) have been delineated and designated as subacute encephalitis, AIDS encephalopathy or AIDS dementia complex (Epstein et al. 1985; Gullotta and Kuchelmeister 1987; Kato et al. 1987; Navia et al. 1986c; Petito et al. 1986; Shaw et al. 1985). Clinically, the prominent features are cognitive decline and/or motor deficits, behavioural dysfunction, finally progressive dementia (Fischer and Enzensberger 1987; Navia et al. 1986b; Price et al. 1991). HIV-induced brain disease may develop even before the systemic immune deficiency (Navia and Price 1987). However, this is the exception to the rule and HIV-associated brain lesions usually occur in the terminal-stage of HIV-infection.

According to the latest recommended neuropathology-based terminology of HIV-associated disease of the nervous system (Budka et al. 1991), the morphological substrate of AIDS dementia complex is represented by 2 major pathological patterns termed HIV encephalitis and HIV leucoencephalopathy (for review see Budka 1989 and 1991).

Our knowledge of the brain pathology of HIV-related CNS manifestations has increased considerably in recent years. However, the clinical diagnosis in the patient's lifetime may be difficult to establish in the individual case. CNS manifestations in patients with AIDS are often not diagnosed in the lifetime of the patients due to various reasons. Firstly, patients with widespread opportunistic lesions may show focal symptoms which may be misinterpreted as apoplexia or may mimick the picture of dementia. Often a risk factor for AIDS is not known, and the HIV infection appears as a first or sole CNS manifestation. Neuropsychiatric complications may be difficult to diagnose if the investigator is not experienced, and false negative results of blood tests for opportunistic agents increase the diagnostic difficulties.

Similar problems may occur at the time of necropsy since detailed data of the clinical history or imaging scans may not always be immediately available. These difficulties especially apply to forensic autopsy cases with sudden and unexpected or violent death including suicide, where clinical data may be lacking completely.

Since 1985 we have examined the brains of 70 patients with AIDS in the CDC stage IV who came to necropsy in the Department of Pathology of Institute or Legal Medicine (Heinrich-Heine-University, Düsseldorf) in a consecutive autopsy series.

The aim of our study was twofold: firstly, to collect data on the CNS manifestations with respect to frequency, distribution and degree of morphological changes. Immunohistochemical and in-situ hybridization studies were performed in order to classify various opportunistic infections, primary CNS lymphomas and HIV-associated brain lesions. HIV-1 structural proteins were demonstrated in the brain tissue by means of commercially available monoclonal antibodies, and the infected cell types were specifically identified.

Secondly, the neurological data were compared with the neuropathological postmortem findings with a view to develop workable data which might improve diagnostic procedures. In this paper we specially focused on the manifestation and topography of opportunistic lesions, the identification of opportunistic agents and the efficacy of specific treatment of opportunistic diseases.

Materials and methods

This consecutive autopsy series included 63 male and 4 female adults as well as 3 children. Two cases of a 7-month-old baby girl and a 4-year-old boy have been reported in more detail elsewhere (Biggemann et al. 1987). Risk factors for AIDS included homosexuality in 35 cases, intravenous drug abuse in 6 and hemophilia in 4 cases; 5 patients had received HIV-contaminated blood transfusions, one child was born to an intravenous drug-addicted mother and one woman had been infected by heterosexual contact. It is noteworthy, that in 18 patients a risk factor for AIDS was not known.

In all but one case with neurological abnormalities ($n = 36$) cranial computer tomography (CCT) and/or magnetic resonance imaging (MRI) had been carried out during the lifetime of the patients. MRI scans were performed using a spin-echo technique (Diasonics) with a 0.35 Tesla superconducting magnet. The T2-weighted images were obtained with repetition time (TR) = 2500 msec and echo time (TE) = 60 msec. CCT was performed using a Diasonics scanner.

After autopsy the brains were cut into frontal sections after 4 weeks fixation in 4% buffered formalin. For light microscopy tissue samples were taken from the frontal, temporal, parietal and occipital cortex and subcortical white matter, the hippocampus, basal ganglia, midbrain, pons, medulla oblongata and cerebellum. Paraffin sections 4 µm thick were stained by H&E, Masson's trichrome, Heidenhain-Wölke, cresyl-violet and Grocott's methenamine silver for the detection of fungi.

Immunohistochemistry was performed on selected paraffin sections. The slides were incubated overnight with a panel of com-

mercially available antibodies (Dako Diagnostica, Hamburg, FRG) after dilution in 5% bovine albumin in phosphate buffered saline, pH 7.6 (PBSA). The anti-tissue macrophage monoclonal antibodies (MAb) Mac 387 and CD 68 and polyclonal antibodies against the glial fibrillary acid protein (GFAP) and myelin basic protein were used for characterization of multinucleated giant cells, microglial nodules and the degree of gliosis and demyelination. Malignant lymphomas were specified by Dako-4KB5 and Dako-UCHL1 MAb against B- and T-lymphocytes and by polyclonal antibodies against IgG, IgA, IgM and kappa and lambda light chains. In order to identify opportunistic agents, a MAb directed against CMV and a rabbit polyclonal antiserum against Toxoplasma gondii (Biggemann et al. 1987) were applied.

For demonstration of the HIV-1 core protein p24 the MAb, Kal-1 (Dako Diagnostica) was used in a dilution of 1:15 in PBSA after predigestion with pronase.

For staining of the monoclonal antibodies biotinylated horse anti-mouse IgG and the ABC-P complex (Vector laboratories, Burlingame, CA, USA) were sequentially applied. The polyclonal antibodies were submitted to a 3-step PAP-procedure as previously described (Neuen et al. 1987). The peroxidase was developed using 3.3′-diaminobenzidine (Sigma, Munich, FRG) and amino-ethyl-carbazole (Enzo Biochem, New York, USA) respectively. The slides were counterstained with hematoxylin. Negative controls were performed by omission of the primary antibodies.

Double-staining was achieved as follows: the first primary antibody was applied using the ABC-method with diaminobenzidine as a brown dye. Sequentially, the slides were incubated with the second primary antibody following the alkaline phosphatase-anti-alkaline phosphatase (APAAP) procedure (Dako Diagnostica, Hamburg, FRG). Naphthol AS-MX phosphate dissolved in dimethylformamide (Enzo Biochem, New York, USA) was used as red chromogen.

In-situ hybridization was carried out on paraffin sections using commercially available biotinylated DNA probes against CMV and JC virus (Enzo Biochem, New York, USA). Briefly, the procedure was as follows: the hybridization mixture was applied to the deparaffinized slides. These were covered with a coverslip and placed on a heating temperature block adjusted to 92°C for 3 mins to denaturate the double stranded DNA. After incubation at room temperature for 20 mins the coverslips were removed, and the slides were immersed in wash solution (50% formamide, 0.1 × PBS) for 10 mins and a final rinse in PBS-buffer. For visualization the ABC complex and amino-ethyl-carbazole as chromogen were sequentially applied.

On selected slides, in-situ hybridization was combined with a secondary incubation with GFAP in a PAP-procedure as described above using diaminobenzidine as the second chromogen.

Results

The main causes of death in the present series are detailed in Table 1. The majority of patients had died of respiratory insufficiency ($n = 48$). In 15 cases intracranial hemorrhages ($n = 2$) or severe brain edema ($n = 13$) led to central regulation failure. In one of these cases a severe rise of intracranial pressure resulted in brain death. Three patients each died from cardiac arrest and septic peritonitis complicating intestinal Kaposi sarcoma respectively. 2 male patients were found dead in their appartments and a forensic autopsy was performed: in one case atypical drowning in the bathtub was found to be the cause of death. The other man had died of severe coronary insufficiency leading to cardiac arrest.

The neuropathological findings are summarized in Table 2. In 14 cases (20%) the features were consistent with HIV-induced brain lesions including 12 cases with HIV encephalitis and 2 cases with HIV leucoencephalopathy rather than HIV encephalitis. The findings in these HIV-associated lesions are detailed elsewhere (Neuen-Jacob et al. 1992) and will not be a subject of the present paper.

Table 1. Pathological findings leading to death in 70 patients with AIDS

Cause of death	No. of cases
Respiratory insufficiency due to[a]:	48 (69%)
Atypical pneumonia	31 (44%)
Pneumocystis carinii pneumonia	12 (17%)
Fungal pneumonia	4 (6%)
CMV pneumonia	1 (1%)
Kaposi sarcoma of the lung	4 (6%)
Miliary tuberculosis	3 (4%)
Central regulation failure following:	15 (21%)
Brain edema due to encephalitis/lymphoma[b]	13 (19%)
Massive intracranial bleeding	2 (3%)
Apnoe after seizure	1 (1%)
Cardiac arrest due to:	3 (4%)
Cardiomyopathy	1 (1%)
Viral myocarditis	1 (1%)
Coronary insufficiency	1 (1%)
Septic peritonitis complicating intestinal Kaposi sarcoma	3 (4%)
Atypical drowning	1 (1%)

[a] Including 5 cases with 2 or more concomitant affections
[b] Including 1 case with brain death

Table 2. Neuropathological findings in 70 patients with AIDS

Neuropathological features	No. of cases
HIV-1 associated brain lesions	14 (20%)
HIV encephalitis	12 (17%)
HIV leucoencephalopathy	2 (3%)
Opportunistic diseases	27 (39%)
Opportunistic infections	
Toxoplasmosis[a]	15 (21%)
Aspergillus encephalitis	1 (1%)
Candida encephalitis	2 (3%)
CMV encephalitis	6 (9%)
Progressive multifocal leucoencephalopathy (PML)	2 (3%)
Primary CNS lymphoma	6 (9%)
Metastatic lymphoma	1 (1%)
Non-specific lesions including:	
Ischemic changes	18 (26%)
Hemorrhages	4 (6%)
Infarctions	4 (6%)
Angioma	3 (4%)
Teleangiektasia	2 (3%)
Unspecific vasculitis	2 (3%)
Encephalitis of unknown origin	1 (1%)
Cerebellar dysplasia	2 (3%)

[a] Including 2 cases under antibiotic treatment

Table 3. Correlation of clinical and neuropathological (NP) diagnosis in 27 patients with opportunistic diseases

S-No.	Clinical diagnosis	CCT/MRI findings	NP-diagnosis
347/85	Tuberculous lesions	CT: Bilateral hypodense lesions	Toxoplasmosis
78/86	Viral encephalitis	CT: Ring-enhancing lesions	Toxoplasmosis
463/86	Tuberculous lesion	CT: Contrast-enhancing lesion	Toxoplasmosis
542/88	Toxoplasmosis	CT: Ring-enhancing lesions	Toxoplasmosis
561/88	Toxoplasmosis	CT: Ring-enhancing lesions	Toxoplasmosis
31/89	Toxoplasmosis	CT: Ring-enhancing lesions	Toxoplasmosis
107/89	HIV encephalopathy	MRI: Subcortical hyperintensity	Toxoplasmosis[a]
116/89	Toxoplasmosis	CT: Ring-enhancing lesions	Toxoplasmosis
120/89	Cerebral apoplexia	CT: Unilateral hyperdense lesion	Toxoplasmosis
450/89	HIV encephalopathy	MRI: Normal scan	Toxoplasmosis[a]
203/90	HIV encephalopathy	MRI: Normal scan	Toxoplasmosis
428/91	Toxoplasmosis	CT: Ring-enhancing lesions	Toxoplasmosis
31/92	Toxoplasmosis	CT: Basal ganglia ring-enhancing lesions	Toxoplasmosis
515/87	Aspergillus infection	Not performed	Aspergillus encephalitis
679/88	HIV encephalopathy	MRI: Ependymitis	CMV ependymitis
200/90	Intracranial hemorrhage	CT: Intracranial hyperdense lesions	Intracranial hemorrhages CMV ependymitis
63/91	Gastrointestinal CMV infection	Not performed	CMV encephalitis
45/86	PML	CT: Right parietal hypodense lesion	PML
158/90	Cerebellar infarction	CT: Cerebellar hypodense lesion	PML
7/86	Opportunistic infection	CT: Right deep hypodense area	Lymphoma
470/88	CMV encephalitis	CT: Multiple hypodense lesions	Lymphoma
386/89	HIV encephalopathy	MRI: Cortical atrophy	Lymphoma
124/92	Meningeosis lymphomatosa	MRI: Normal scan	Meningeosis lymphomatosa
114/86	HIV encephalopathy	CT: Cortical atrophy	CMV encephalitis, fungal superinfection
469/87	Focal encephalitis/DD tumour	CT: Right basal ganglia hypodense lesion	Toxoplasmosis, CMV superinfection
212/88	1) Toxoplasmosis, under treatment 2) Cerebellar tumour	CT: 1) Multiple ring-enhancing foci on improve under treatment 2) Cerebellar hyperdense lesion	Candida encephalitis, Toxoplasmic abscess, Cerebellar lymphoma
135/90	Rhombencephalitis (DD Toxo, fungi, CMV)	MRI: Cortical atrophy and internal hydrocephalus	Toxoplasmosis, Lymphoma

[a] = Presenting with disseminated microglial nodule encephalitis, published elsewhere
CCT = cranial computer tomography, MRI = magnetic resonance imaging, PML = Progressive multifocal leucoencephalopathy, DD = differential diagnosis

Opportunistic diseases occurred in 27 cases (39%). Toxoplasmosis was noted to be the most frequent opportunistic infection and was observed in 15 cases (21%). CMV-encephalitis, fungal infections due to *candida* or *aspergillus* were found with decreasing frequency. Primary CNS lymphomas were observed in 6 cases, metastatic lymphoma in 1 case. Multiple concomitant lesions due to infection with various opportunistic agents and/or malignant lymphoma occurred in 4 cases. Non-AIDS specific changes included ischemic nerve cell damage due to respiratory insufficiency, purpuric or mass hemorrhages, infarctions, angioma, teleangiectasia and unspecific vasculitis. In one case an encephalitis of unknown etiology was found which could not be specified despite immunohistochemistry.

In those 27 patients with fatal opportunistic infections and primary CNS lymphomas the clinical diagnosis diverged in 15 cases (55%) from the underlying pathology (Table 3), probably due to the following reasons: 8 patients were diagnosed in the early AIDS period without sophisticated diagnostic procedures, and 6 cases reflect the non-specific findings in cranial computer tomography or magnetic resonance imaging. Moreover, in one hitherto asymptomatic 64-year-old patient with a sudden onset of hemiparesis, the cranial CT showed a unilateral hyperdense lesion. Due to the patient's age and the lack of any diagnostic hint for AIDS a cerebral apoplexia was suspected. However, autopsy disclosed severe cerebral toxoplasmosis, and the patient was found to be HIV-positive, indicating an advanced stage of AIDS with primary CNS manifestation.

Morphologically, the different forms of AIDS-related cerebral manifestations showed characteristic distribution patterns which deserve some further remarks.

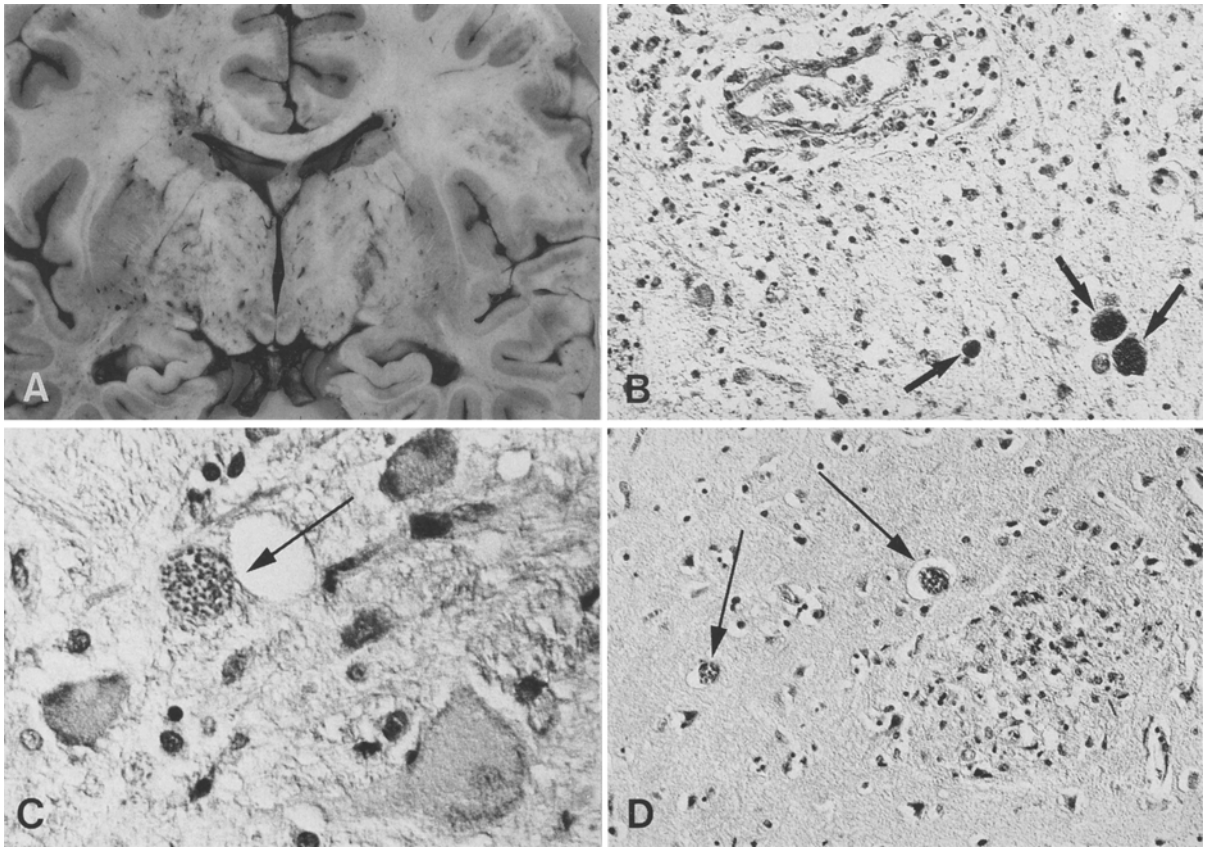

Fig. 1A–D. Toxoplasmosis. **A** Frontal section (S 78/86) showing multiple ill-defined necrotizing lesions in the subcortical white matter and basal ganglia. **B** Necrotizing lesion with vasculitis and pseudocysts *(arrow)* in the vicinity. H&E, ×140. **C** Single pseudocyst *(arrow)* adjacent to neurones in the basal ganglia. H&E, ×270. **D** Microglial nodule encephalitis in a case clinically mimicking AIDS dementia (S 107/89). Note single pseudocysts *(arrow)* in the adjacent tissue. H&E, ×345

Cerebral toxoplasmosis

Typically, gross examination revealed widespread, ill-defined, partly hemorrhagic and often confluent areas of necrosis, which were accompanied by perifocal edema (Fig. 1A). These changes were preferentially located in the subcortical or periventricular white matter of the cerebral hemispheres, the basal ganglia or the cerebellum. The lesions corresponded to the typical CCT and MRI findings of contrast enhancing nodular structures and closely correlated with the clinically evident focal neurological deficits.

Histologically, extensive necrosis with scanty plasmacellular inflammation or macrophage infiltration was evident. Fibrinoid necrosis of blood vessels or thrombosis were common features. After careful examination small quantities of toxoplasmic pseudocysts were detected by routine methods (Fig. 1B, C), and the amount of toxoplasmic agents appeared to be related to the degree of deterioration of the immune status.

In addition to multiple encysted bradyzoites, numerous free or intracytoplasmic tachyzoites were visualized immunohistochemically at the periphery of the lesions and within adjacent neuropils (Fig. 4A), occasionally attacked by macrophages (Fig. 4B). In the surrounding tissue some glial nodules were observed, occasionally containing a single pseudocyst. In one case (S 31/92) the brain showed severe tissue destruction with large necrotizing lesions and severe ependymitis despite antibiotic treatment. By routine methods no bacteria, fungi or protozoons could be detected. However, immunohistochemically, unusually numerous free trophozoites were visualized within and adjacent to the necroses. Only exceptional pseudocysts were labeled by the antiserum against toxoplasma gondii.

In contrast to this *necrotizing form of toxoplasmic encephalitis* we observed a distinctive pattern in 2 patients with toxoplasmosis clinically mimicking HIV dementia. In both cases (S107/89, S 450/89) the MRI scans were normal or showed tiny lesions in the basal ganglia (Table 3). Macroscopically, the brains were completely inconspicious. However, microscopical examination disclosed *diffuse disseminated microglial nodule encephalitis* (Fig. 1D) with abundant toxoplasmic agents (Arendt et al. 1991).

Cytomegalovirus (CMV) infection

Macroscopically, the morphological changes following CMV infection were not noticeable, and only in 2 (S 697/

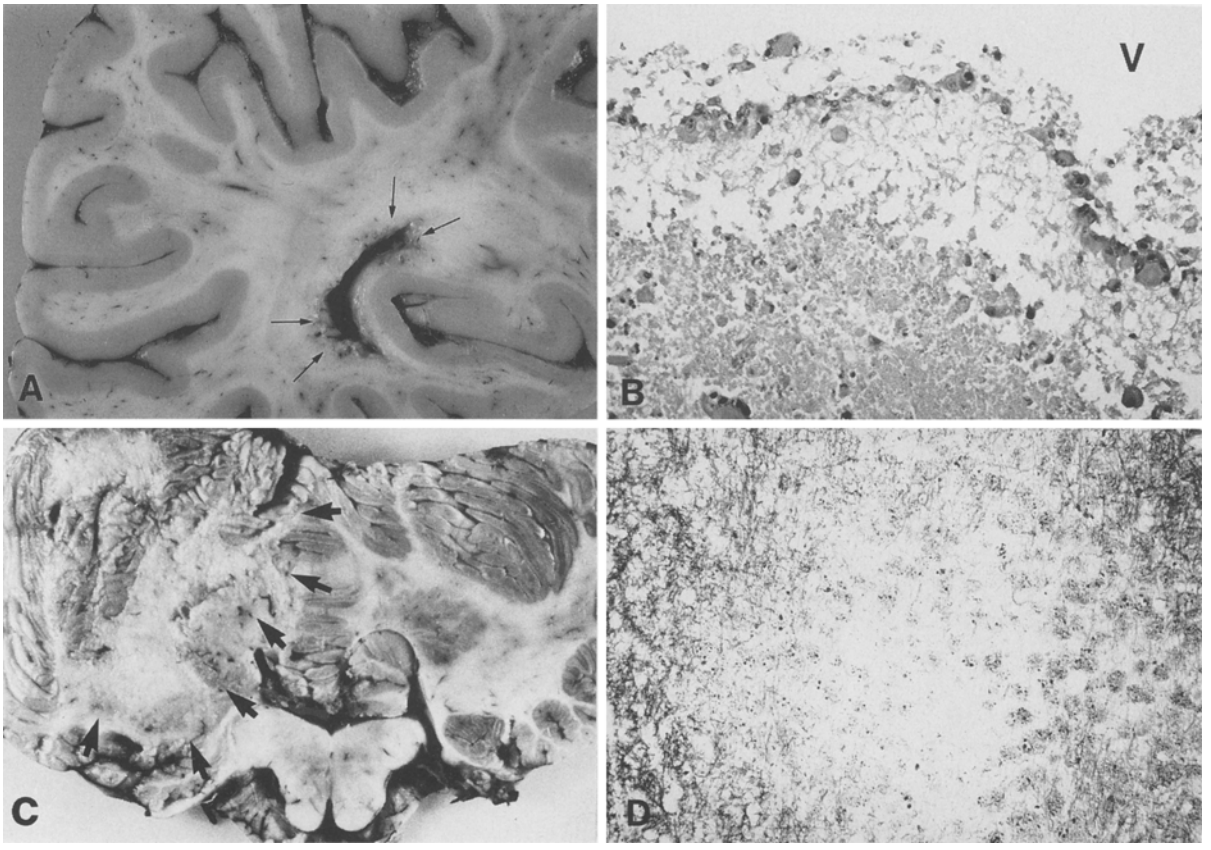

Fig. 2. A–B CMV encephalitis, **C–D** PML. **A** Frontal section (S 114/86) with slight signs of ependymitis *(arrows)*. **B** Extensive destruction of the periventricular region. Replacement of the ependyma by cytomegalic cells. *V* = ventricular lumen. H&E, ×90. **C** Large demyelinating lesion *(arrows)* in the left cerebellar hemisphere (S 158/90). **D** Focal demyelination and proliferation of lipid phagocytes. Heidenhain, ×90

88, S 113/86) out of 6 cases was there evidence of slight ependymitis (Fig. 2A).

Histological examination of these cases revealed extensive destruction of the periventricular region. The ependyma was replaced by multinucleated giant cells showing intranuclear basophilic inclusions resembling an owl's eye, which were suggestive of CMV infection (Fig. 2B). In the latter case, additional *candida* superinfection was apparent. Furthermore, in the temporal cortex numerous intranuclear cytomegalic inclusions were observed affecting astrocytes as well as single neurones. In addition, multiple microglial nodules were scattered among the cerebral cortex and basal ganglia indicating widespread CMV encephalitis which had not been diagnosed clinically.

The brains of the other 4 cases showed no gross abnormalities. However, incidental microscopical findings included subependymal proliferation of reactive astrocytes with cytomegalic intranuclear inclusions (Fig. 4C) and single microglial nodules exceptionally containing an owl's eye cell.

In contrast to these minor changes which might easily be overlooked, the amount of infected cells could readily be estimated by means of in-situ hybridization. CMV nucleic acids were clearly demonstrated even in isolated astrocytes in the vicinity of microglial nodules thus confirming the diagnosis of CMV-encephalitis (Fig. 4D). Similar results were obtained by immunohistochemical methods using the anti-CMV antibody which strongly labeled the nuclei of the infected cells.

Progressive multifocal leucoencephalopathy (PML)

We observed 2 cases with PML leading to extensive tissue destruction. In one case (S 48/86) the frontal sections showed large confluent areas of diffuse white matter degeneration in the right cerebral hemisphere and multiple smaller foci of demyelination in the midbrain and cerebellum. In the second case (S 158/90) widespread confluent demyelinating lesions in the left cerebellar hemisphere and adjacent parts of the pons were noted (Fig. 2C). Clinically, a large hypodense cerebellar lesion had been misinterpreted as an anaemic infarction.

Microscopically, both cases showed patchy myelin loss and marked proliferation of astrocytes and bizarre swollen hyperchromatic oligodendrocytes with large intranuclear inclusions (Fig. 2D). By means of in-situ hybridization using a biotinylated DNA-probe, abundant JC-Virus nucleic acids were detectable in the nuclei of the oligodendrocytes. Combined staining with GFAP (Fig. 4E) revealed strong GFAP immunoreactivity in the

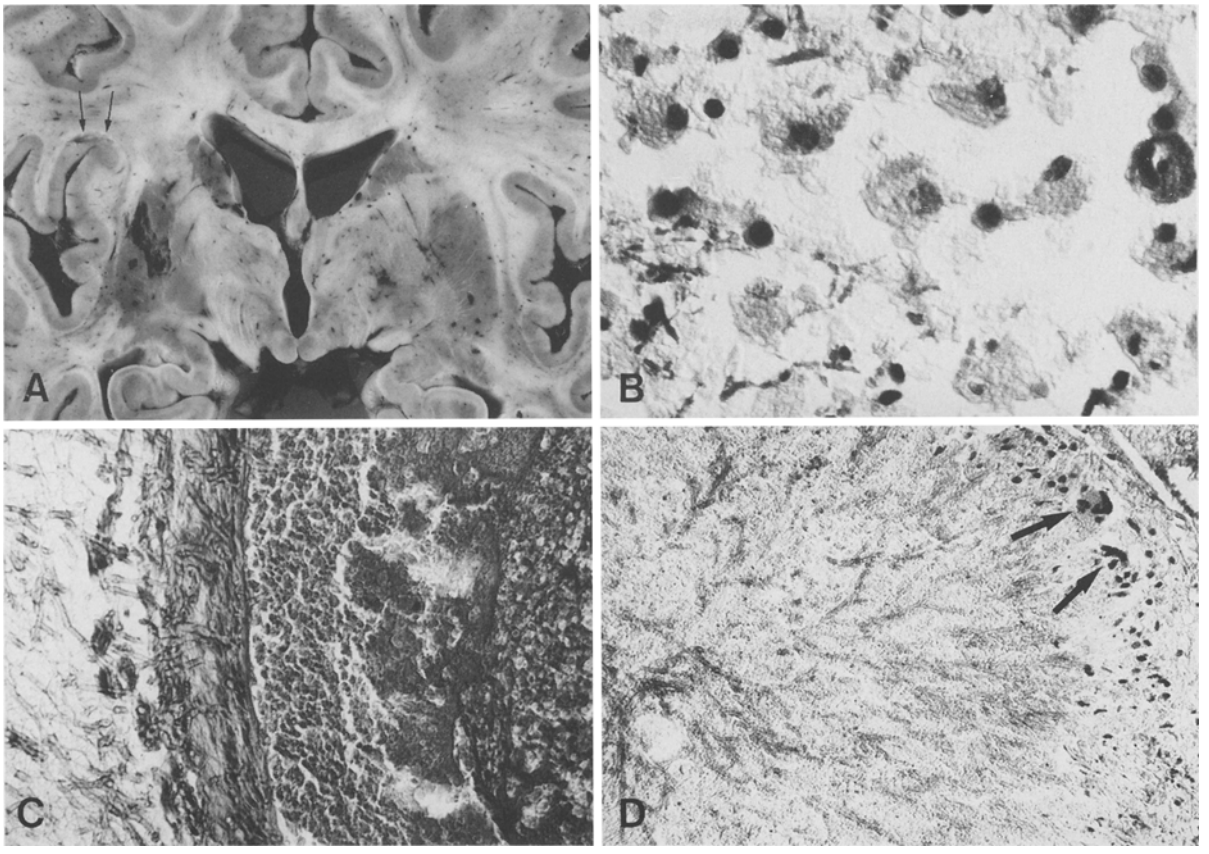

Fig. 3A–D. Fungal infections. **A** Frontal section (S 212/88) showing cystic lesions in the left insula *(arrow)* and basal ganglia. **B** Concomitant infection with CMV and candida (S 114/86). H&E, ×345. **C** Thrombosed vessel. Multiple dichotomously branching septate hyphae penetrating the necrotic vessel wall (S 515/87). Masson's trichrome, ×140. **D** Large necrotic lesion filled with numerous aspergillus hyphae. Note multinucleated giant cells of foreign body type *(arrows)* at the periphery. H&E, ×140

processes of reactive astrocytes which formed a fine network around the infected oligodendrocytes. The astrocytes remained negative for JC virus hybridization indicating that oligodendrocytes and not astrocytes were the target cells for the JC-virus.

Fungal infections

A case with *candida*-encephalitis (S 212/88) showed multiple well-defined, partly cystic lesions in the cerebral cortex, the subcortical white matter and the basal ganglia mimicking the picture of infarction due to hypertonia (Fig. 3A). Occasionally, the lesions were filled with pus. Microscopically, the cavitations revealed abundant macrophage activity, vascular response and glial proliferation. There was no arteriosclerosis. In the center of these abscesses multiple *candida* organisms were easily identifiable, as well as in a second case (S 114/86) with concomitant CMV encephalitis (Fig. 3B).

CNS infection with *aspergillus* was noted in one patient (S 515/87). Multiple, poorly circumscribed foci of softening affected the cerebral cortex and adjacent meninges, subcortical white matter and right caudate nucleus. Histologically, the prominent features were severe necrotizing vasculitis and fungal thrombosis with marked perivascular infiltration by macrophages. The vessels were often filled with numerous dichotomously branching septate hyphae which partly penetrated the necrotic vessel wall (Fig. 3C). Occasionally, the necrotic abscesses were demarcated by some multinucleated giant cells of foreign body type (Fig. 3D).

Malignant lymphomas

Primary CNS lymphomas were observed in 6 patients who had all shown a rapidly deteriorating clinical course. At autopsy, the macroscopic picture was that of single, unilateral mass-occupying ill-defined areas of softening and swelling which were located predominantly in the cerebral or cerebellar hemispheres (Fig. 5A).

Careful histological examination disclosed widespread, often multicentrical tumour infiltration. Microscopically, the basal ganglia were frequently involved with some predilection for thalamus, caudate nucleus and internal capsule. Other sites included cerebellum and brain stem, which were often affected concurrently, possibly due to metastasis via the cerebrospinal fluid.

In every case, including a seventh case with metastatic lymphoma, extensive meningeal infiltration with characteristic angio-centric invasion of the brain parenchyma was noted. At the periphery the tumour cells were arranged in perivascular collars mimicking the pattern of

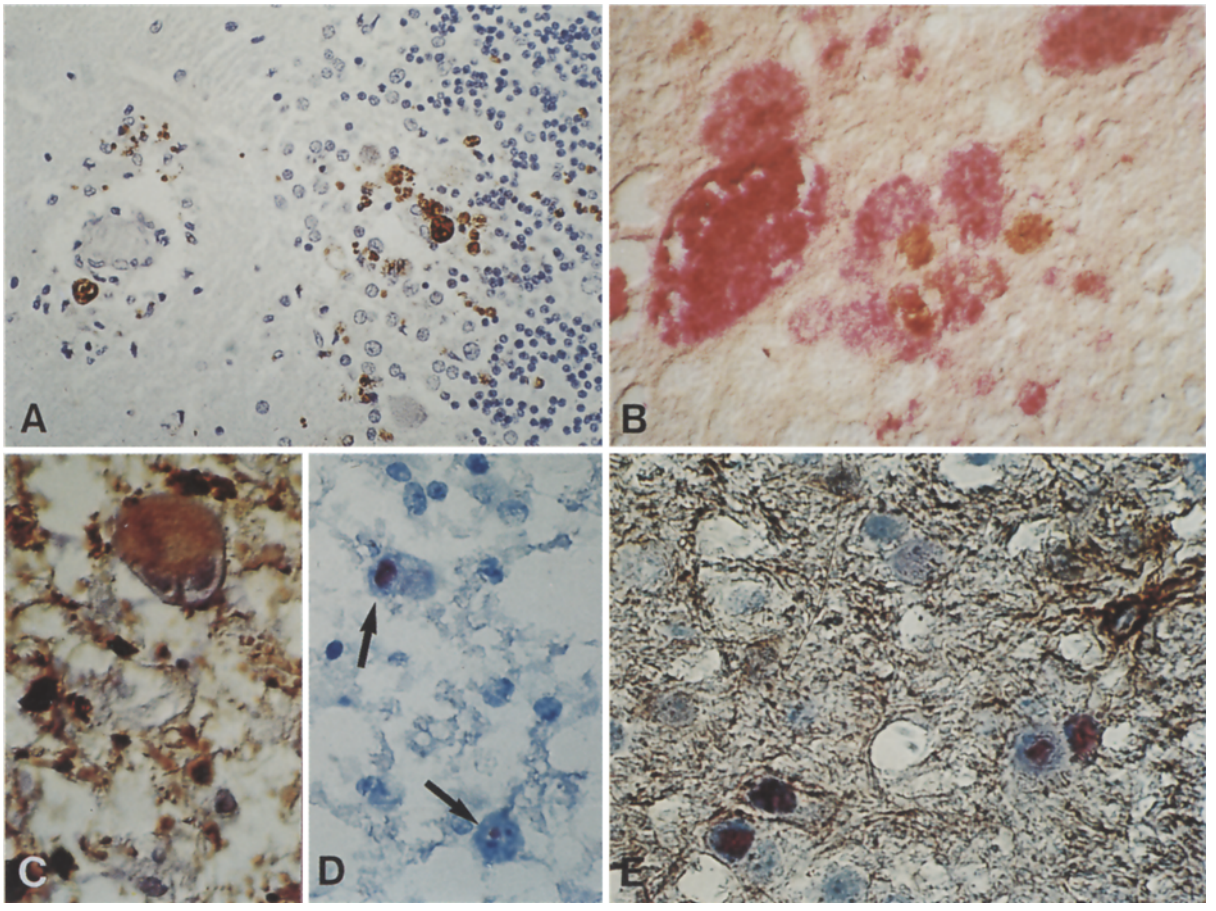

Fig. 4A–E. Immunohistochemistry and in-situ hybridization of opportunistic infections. **A–B** Toxoplasmosis. **A** Multiple pseudocysts and free tachyzoites in the cerebellum visualized by the toxoplasma antiserum, ×220. **B** High magnification showing toxoplasma pseudocysts attacked by macrophages. Double labeling with toxoplasma antiserum (red dye) and anti-macrophage antibody CD 68 (brown), ×860. **C, D** CMV encephalitis. **C** GFAP-positive astrocytes containing cytomegalic intranuclear inclusions. GFAP, ×345. **D** CMV infection confirmed by in-situ hybridization for CMV *(arrow)*, ×345. **E** In a case with PML (S 45/86) JC virus nucleic acids (red) detectable in oligodendrocytes. Combined staining with GFAP shows strong immunoreactivity in the processes of reactive astrocytes (brown), ×400

encephalitis (Fig. 5B). However, there was diffuse parenchyma infiltration, and in the more deeply lying structures the lymphoma cells formed dense tumourous aggregates of intense cellularity and high mitotic activity. Fibrinoid necroses of the vessel walls were common giving rise to large tumour necroses. In the adjacent brain tissue marked astrocytic gliosis was obvious.

The cell differentiation in all cases resembled an immunoblastic lymphoma. Immunohistochemically, the lymphoma cells could be identified as B-lymphocytes and mainly showed a monoclonal immunoglobulin synthesis consistent with malignant B-cell-lymphoma.

Furthermore, there was no evidence for HIV-infected cells in cases with opportunistic diseases or non-AIDS related findings.

Discussion

Comparable to other series (Gullotta et al. 1991; Lang et al. 1989; Moskowitz et al. 1984a; Navia et al. 1986a; Sharer and Kapila 1985), in our study *toxoplasmosis* was noted to be the most frequent opportunistic infection of the brain and was observed in 15 patients (21%). In 7 of these patients (46%) contrast-enhancing lesions in CT or MRI scans led to the diagnosis of toxoplasmosis. This relatively high percentage is possibly due to improved clinical experience concerning the management of AIDS patients as well as to the usually severe brain tissue destruction resulting in mass-occupying lesions. However, it is not possible to distinguish between toxoplasmosis or other opportunistic infections and CNS lymphomas by imaging techniques alone, since hypodense lesions are non-specific features (Table 3), and even normal MRI scans do not exclude a toxoplasmic infection.

In 2 cases with clinical symptoms of dementia the MRI scans were normal or showed only tiny lesions in the basal ganglia leading to the clinical diagnosis of HIV-encephalopathy. At autopsy, the frontal sections of the brains were absolutely inconspicious. However, microscopical examination disclosed widespread *microglial nodule encephalitis,* and unusually numerous encysted bradyzoites and free tachyzoites were visualized by means of immunohistochemistry indicating severe cerebral toxoplasmosis (Arendt et al. 1991). Both patients had shown

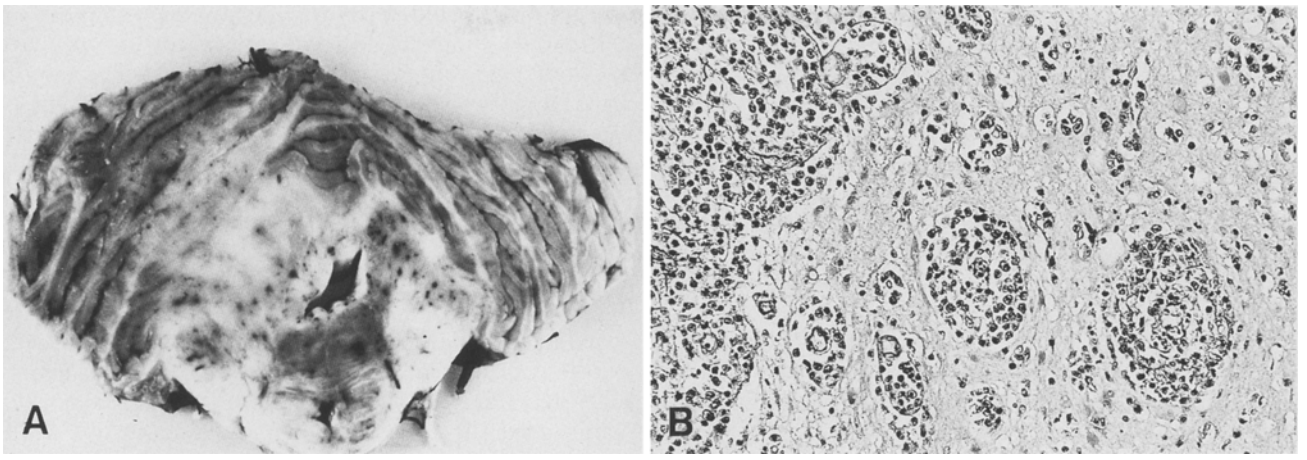

Fig. 5A, B. Malignant lymphoma. **A** Large ill-defined mass occupying lesion in the left cerebellar hemisphere with perifocal edema (S 212/88). **B** Extensive meningeal tumour infiltration with characteristic angiocentric invasion of brain parenchyma mimicking the pattern of encephalitis. Reactive astrocytosis. Tibor-pap, ×90

a disastrous immunological status. This justifies the assumption, that this special form of toxoplasmic encephalitis, clinically mimicking HIV dementia, is a distinct manifestation of cerebral toxoplasmosis with poor prognosis due to a final breakdown of the immune system.

In 2 patients with toxoplasmosis (S 31/89, S 135/90) antibiotic treatment led to a marked clinical improvement but the patients died due to other reasons. Histologically, in these cases only residual necrosis with perifocal gliosis was present. There was neither histological nor immunohistochemical evidence for toxoplasmic agents indicating successful antibiotic therapy. Therefore, in the case of suspected toxoplasmosis empirical antibiotic treatment might be justified, and an improvement of the neurological signs and CT/MRI scans might support this tentative diagnosis.

In contrast to the prominent morphological changes in cases with toxoplasmosis, it was practically impossible to establish the specific diagnosis of *CMV-encephalitis* ante mortem, since the serological identification was not always available due to false negative results and the radiological findings were rather unspecific including cortical atrophy, signs of ependymitis as well as normal scans. This might in part be due to microscopically small lesions which are below the detection limit. Thus, the degree of CNS involvement by CMV is usually highly underestimated clinically (Donovan Post et al. 1986). In fact, at autopsy in 2 out of 4 cases the brains were absolutely inconspicious by gross inspection, and the typical owl's eye cells were detected only after careful histological study. However, immunohistochemistry and in-situ hybridization are highly sensitive and reliable methods for the identification of CMV-infected cells, and also isolated cells were specifically labeled as we could previously show in the eyes of an AIDS patient with CMV-retinitis (Schmitt-Gräff et al. 1990). Interestingly, in all cases the periventricular region seemed to be the site of predilection indicating possible viral spread via the cerebrospinal fluid. In this regard, it might be speculated that signs indicative for ependymitis should be suggestive of CMV infection.

In cases with *progressive multifocal leucoencephalopathy,* the CT findings as well as the morphological changes were more prominent and led to extensive brain tissue destruction. Clinically, in one case PML had already been suspected, in the second case a cerebellar hypodense mass lesion had been misinterpreted as ischemic cerebellar infarction. In both cases the complete unilateral hemisphere was involved by large confluenting demyelinating lesions, and the diagnosis was ascertained by in-situ hybridization. In our mind, CT or MRI scans showing large demyelinating lesions involving almost a complete hemisphere are suspicious of PML. Interestingly, the exclusive involvement of the cerebellum or brainstem in cases with PML is the exception to the rule as Kuchelmeister et al. (1991) have reported in their study on 15 cases of PML in HIV-seropositive patients. In our cases there was no evidence for co-infection with HIV as has been reported by Vazeux et al. (1990) in two cases with PML.

In contrast to the striking macroscopical findings in cases with PML, the features were more difficult to diagnose in cases with primary *CNS lymphomas*. These cases showed ill-defined mass-occupying oedematous lesions. However, the extent of brain tissue infiltration was microscopically much higher than was assumed after visual inspection, and the lack of tissue reactions correlated with the progressive clinical course rapidly deteriorating to death. The patients' severe condition did not allow the performance of all diagnostic procedures, and in one case only the diagnosis was made ante mortem.

In contrast to the opportunistic infections and primary CNS lymphomas, which are secondary due to the immune deficiency, primary *HIV-related brain lesions* have been linked to the presence of HIV-1 in the brain. This assumption was substantiated by immunological and molecular biological investigations.

By means of southern blot analysis and in situ hybridization, HIV RNA and DNA sequences have been de-

tected in the brains of AIDS patients suffering from AIDS encephalopathy (Koenig et al. 1986; Price et al. 1988; Shaw et al. 1985; Stoler et al. 1986; Vazeux et al. 1987). HIV-1 was isolated from the brain tissue and the cerebrospinal fluid (Gartner et al. 1986; Ho et al. 1985; Levy JA et al. 1985). HIV structural proteins have been detected by means of immunohistochemistry in the brain tissue of AIDS patients with HIV-related dementia (Budka 1990; Gabuzda et al. 1986; Pumarola-Sune et al. 1987; Schindelmeiser and Gullotta 1991). In our study there was no evidence for HIV-1 infected cells in those cases with opportunistic infections, CNS lymphomas or non-AIDS-related findings. Only in cases with HIV-associated brain lesions were cells of macrophage/histiocytic phenotype found which were immunoreactive for the HIV-1 p24 MAb indicating direct infection of the brain tissue with the HIV (Arendt et al. 1989; Neuen-Jacob et al. in press).

Very recently, CSF-studies disclosed elevated alpha-tumor necrosis factor levels in later stages of HIV-infections with HIV-induced brain disease or opportunistic infections affecting the CNS (Grimaldi et al. 1991). These findings suggest that alpha-tumor necrosis factor represents a useful marker for active infection/inflammation of the CNS indicating possible cytokine-related reactions involved in the production of CNS injury.

In this respect, it should be emphazised, that despite the still enigmatic pathomechanisms of HIV-1 associated dementia, the clinical signs of cognitive, motor and behavioural dysfunctions are relatively characteristic and allow an early diagnosis by an experienced neurologist.

With respect to our autopsy data, we would like to conclude that the distribution and extent of the cerebral lesions visible in CCT or MRI scans may be helpful in the differential diagnosis before death. As we could demonstrate, large demyelinating lesions involving almost a complete hemisphere were most suspicious for PML, whereas single or multiple ring-enhancing lesions were typically associated with toxoplasmosis. The lesions due to CNS lymphomas were more ill-defined and rarely resembled a tumourous process. Signs of ependymitis were consistent with CMV-encephalitis, since the morphological changes in those cases were predominantly restricted to the periventricular region.

However, there may be exceptions to the rule, and each case should be considered individually.

In order to correlate the clinical, imaging and morphological findings, careful neuropathological studies in close interaction with the clinicians are warranted including macroscopical and histological investigations and the use of immunohistochemistry and in-situ hybridization which are superior to routine histology for the demonstration of opportunistic agents.

In our opinion, in addition to routine diagnostic procedures, intra vitam stereotactic brain biopsies should be performed in patients with doubtful cerebral lesions without response to tentative therapy. In particular toxoplasma parasites (Moskowitz et al. 1984b), CMV, fungal infections and PML as well as malignant lymphomas could specifically be identified by the use of immunohistochemistry and in-situ hybridization. In 2 of our own patients PML could easily be diagnosed by stereotactic brain biopsy (unpublished data). In the case of primary HIV-induced brain lesions the morphological diagnosis might be more difficult to establish due to the scarcity of the characteristic features which might require larger tissue samples. However, stereotactic brain biopsy could serve as a complementary diagnostic tool in the differential diagnosis of Neuro-AIDS enabling a rapid clinical diagnosis followed by adequate specific treatment.

With regard to our autopsy data it seems to be justified to speculate that the CNS manifestation of AIDS should be considered or excluded in all patients showing neurological symptoms of unknown etiology. Neuro-AIDS may mimic the clinical pictures of apoplexia or dementia, and the lack of known risk factors for AIDS does not exclude the possibility of a first and/or sole manifestation of AIDS in the CNS. Toxoplasmosis especially may present with unilateral mass lesions which are misinterpreted as infarction. Furthermore, in persons with a high risk of AIDS a sudden and unexpected or violent death including suicide may be more frequently observed (Püschel et al. 1985, 1987).

The cerebral manifestation of AIDS may represent the cause of death due to severe brain edema following encephalitis and/or lymphoma. The rise in intracranial pressure may even lead to brain death as in 1 of our 70 patients. It has to be considered that sudden events mimicking the clinical picture of apoplexia may be caused by massive intracerebral bleedings in cases with toxoplasmic or fungal vasculitis. Thus, the forensic autopsy should be more extensive to exclude any form of Neuro-AIDS in patients with a sudden death.

Furthermore, cognitive decline or behavioural changes due to opportunistic encephalitis or HIV encephalitis may contribute to a suicide or accident as in 1 of our patients who died of atypical drowning in the bathtub. Thus it is crucial to ensure the diagnosis with respect to forensic and epidemiological consequences. Finally, CNS lesions are more widespread than assumed in patients with AIDS and often are not diagnosed during the patient's lifetime since they may be asymptomatic.

Acknowledgements. Reproductions of colour photographs were kindly supported by the AIDS-Stiftung Heinz-Ansmann, Düsseldorf

References

Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV (1986) The neuropathology of AIDS. UCLA experience and review. Am J Pathol 124:537–558

Arendt G, Hefter H, Elsing C, Neuen-Jacob E, Strohmeyer G, Freund HJ (1989) Neue elektrophysiologische Befunde zur Häufigkeit der Gehirnbeteiligung bei klinisch-neurologisch asymptomatischen HIV-Infizierten. Z EEG-EMG 20:280–287

Arendt G, Hefter H, Figge C, Neuen-Jacob E, Nelles HW, Elsing C, Freund HJ (1991) Two cases of cerebral toxoplasmosis in AIDS-patients mimicking HIV-related dementia. J Neurol 238:439–442

Berger JR, Mastiowik L, Fischl M, Kelley E (1987) The neurological complications of AIDS: frequently the initial manifestation. Neurology 34 (Suppl 1):134–135

Biggemann B, Voit T, Neuen E, Wechsler W, Kramer H, von Kries R, Wahn V (1987) Neurological manifestations in three German children with AIDS. Neuropediatrics 18:99–106

Budka H (1989) Human immunodeficiency virus (HIV)-induced disease of the central nervous system: pathology and implications for pathogenesis. Acta Neuropathol 77:225–236

Budka H (1990) Human immunodeficiency virus (HIV) envelope and core proteins in CNS tissues of patients with the acquired immune deficiency syndrome (AIDS). Acta Neuropathol 79: 611–619

Budka H (1991) Neuropathology of human immunodeficiency virus infection. Brain Pathol 1:163–175

Budka H, Wiley CA, Kleihues P, Artigas J, Asbury AK, Cho ES, Cornblath DR, Dal Canto MC, DeGirolami U, Dickson D, Epstein LG, Esiri MM, Giangaspero F, Goszotonyi G, Gray F, Griffin JW, Hénin D, Iwasaki Y, Janssen RS, Johnson RT, Lantos PL, Lyman WD, McArthur JC, Nagashima K, Peress N, Petito CK, Price RW, Rhodes RH, Rosenblum M, Said G, Scaravilli F, Sharer LR, Vinters HV (1991) HIV-associated disease of the nervous system: review of nomenclature and proposal for neuropathology-based terminology. Brain Pathol 1:143–152

Donovan Post MJ, Hensley GT, Moskowitz LB, Fischl M (1986) Cytomegalic inclusion virus encephalitis in patients with AIDS: CT, clinical and pathologic correlation. Am J Roentgenol 146: 1229–1234

Epstein LG, Sharer LR, Joshi VV, Fojas MM, Koenigsberger MR, Oleske JM (1985) Progressive encephalopathy in children with acquired immune deficiency syndrome. Ann Neurol 17: 488–496

Fischer PA, Enzensberger W (1987) Neurological complications in AIDS. J Neurol 234:269–279

Gabuzda DH, Ho DD, de la Monte SM, Hirsch MS, Rota TR, Sobel RA (1986) Immunohistochemical identification of HTLV-III antigen in brains of patients with AIDS. Ann Neurol 20: 289–295

Gartner S, Markovits P, Markovits DM, Betts RF, Popovic M (1986) Virus isolation from and identification of HTLV-III/LAV-producing cells in brain tissue from a patient with AIDS. JAMA 256:2365–2371

Gill PS, Levine AM, Meyer PR, Boswell WD, Burkes RL, Parker JW, Hofman FM, Dworsky RL, Lukes RJ (1985) Primary central nervous system lymphoma in homosexual men. Clinical, immunologic and pathologic features. Am J Med 78:742–748

Grimaldi LME, Martino GV, Franciotta DM, Brustia R, Castagna A, Pristera R, Lazzarin A (1991) Elevated alpha-tumor necrosis factor levels in spinal fluid from HIV 1-infected patients with central nervous system involvement. Ann Neurol 29:21–25

Gullotta F, Kuchelmeister K (1987) Neuropathologische Befunde bei HIV-Encephalopathie. Verh Dtsch Ges Path 71:505

Gullotta F, Kuchelmeister K, Bergmann M, Schindelmeiser J, Masini T, Cappricci E, Angeli G, Ramponi A (1991) Das ZNS bei AIDS und bei asymptomatischen HIV-Trägern. Verh Dtsch Ges Path 75:183–184

Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JC, Groopman JE, Resnick L, Felsenstein D, Andrews CA, Hirsch MS (1985) Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N Engl J Med 313:1493–1497

Kato T, Hirano A, LLena JF, Dembitzer HM (1987) Neuropathology of acquired immune deficiency syndrome (AIDS) in 53 autopsy cases with particular emphasis on microglial nodules and multinucleated giant cells. Acta Neuropathol (Berlin) 73:287–294

Koenig S, Gendelman HE, Orenstein JM, Dal Canto MC, Pezeshkpour GH, Yungbluth M, Janotta F, Aksamit A, Martin MA, Fauci AS (1986) Detection of AIDS virus in macrophages in brain tissue from patients with encephalopathy. Science 233:1089–1093

Kuchelmeister K, Gullotta F, Bergmann M, Angeli G, Masini T (1991) Die progressive multifokale Leukoencephalopathie (PML) bei AIDS: Morphologische und topographische Besonderheiten. Verh Dtsch Ges Path 75:189–190

Lang W, Miklossy J, Deruaz JP, Pizzolato GP, Schaffner T, Gessaga E, Kleihues P (1989) Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. Acta Neuropathol (Berl) 77:379–390

Lantos PL, McLaughlin JE Scholtz CL, Berry CL, Tighe JR (1989) Neuropathology of the brain in HIV infection. Lancet I:309–311

Laskin OL, Stahl-Bayliss CM, Morgello S (1987) Concomitant Herpes simplex virus type A and Cytomegalovirus ventriculoencephalitis in acquired immunodeficiency syndrome. Arch Neurol 44:843–847

Levy JA, Shimabukuro J, Hollander H, Mills J, Kaminsky L (1985) Isolation of AIDS-associated retroviruses form cerebrospinal fluid and brain of patients with neurological symptoms. Lancet II:586–588

Levy RM, Bredesen DE, Rosenblum ML (1985) Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience and UCSF and review of the literature. J Neurosurg 62:475–495

Moskowitz LB, Gregorius JB, Hensley GT, Berger JR (1984a) Cytomegalovirus induced demyelination associated with acquired immune deficiency syndrome. Arch Pathol Lab Med 108:873–877

Moskowitz LB, Hensley GT, Chan JC, Conley FK, Donovan Post MJ, Gonzales-Arias SM (1984b) Brain biopsies in patients with acquired immune deficiency syndrome. Arch Pathol Lab Med 108:368–371

Navia BA, Petito CK, Gold JWM, Cho EE, Jordan BD, Price RW (1986a) Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neuropathological findings in 27 patients. Ann Neurol 19:224–238

Navia BA, Jordan BD, Price RW (1986b) The AIDS dementia complex: I. Clinical features. Ann Neurol 19:517–524

Navia BA, Cho ES, Petito CK, Price RW (1986c) The AIDS dementia complex: II. Neuropathology. Ann Neurol 19:525–535

Navia BA, Price RW (1987) The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. Arch Neurol 44:65–69

Neuen E, Seitz RJ, Langenbach M, Wechsler W (1987) The leakage of serum proteins across the blood-nerve barrier in hereditary and inflammatory neuropathies. An immunohistochemical and morphometric study. Acta Neuropathol (Berl) 73:53–61

Neuen-Jacob E, Arendt G, Wendtland B, Jacob B, Schneeweis M, Wechsler W (1992) Frequency and topographical distribution of CD68-positive macrophages and HIV-1 core proteins in HIV-associated brain lesions. Clin Neuropathol, submitted

Petito CK, Cho ES, Lemann W, Navia BA, Price RW (1986) Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. J Neuropathol Exp Neurol 45:635–646

Price RW, Brew B, Sidtis J, Rosenblum M, Scheck AC, Cleary P (1988) The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. Science 239:586–592

Price RW, Sidtis JJ, Brew BJ (1991) AIDS dementia complex and HIV-1 infection: a view from the clinic. Brain Pathol 1:155–162

Püschel K, Tenner-Racz K, Racz P, Dietrich M, Kern P, Schmitz H, Lieske K (1985) AIDS-Todesfälle in Hamburg (Stand: Februar 1985) – Rechtmedizinische Aspekte. Z Rechtsmed 95: 113–121

Püschel K, Lieske K, Hashimoto Y, Karch H, Laufs R, Racz P, Janssen W (1987) HIV-Infection in forensic autopsy cases. Forensic Sci Int 34:169–174

Pumarola-Sune T, Navia BA, Cordon-Cardo C, Cho ES, Price RW (1987) HIV antigen in the brains of patients with the AIDS dementia complex. Am Neurol 21:490–496

Schindelmeiser J, Gullotta F (1991) HIV-p24-antigen-bearing macrophages are only present in brains of HIV-seropositive patients with AIDS-encephalopathy. Clin Neuropathol 10:109–111

Schmitt-Gräff A, Neuen-Jacob E, Rettig B, Sundmacher R (1990) Evidence for cytomegalovirus and human immunodeficiency virus infection of the retina in AIDS. Virchows Arch A 416: 249–253

Sharer LR, Kapila R (1985) Neuropathologie observations in acquired immunodeficiency syndrome (AIDS). Acta Neuropathol (Berl) 66:188–198

Shaw GM, Harper ME, Hahn BH, Epstein LG, Gajdusek DC, Price RW, Navia BA, Petito CK, O'Hara CJ, Groopman JE, Cho ES, Oleske JM, Wong-Staal F, Gallo RC (1985) HTLV-III infection in brains of children and adults with AIDS encephalopathy. Science 227:177–181

Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB (19834) Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol 14:403–418

So YT, Beckstead JH, Davis RL (1986) Primary central nervous system lymphoma in acquired immune deficiency syndrome: a clinical and pathological study. Ann Neurol 20:566–572

Stoler MH, Eskin TA, Benn S, Angerer RC, Angerer LM (1986) Human T-cell lymphotropic virus type III infection of the central nervous system. A preliminary in situ analysis. JAMA 256:2360–2364

Vazeux R, Brousse N, Jarry A, Henin D, Marche C, Vedrenne C, Mikol J, Wolff M, Michon C, Rozenbaum W, Bureau JF, Montagnier L, Brahic M (1987) AIDS subacute encephalitis. Identification of HIV-infected cells. Am J Pathol 126:403–410

Vazeux R, Cumont M, Girard PM, Nassif X, Trotot P, Marche C, Matthiesen L, Vedrenne C, Mikol J, Henin D, Katlama C, Bolgert F, Montagnier L (1990) Severe encephalitis resulting from coinfections with HIV and JC virus. Neurology 40:944–948

Woods GL, Goldsmith JC (1990) Aspergillus infection of the central nervous system in patients with acquired immunodeficiency syndrome. Arch Neurol 47:181–184