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The Central Nervous System in AIDS

Neurology · Radiology · Pathology · Ophthalmology

With a Foreword by M. L'age

With 128 Figures and 25 Tables

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Foreword

The epidemic of AIDS is now entering its second decade. Looking back upon the progress that medical science has made thus far, both the significance and the limitations of basic and clinical research become apparent.

The discovery of the human immunodeficiency virus (HIV) has initiated fascinating research in retrovirology, molecular biology, and immunology, resulting in a dramatic increase in our knowledge of the pathomechanisms of cellular HIV infection. However, our understanding of how the cellular infection leads to destruction of the immunological network, ending in the acquired immune deficiency syndrome (AIDS), remains to be elaborated. The development of antiretroviral agents, dideoxy nucleosides, tetrahydroimidazobenzodiazepinone (TIBO), and other benzodiazepene-related reverse transcriptase inhibitors, protease inhibitors, and others is promising, but their clinical use so far clearly shows that we are far from curing HIV infection. At best we can expect a slowing down in the progression of immunodeficiency, frequently at the expense of toxic side effects. The development and administration of vaccines and immunnomodulating agents are still in the phase of clinical experimentation.

A decade of medical confrontation with the clinical picture of HIV infection and AIDS has clarified some aspects of the course of the disease from HIV infection to AIDS and its puzzling clinical manifestation. Clinicians have become specialized, and there has been close interdisciplinary cooperation among immunologists, gastroenterologists, pulmonologists, oncologists, neurologists, dermatologists, ophthalmologists, surgeons, radiologists, pathologists, and microbiologists. Their research on AIDS-related diseases has been directed at developing fast and safe strategies for the prophylaxis, diagnosis, and therapy of these diseases.

Remarkable success has been achieved in lengthening the life expectancy of persons diagnosed as having AIDS: from 3–6 months in 1985 to 18–24 months in 1991. The spectrum of pulmonary and gastrointestinal diseases in AIDS is well described. Several therapeutic protocols for bacterial, viral, protozoal, or fungal infections of the lung and gastrointestinal tract are now established. The introduction of aerosolized pentamidine as primary prophylaxis of *Pneumocystis carinii* pneumonia (PCP) has reduced the incidence of PCP in Berlin by half since 1989. The mortality rate of acute PCP has declined from 20 % in 1985 to less than 5 % in 1991 in clinical AIDS centers. One of the unsolved problems is the treatment of disseminated pulmonary Kaposi's sarcomatosis.

However, the therapeutic and preventive strategies available for gastrointestinal manifestations of AIDS to date are far from perfect. Although several acute opportunistic infections are treatable, there is no cure for cryptosporidiosis or microsporidiosis. The maintenance therapy in cytomegalovirus infection of the gastrointestinal tract (and retina) remains one of the major clinical problems due to the chronic intoxication and decreasing effectiveness of long-term antiviral chemotherapy. Pathogenesis of the diarrhea wasting syndrome is unsolved and a topic of intensive research, but an effective treatment is not in sight.

Of particular relevance to the clinician is the changing clinical picture of AIDS, noticed in several AIDS centers, due probably to antiviral therapy for HIV infection and prophylaxis of AIDS-related opportunistic infections. Deficiencies in the management of multiple infections and tumors have become obvious.

This book deals with one of the most complex issues in AIDS, the affection of the CNS in the progression

of HIV infection. Various pathogens, including HIV, opportunistic infectious agents, cytokines, and antiretroviral and antimicrobial agents can result in a slow but progressive destruction of CNS morphology and function, confronting the clinician with new neurological syndromes and frequently leaving him rather helpless with respect to diagnosis and treatment.

The goal of the editors and authors is to provide appropriate bridges between basic and clinical medicine by incorporating the latest advances in pathology and diagnosis into their contributions.

The explosive spread of HIV infection to global dimensions urgently requires intensification of international cooperation in basic and clinical research as well as its financial and political support by governments.

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Chapter 1

Clinical Neurology in AIDS

P. Portegies

■ Introduction

In patients with HIV-1 infection, the nervous system is commonly affected (Snider et al. 1983; Levy et al. 1985 a; McArthur 1987; De Gans et al. 1989). Neurological involvement occurs in at least 40 % of patients, who usually already meet the CDC clinical criteria for AIDS (Centers for Disease Control 1987), and it is the presenting manifestation in 10 % of HIV-infected patients. At autopsy, 80 %–90 % are found to have neuropathological abnormalities (Anders et al. 1986). Each part of the neuraxis may be involved. Although this spectrum of neurological complications is well known and includes opportunistic infections, neoplasms, and complications caused by or related to HIV-1 itself, newly recognized clinical syndromes or atypical courses of neurological diseases in HIV-1 infected are still being reported. Some of the neurological complications occur in the early and clinically latent phases of the infection, and others are associated with advanced HIV-1 infection. Examples of these include the following:

1. Early complications
   a) Acute syndromes associated with initial infection
   b) Multiple sclerosis-like illness
   c) Aseptic meningitis and HIV-1 related headache
   d) Demyelinating neuropathies
2. Late complications
   a) AIDS dementia complex
   b) Vacuolar myelopathy
   c) Peripheral neuropathy
   d) Myopathies
   e) Cerebrovascular complications
   f) Seizures
   g) Opportunistic infections and neoplasms
      Cerebral toxoplasmosis
      Cryptococcal meningitis
      Progressive multifocal leukoencephalopathy
      Cytomegalovirus infections
      Syphilis
      Primary CNS lymphoma
      Meningitis lymphomatosa

From a clinical point of view (for instance, in differential diagnosis) it is therefore reasonable and useful to correlate the neurological complications to the level of immune compromise (CD4 cell count). Furthermore it is important to appreciate that very often different neurological complications may occur in a single patient. Thus, complications may develop addi-

Table 1.1 Incidences of neurological complications in AIDS

Cerebral toxoplasmosis	10%–20%
Cryptococcal meningitis	5%–10%
PML	2%–5%
CMV polyradiculomyelopathy	2%(?)
CMV encephalitis	<1%(?)
Primary CNS lymphoma	2%–13%
Meningitis lymphomatosa	0.5%–3%
Aseptic meningitis	<5%(?)
AIDS dementia complex[a]	5%–33%
Vacuolar myelopathy	20%–25%
Polyneuropathy	10%–35%
Myopathy	<10%(?)

[a] The incidence of ADC has declined since the introduction of zidovudine.

Table 1.2 Histopathology of Focal Brain Lesions in AIDS

Before empirical toxotherapy (1986; n=443; De La Paz and Enzmann 1988)		After empirical toxotherapy (1991; n=50; Levy et al. 1991)	
Toxoplasmosis	50%–70%	Toxoplasmosis	28%
Lymphoma	10%–25%	Lymphoma	28%
PML	10%–22%	PML	28%
Nondiagnostic	10%	Nondiagnostic	8%
Candida abscess	3%	HIV encephalopathy	6%
Cryptococcoma	2%	Cryptococcoma	2%
Kaposi's sarcoma	2%	Atypical mycobacteria	2%
Tuberculoma	1%	Stroke	2%
Herpes simplex	1%	Metastasis	4%

tional to those previously diagnosed, and several neurological problems may even occur simultaneously.

The incidence of the most important neurological complications in patients with AIDS as reported in the literature are given in Table 1.1 (Snider et al. 1983; Levy et al. 1985a; McArthur 1987; De Gans et al. 1989). The problems in neuro-AIDS are numerous and complicated. Many questions are still unanswered, and new problems are emerging. Clinicians dealing with the neurological problems of HIV-1 infection should always remain alert and flexible. This chapter reviews what is currently known in this area.

■ Opportunistic Infections

Cerebral Toxoplasmosis

Infection with the intracellular protozoon *Toxoplasma gondii* has a worldwide distribution, is most often subclinical, and results in seropositivity and chronic, latent infection in immunocompetent individuals (McGabe et al. 1990; Luft et al. 1985). However, it may present with lymphadenopathy or mononucleosis like illness in otherwise healthy adults. Intracranial mass lesions or diffuse meningoencephalitis occur sporadically. *Toxoplasma* cysts remain present in all tissues during latent infection. The seroprevalence in adults varies geographically and depends on certain risk factors, such as eating habits. Cerebral toxoplasmosis is the leading cause of focal brain disease in AIDS patients (Table 1.2) and has a prevalence of 3%–40%, depending on the seroprevalence. Cerebral toxoplasmosis is the presenting opportunistic infection in at least 5% of the AIDS patient population (Pons et al. 1988).

Clinically, patients with cerebral toxoplasmosis present with constitutional symptoms, headache, and fever, followed by focal neurological abnormalities, including focal seizures, aphasia, hemiparesis, and homonymous hemianopsia, depending on the localization of the lesions (Navia et al. 1986a). This combination of focal abnormalities and signs of a global encephalopathy is very suggestive. Brain imaging is very important in establishing the diagnosis. Computed tomography (CT) normally reveals multiple hypodense areas, usually with mass effect, and contrast enhancement (ring pattern or irregular nodular) (Levy et al. 1986). Magnetic resonance imaging (MRI) is more sensitive in detecting lesions. Serology is only occasionally diagnostic at the time that CNS toxoplasmosis develops; IgM antibodies are rarely demonstrable, and a fourfold rise in a preexisting low IgG antibody titer or a high IgG antibody titer (>1:512 in the Sabin-Feldman dye test), consistent with recrudescent infection, is usually absent. Likewise, antibody tests in CSF are rarely diagnostic and are even negative in many patients. Even negative serology tests in CNS toxoplasmosis have been described.

In AIDS patients with suspected cerebral toxoplasmosis, based on clinical findings and CT scan abnormalities, empirical treatment is justifiable, reserving brain biopsy for atypical or refractory cases. The most effective therapy is a combination of pyrimethamine (50 mg daily) and sulfadiazine (6–8 g daily; Luft and Remington 1987; Leport et al. 1988). Oral folinic acid is given to prevent hematological side effects. A considerable number of patients develop a rash due to the sulfadiazine. In these cases clindamycin may represent an alternative therapy. A recent multicenter Eu-

ropean trial has established that these regimens are equally effective (Katlama et al. 1991). Six weeks induction treatment must be followed by lifelong maintenance therapy. For this secondary prophylaxis against toxoplasmosis the pyrimethamine/sulfadiazine combination is effective, but the value of pyrimethamine alone at a daily dose of 50 mg is controversial. Also of note in the therapy of toxoplasmosis is that several newer agents (566C80 and azithromycin) seem effective, according to initial data. Corticosteroids may be used for lesions associated with edema and mass effect.

Cryptococcal Meningitis

Cryptococcal meningitis is the most common mycotic infection involving the nervous system in patients with HIV infection. The fungus *Cryptococcus neoformans* has a worldwide distribution, is commonly encountered in the feces of pigeons, and is associated with disease in both immunocompetent and immunosuppressed patients (Pons et al. 1988). Meningitis results from hematogenous dissemination after a frequently asymptomatic pulmonary infection. The prevalence of this life-threatening opportunistic infection among AIDS patients is 2 %–7.5 % (Pons et al. 1988; Dismukes 1988). Clinically the disease manifests as subacute or chronic meningitis with headache, altered mentation, and fever. Headache may become severe, with nausea and vomiting. Neck stiffness is frequently absent. Papilledema (with occasionally visual loss) and sixth-nerve palsy may be present (Dismukes 1988; Chuck and Sande 1989).

The diagnosis is based on CSF analysis: variable mononuclear pleocytosis, with mildly elevated protein and low glucose level. However, these CSF parameters may all be normal in patients with AIDS. CSF opening pressure is usually increased. The fungus can easily be recognized in india-ink preparation. Cryptococcal polysaccharide capsular antigen is nearly always positive in the CSF and serum, as are fungal cultures of CSF. Brain CT scan is usually normal or shows nonspecific abnormalities; occasionally mass lesions (e. g., cryptococcoma) are present.

Standard therapy with amphotericin B with intravenously (0.3 mg/kg daily) with or without oral flucytosine (150 mg/kg daily) is effective in about 60 % of cases (Chuck and Sande 1989; Sugar et al. 1990). Newer agents, such as the oral triazoles fluconazole and itraconazole, appear to be attractive alternatives to amphotericin, and studies are underway (Denning et al. 1989). Although there is some evidence suggesting that amphotericin B in combination with flucytosine has superior mycological and clinical efficacy compared to fluconazole in the acute treatment of cryptococcal meningitis, the issue remains controversial (Larsen et al. 1990). Because relapse is so common in AIDS patients, maintenance treatment (after 6–8 weeks of induction) is recommended. Fluconazole (100–200 mg daily) is highly effective in preventing relapses (Bozette et al. 1991).

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection which is estimated to occur in up to 4 % of patients with AIDS (Berger et al. 1987). PML is a subacute demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and probably astrocytes by a papova virus, usually the polyomavirus JC (Ästrom et al. 1958; Richardson 1961).

The onset is insidious, with symptoms and signs suggesting multifocal disease. Hemiparesis is the most common presenting symptom. Headache and seizures are rare, and signs of elevated intracranial pressure are characteristically absent. The disease usually evolves relentlessly until the patient dies. The CSF shows no specific abnormalities. Cranial MRI reveals single or multiple areas of high signal intensity on long TR/TE images, which are predominantly localized in the white matter and usually non enhancing after administration of contrast (Olsen et al. 1988; Ramsay and Geremia 1988). Mass effect and gray matter involvement have been described but are uncommon (Mark and Atlas 1989). The lesions are not confined to a vascular territory and are less diffusely distributed than MRI abnormalities in AIDS dementia complex (Balakrishnan et al. 1990). Pathological abnormalities include demyelination, enlarged oligodendrocytes with intranuclear inclusion bodies and bizarre, enlarged astrocytes (Ästrom et al. 1958; Richardson 1961). The papova particles can be seen in the intranuclear inclusions of the oligodendrocytes (Zu Rhein and Chou 1965).

Although occasionally prolonged survival and spontaneous partial recovery in AIDS-associated PML have been described (Berger and Mucke 1988), the prognosis in these patients is generally poor, and the average life expectancy from disease onset is less than 1 year. An effective treatment for PML in patients with AIDS has not been identified, but there

have been several anecdotal reports of the efficacy of cytosine arabinoside given intrathecally (Britton et al. 1991) or intravenously (Portegies et al. 1991). Larger studies are underway.

Cytomegalovirus-Infections

Cytomegalovirus (CMV) has been associated with three neurological syndromes: CMV encephalitis, CMV polyradiculomyelopathy, and CMV multifocal neuropathy. These syndromes usually occur when the CD4 cell count is very low (Said et al. 1991). CMV multifocal neuropathy is discussed below (see "Peripheral Neuropathies").

CMV Encephalitis

The clinical features of CMV encephalitis are not clear. Characteristics include subacute neurological deterioration – sometimes clinically indistinguishable from AIDS dementia complex (ADC) or PML – with or without focal abnormalities, with fever and seizures. CT scan may reveal subependymal enhancement compatible with ventriculitis. Sometimes the virus can be isolated from the CSF, but the specificity of isolation of CMV is currently unknown. Often the identification of CMV is based on typical intranuclear inclusions or identification of CMV antigen by immunocytochemistry, or both at postmortem neuropathological examination. The relative importance of CMV infection in many cases is unclear, and CMV often coexists with other infectious agents. Data on treatment are not available yet.

CMV Polyradiculomyelopathy

CMV polyradiculomyelopathy or polyradiculitis has been recognized increasingly in patients with AIDS (Eidelberg et al. 1986). Patients present with lower extremity and sacral paresthesias or pain, followed by a rapidly progressive flaccid paraparesis, with areflexia and sphincter disturbances. Sensory disturbances are usually mild. The CSF generally reveals a pleocytosis with predominance of polymorphonuclear leukocytes (De Gans et al. 1990 a). CMV has been detected in the CSF by several techniques, including culture, immunocytochemistry, in situ hybridization, and the detection of cytomegalic cells by cytological examination. Myelographic examination may show thickened adherent lumbar nerve roots (Borgstein et al. 1989). At autopsy, spinal roots have revealed extensive multifocal necrosis, acute inflammatory infiltrates, and vasculitis. Typical CMV inclusions are seen within endoneural inflammatory cells, Schwann's cells, and endothelial cells (Miller et al. 1990).

Treatment with ganciclovir (dihydroxypropoxymethylguanine), started early in the course of the disease, may stop progression or even cause some improvement (Miller et al. 1990; De Gans et al. 1990 b). The recommended regimen with ganciclovir is 5 mg/kg intravenously every 12 h. for 2–3 weeks, followed by maintenance therapy, 5 mg/kg per day, 5 days per week.

Other Opportunistic Infections

Neurosyphilis

The diagnosis of neurosyphilis in HIV-1 infected patients may be exceptionally difficult (Davis 1990; Hook 1989). Several factors account for this. First, in 40 %–60 % of HIV-1 infected patients the CSF shows pleocytosis, elevated protein, elevated immunoglobulin G synthesis rate, and oligoclonal bands, making it impossible to use these CSF findings as an indicator of active neurosyphilis (Marshall et al. 1988). Second, the signs and symptoms of the clinical syndromes caused by HIV-1 infection (strokes, myelopathy, dementia), can also occur in neurosyphilis (Davis 1990; Hook 1989; Katz and Berger 1989). Third, the CSF serological tests for neurosyphilis (Venereal Disease Research Laboratory; fluorescent treponemal antibody absorption) may be negative in HIV-1 infected individuals with *T. pallidum* in the CSF (Hicks et al. 1987; Feraru et al. 1990). Furthermore, *T. pallidum* in the CNS may be more aggressive in HIV-1 infected individuals, and the complications may be atypical (Johns et al. 1987). In addition to meningovascular syphilis, a polyradiculopathy has also been described (Lanska et al. 1988). Patients who presented with meningovascular syphilis after adequate treatment for primary syphilis (Johns et al. 1987), and neurological relapse after adequate treatment for secondary syphilis have been described (Berry et al. 1987).

Unsuspected neurosyphilis is relatively common in HIV-1- infected individuals (Berger 1991), and neurosyphilis should always be considered in the differential diagnosis of neurological disease in HIV-infected persons. CSF examination should be performed in all HIV-1 seropositive persons with neurological com-

plaints and a history of syphilis or serological evidence of syphilis, regardless of prior treatment. If neurosyphilis is suspected, patients should be treated for at least 10 days with aqueous penicillin G, 2–4 x 10^6 U intravenously every 4 h (12–24 x 10^6 U each day; Centers for Disease Control 1988).

Listeriosis

Listeria is a gram-positive, rod-shaped, aerobic bacterium that is widespread in nature. Although infection with *Listeria monocytogenes* (usually meningitis, sometimes brain abscess) has been reported in HIV-1 infected individuals and patients with AIDS, the incidence remains low (Mascola et al. 1988). Diagnosis of *Listeria* meningitis and treatment with high-dose intravenous penicillin or ampicillin is the same in AIDS patients and in immunocompetent individuals.

Tuberculosis

Disseminated mycobacterial infections occur frequently in patients with AIDS. CNS complications are uncommon and may be caused both by *Mycobacterium tuberculosis* and by *M. avium intracellulare.* Meningitis and mass lesions (tuberculous brain abscess, tuberculoma) due to *M. tuberculosis* have been described (Bishburg et al. 1986). In case of a mass lesion brain biopsy is necessary to confirm the diagnosis. The established treatment for CNS tuberculosis is an antibiotic regimen consisting of isoniazide, rifampin, pyrazinamide, and streptomycin. The use of steroids is controversial. *M. avium intracellulare* infection of the CNS is very rare.

Aspergillosis

Almost all cases of invasive aspergillosis are caused by the fungus *Aspergillus fumigatus.* CNS *Aspergillus* infections are uncommon. Meningitis, meningoencephalitis, brain abscess, and granuloma have been described. The diagnosis is usually made by demonstration and culture of the fungus from biopsy material. Brain abscess and meningitis have been described in patients with AIDS (Koppel et al. 1985). Surgical excision and amphotericin B are recommended.

Candidiasis

Candida infections, usually oral candidiasis or esophagitis, occur frequently in AIDS patients. CNS infections are rare. Only a few patients with AIDS and CNS *Candida* (micro) abscesses have been described (Levy et al. 1983). Diagnosis was made by culture of tissue obtained by brain biopsy. Amphotericin B and surgical excision in the case of a large abscess are recommended.

Herpes Simplex Virus Infection

Herpes simplex virus (HSV) encephalitis and myelitis have rarely been reported in patients with HIV-1 infection. The clinical presentation of HSV encephalitis, with fever, seizures, and focal neurological abnormalities is similar in immunocompetent and HIV-1 infected individuals (Dix et al. 1985). However, chronic HSV encephalitis may occur in patients with AIDS. Acyclovir administered intravenously is the treatment of choice.

Varicella-Zoster Virus Infection

Although cutaneous zoster occurs frequently in HIV-1 infected individuals, neurological complications of infection with varicella-zoster virus (VZV) have infrequently been reported in patients with AIDS. VZV-associated neurological complications include encephalitis, cerebral angiitis, multiple cranial neuropathies, and radiculomyelitis (Dix et al. 1988). Usually these syndromes are related to cutaneous zoster in time of occurrence. VZV has been cultured from the CSF in some cases. Treatment with acyclovir is recommended, but relapses occur frequently after discontinuation of therapy.

■ Neoplasms of the Nervous System

Primary CNS Lymphoma

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin lymphoma arising within and confined to the nervous system. The incidence of PCNSL has increased rapidly over the past 10 years. Of HIV-1 infected patients 0.6% present with PCNSL, and 2%–13% of AIDS patients can be expected to devel-

op PCNSL (Levy et al. 1985 a; Rosenblum et al. 1988). PCNSL is the second most frequent CNS mass lesion in adults with AIDS and the most frequent in children with AIDS (De La Paz et al. 1988).

Clinically, most of the patients present with lethargy, confusion, memory loss, and personality change (So et al. 1986). The remaining patients present with hemiparesis, dysphasia, seizures, and cranial nerve deficits (Baumgartner et al. 1990). The CT appearance of PCNSL in AIDS patients is generally described as an enhanced mass or multiple masses exhibiting diffuse or ring enhancement with a predilection for the corpus callosum, basal ganglia, and periventricular areas. However, toxoplasmosis may also appear as solitary of multiple, ring- or nodular-enhancing masses. It is therefore generally accepted that PCNSL is indistinguishable from toxoplasmosis (Dina 1991). In the majority of PCNSL cases multiple lesions can be seen on MRI/CT (Cincillo et al. 1990). However, among solitary lesions on MRI there is a predominance of lymphoma. Thus, a solitary mass on MRI should be observed more closely, during empirical treatment with antitoxoplasmosis therapy. This is especially true if the mass is hypointense on T2-weighted images.

CSF examination is recommended, if not contraindicated because of mass effect of the tumor. Positive cytology is found in 25 % of patients with PCNSL, and this can eliminate the need for diagnostic biopsy. At autopsy, 100 % of patients have leptomeningeal seeding. Histological confirmation remains essential, and this should preferably be done by stereotactic biopsy (Baumgartner et al. 1990). Corticosteroid administration can produce shrinkage of the tumor seen on CT/MRI, due to lysis of tumor cells, but this necrosis in the tumor makes it more difficult to establish the diagnosis. Therefore when the diagnosis of PCNSL is being considered corticosteroids should be withheld. Histologically the majority of PCNSLs are large cell tumors of B-cell origin and of high malignancy.

Radiotherapy is the treatment of choice. Patients with PCNSL may respond both clinically and radiologically to whole-brain radiotherapy (4000 cGy) (Baumgartner et al. 1990). If possible, a boost of 1500 cGy to the tumor bed can be added. With radiotherapy median survival can be prolonged to 4–5 months (Baumgartner et al. 1990). Leptomeningeal lymphoma should be treated with intrathecal chemotherapy: methotrexate or cytosine arabinoside, using an Ommaya reservoir. Systemic chemotherapy is usually withheld in AIDS patients.

Meningitis Lymphomatosa

Of AIDS patients with systemic non-Hodgkin's lymphoma (usually high-grade B-cell neoplasms) 12 %–33 % have leptomeningeal infiltration with a positive CSF cytological examination at diagnosis (Kaplan et al. 1989). Because of this high incidence all AIDS patients with systemic lymphoma should receive CSF examination as part of their staging evaluation. Leptomeningeal lymphoma causes headache, encephalopathy, cranial nerve palsies, radicular pain, cauda equina syndrome, or hydrocephalus. Cytological examination is the single most useful test for leptomeningeal lymphoma. Sometimes subarachnoid nodules or thickened roots can be seen on myelography.

Intrathecal chemotherapy with methotrexate (or cytosine arabinoside) is the primary treatment. An Ommaya reservoir should be inserted. Radiotherapy can be added to the symptomatic region.

Intracerebral Kaposi's Sarcoma

Only a few cases of Kaposi's sarcoma metastatic to the brain have been reported (Levy et al. 1985 b). On neuropathological examination these intracerebral Kaposi's sarcomas were necrotic and hemorrhagic. Most patients have been diagnosed at autopsy. Data on treatment are not available.

■ HIV-Related Syndromes

Primary HIV Infection and Aseptic Meningitis

Primary HIV Infection

Shortly after the mononucleosislike illness that is associated with initial infection by HIV-1 (Tindall and Cooper 1991), patients may develop a variety of neurological disorders. These may occur from days to weeks after the seroconversion and evolve acutely or subacutely. Aseptic meningoencephalitis, myelopathy, peripheral neuropathy, brachial neuritis, facial palsy, and Guillain-Barré syndrome have all been described (Brew et al. 1989 a). Headaches, retro-orbital pain, and photophobia are frequent during primary HIV infection.

CSF often reveals a mononuclear pleocytosis and raised protein. HIV has been isolated from the CSF, and HIV p24 antigen has been detected during primary HIV infection. Elevated neopterin and beta-2-microglobulin levels have been detected in the CSF, in patients with and without clinical meningitis, suggesting that the cellular immune system in the CNS is activated during primary HIV infection. The CT scan of the brain is normal, but the electroencephalogram may show focal or diffuse slowing. The neurological manifestations of the primary HIV infection are self-limited, and most patients recover within a few weeks.

Aseptic Meningitis

An aseptic meningitis may occur at the time of seroconversion and in later stages of HIV-1 infection while the patient is systemically well (Hollander and Stringari 1987). This aseptic meningitis has been divided into acute and chronic forms. Patients present with headache, fever, and meningeal signs. Cranial neuropathies – especially V, VII, and VIII and long tract involvement – have been noted (Hollander and Stringari 1987). Bell's palsy sometimes recurs. The CSF shows a mild mononuclear pleocytosis, with slightly elevated protein levels. The meningitis is presumed to result from direct HIV-1 infection of the meninges because HIV-1 can be readily isolated from the CSF. Most cases have a self-limited monophasic course, but the syndrome tends to recur.

Some HIV-1 infected patients have acute or chronic, relapsing headaches without a raised CSF cell count. This headache has recently been termed HIV-1 related headache (Brew and Miller 1991). It is suggested that this condition is either analogous to or identical with HIV-related aseptic meningitis. The lack of a CSF pleocytosis in such patients may simply reflect the advanced state of immunosuppression. Low doses of amitriptyline are effective in these headaches.

CSF Abnormalities in Asymptomatics

It is important to appreciate that a mild mononuclear pleocytosis (usually less than 100 mononuclear cells) with or without elevated protein is common and well-known in HIV-1 infected individuals (Marshall et al. 1988). It has become increasingly clear that these "background" CSF abnormalities may be confusing in establishing a diagnosis of neurosyphilis, aseptic meningitis, or inflammatory neuropathies.

AIDS Dementia Complex

One of the most important neurological syndromes in patients with AIDS is ADC, or HIV-1 encephalopathy (Navia et al. 1986b,c; Price et al. 1988). Other terms used include AIDS encephalopathy and subacute encephalitis. The term HIV-1 encephalitis should be reserved for a subgroup of ADC which is associated with productive HIV-1 infection of the brain.

The dementia is characterized by disturbances in cognition, motor performance, and behavior (Navia et al. 1986b). Patients complain of decreased concentration, forgetfulness, and slowing of thought. Tasks take more time to complete and must be well planned in advance. Patients become apathetic and lose interest in everything. As a consequence they may become socially withdrawn, which is often mistaken for depression. Motor symptoms include clumsiness, tremor, poor balance, unsteadiness of gait, and slowing of rapidly alternating movements. Organic psychosis may develop in some patients. Cortical symptoms such as aphasia, alexia, and agraphia are lacking. The Mini-Mental State Examination is often normal although responses are delayed. Saccadic and pursuit eye movements are often slowed and inaccurate. Fine finger movements are slowed, snout response is common, and deep tendon reflexes are brisk. With time, increasing psychomotor slowing may progress to severe dementia with akinetic mutism, paraparesis, and incontinence. The clinical and neuropsychological abnormalities in ADC are compatible with what has been called subcortical dementia (Albert et al. 1974). In order to stage ADC the following scheme has been developed that stratifies patients from 0 to 4 (Price and Brew 1988):

Stage 0 (normal): Normal mental and motor function.

Stage 0.5 (subclinical: Minimal or equivocal symptoms without impairment of work or activities of daily living (ADL). "Background" neurological signs such as slowed fine finger movements, primitive reflexes, etc. may be present.

Stage 1 (mild): Cognitive and/or motor deficit that compromises the performance of the more demanding aspects of work or ADL. Patients can walk without assistance.

Stage 2 (moderate): Cognitive deficit makes the patient unable to perform work or the more demanding aspects of ADL. The patient may require a single prop for ambulation.

Stage 3 (severe): Cognitive deficit makes it possible

for the patient to perform only the rudimentary tasks. The patient cannot follow news or sustain a conversation of any complexity. The patient requires a walker or personal support for ambulation.

Stage 4 (end-stage): Cognitive deficit has reached the point where the patient has virtually no understanding of surroundings and is virtually mute. The patient is paraparetic or paraplegic, often with double incontinence.

The epidemiology and course of ADC have not yet been precisely defined, and these have been influenced by the introduction of zidovudine (Portegies et al. 1989a). However, recent prevalence studies suggest that still one third of patients with AIDS eventually develop a mild or severe form of ADC (Perdices et al. 1991). The question of whether neuropsychological dysfunction starts in the early phases of HIV-1 infection remains controversial. Several groups have documented impaired neuropsychological test performance in the absence of any symptoms in small groups of HIV-1 infected individuals (Grant et al. 1987; Wilkie et al. 1990), while other larger studies have not shown any deficit (McArthur et al. 1989; Selnes et al. 1990). At the present time there is no definite evidence for functionally significant neuropsychological impairment in asymptomatic HIV-1 infected individuals. Furthermore, in patients who develop ADC, there is no protracted decline in neuropsychological performance but rather a precipitous change first affecting psychomotor speed (Selnes et al. 1991). This finding further strengthens existing data that asymptomatic patients do not have gradually increasing neuropsychological dysfunction, and it points away from a cumulative process affecting the brain over a long period of time as the cause of ADC and suggests that it is an acute or subacute process. ADC is thus a late complication in HIV infection and characteristically appears after the development of the major opportunistic infections or neoplasms that define systemic AIDS, although it sometimes occurs before major systemic complications (Navia and Price 1987).

Diagnostic studies are important to exclude treatable infections and tumors. CT and MRI show cortical atrophy, enlargement of ventricles, or both in most patients (Navia et al. 1986b). MRI may reveal patchy of diffuse, increased signal intensity on T2-weighted images, usually in the periventricular white matter and centrum semiovale, without mass effect. However, these neuroradiological abnormalities may occur in patients who are not demented (Jarvik et al. 1988). CSF analysis may reveal mononuclear pleocytosis and increased protein level. HIV-1 antibodies may be found, and HIV-1 itself is cultured from approximately 30% of patients with ADC. HIV-1 p24 core protein in CSF, which is independent of HIV-1 antigen in serum, is detectable in 50% of patients with ADC (Portegies et al. 1989b). In addition to these CSF markers, several immunological markers support a diagnosis of ADC when other causes have been excluded. These include beta-2-microglobulin, neopterin, and quinolinic acid (Brew et al. 1989b, 1990; Heyes et al. 1991). Beta-2-microglobulin and neopterin are markers of immune activation; quinolinic acid is a metabolic product of macrophage activation.

The principal histopathological abnormalities are most prominent in the subcortical structures, notably in the central white matter, basal ganglia, thalamus, brain stem, and spinal cord. The most common of these abnormalities is diffuse pallor of the while matter, which is usually accompanied by astrocytic reaction, perivascular lymphocytes, and brown-pigmented macrophages. Multinucleated cells are found in a subgroup of patients with more severe clinical disease. In these patients the reactive infiltrates are more prominent with foamy macrophages, microglia, and lymphocytes. Recently, substantial neuronal loss in sections of frontal cortex has been demonstrated in HIV-1 infected patients with and without ADC, using newer quantitative methodology (Everall et al. 1991). It is therefore possible that this may play a causal role in the pathogenesis of ADC although it is important to note that there was neuronal loss in patients regardless of the presence of ADC. Consequently, the finding may play only a secondary role.

Zidovudine remains the best substantiated treatment for ADC. Zidovudine crosses the blood-brain barrier well, and treatment was found to be associated with decreasing HIV-1 antigen levels in serum and CSF (De Gans et al. 1988). Beneficial effects of zidovudine in patients with ADC have been described (Schmitt et al. 1988), and since the introduction of zidovudine the incidence of ADC has declined (Portegies et al. 1989a). In those series high doses of zidovudine (1000–1200 mg daily) have been used, and whether low-dose zidovudine (500–600 mg daily) has similar therapeutic and preventive effects is unknown. Preliminary data on dideoxyinosine (ddI) also suggest that it is effective in improving the neuropsychological deficits found in HIV-1 infected children (Butler et al. 1991), but its efficacy in adults is controversial (Yarchon et al. 1989). The utility of dideoxycytidine, (ddC) in ADC is unknown.

Vacuolar Myelopathy

A vacuolar myelopathy has been reported in 20%–25% of AIDS cases. The syndrome is often associated with ADC, but it may occur in isolation. Clinically the syndrome is characterized by a slowly progressive spastic paraparesis and sensory ataxia, sometimes with urinary incontinence. Pathological changes are most prominent in the thoracic cord and closely mimic the pathology of subacute combined degeneration of the spinal cord (Petito et al. 1985). There is degeneration of the posterior and lateral columns of the spinal cord. The vacuolation appears to result from swelling within the layers of the myelin sheaths. The pathogenesis is poorly understood. The myelopathy is probably not the result of productive HIV-1 infection (Rosenblum et al. 1989). Zidovudine seems to have little efficacy although controlled clinical trials are lacking.

Peripheral Neuropathies

Several peripheral neuropathies are associated with HIV-1 infection (Simpson and Wolfe 1991). These include distal symmetrical polyneuropathy or HIV-1 associated predominantly sensory polyneuropathy (HPSP), inflammatory demyelinating polyneuropathies, mononeuropathy multiplex (MM) autonomic neuropathy, CMV polyradiculomyelopathy, and toxic polyneuropathies (associated with ddI and ddC). CMV polyradiculomyelopathy is discussed above (see "Cytomegalovirus Infections"). Some of these, such as the inflammatory demyelinating neuropathies, occur early in HIV-1 infection, and others, such as distal symmetrical polyneuropathy and CMV polyradiculomyelopathy, occur late. The neuromuscular complications of HIV-1 infection are considered common. Several studies suggest that even subclinical neuromuscular involvement occurs frequently (Hall et al. 1991). At least one third of patients with AIDS develop symptoms of neuropathy (So et al. 1988).

Distal Symmetrical Polyneuropathy or HIV-1 Associated Predominantly Sensory Polyneuropathy

Distal symmetrical polyneuropathy, or HPSP, is the most common polyneuropathy in HIV infection. So et al. (1988) diagnosed this polyneuropathy in 35% of 40 unselected hospitalized AIDS patients. The most frequent symptoms are paresthesias, numbness, pain, and dysesthesias affecting the feet. Ankle reflexes are decreased or absent, there is a decreased sensation of pain and vibration in the feet and legs, and weakness is usually mild. The hands are less often involved. In a small proportion of patients pain is the most prominent feature. Most investigators believe that this painful distal sensory neuropathy is a subgroup of HPSP. There is some epidemiological evidence suggesting a relationship with CMV (Fuller et al. 1989). Electrophysiological studies demonstrate a polyneuropathy with features of both axonal degeneration and demyelination; however, pathologically the abnormalities found are predominantly axonal, and the demyelination is largely secondary. HIV has been isolated from peripheral nerves (De La Monte et al. 1988), but the pathogenesis remains unknown. Possible mechanisms include direct viral infection or a cell-mediated immune attack on components of peripheral nerves.

Treatment is limited to providing symptomatic relief with tricyclic antidepressants and anticonvulsants. Zidovudine seems to have little efficacy although controlled trials are lacking.

Inflammatory Demyelinating Polyneuropathies

A demyelinating polyneuropathy may occur acutely or chronically in HIV-infected individuals. These demyelinating neuropathies tend to occur early in the course of HIV infection. HIV-1 associated acute inflammatory demyelinating polyradiculoneuropathy (HIV-1 associated Guillain-Barré syndrome) is similar to Guillain-Barré syndrome in patients not infected with HIV-1. Patients present with progressive weakness, areflexia, and minor sensory signs. However, CSF examination may reveal mild mononuclear pleocytosis and an elevated protein level in HIV-infected patients (Cornblath et al. 1987). The same CSF abnormalities may be found in HIV-1 associated chronic inflammatory demyelinating polyneuropathy. The research criteria have been published recently (Cornblath et al.1991). Electrophysiological studies indicate features of primary demyelination and axonal loss (Cornblath et al. 1987). The pathogenesis of inflammatory demyelinating polyneuropathies may be autoimmune (Arnason 1975). The clinical course of neuropathies in HIV-infected individuals is variable, but most patients improve.

Plasmapheresis has been suggested as the treatment of choice, but steroids may be effective as well (Cornblath et al. 1987). Some patients recover spontaneously.

Mononeuropathy Multiplex

MM is characterized by sensory and motor deficits in the distributions of multiple spinal, cranial, or peripheral nerves. MM is associated with CDC class IV-A and AIDS. CSF reveals both pleocytosis and elevated protein level. Electrophysiological studies suggest axonal neuropathy. Nerve biopsies have revealed necrotizing arteritis (Gherardi et al. 1989). Said et al. (1991) has described a rapidly progressive multifocal neuropathy in four patients with CMV inclusions in peripheral nerves. One of these responded to ganciclovir. This CMV-related multifocal neuropathy was characterized pathologically by multifocal necrotic endoneural nerve lesions and perivascular polymorphonuclear cell infiltration. Clinically the mononeuritis multiplex originally described by Lipkin et al. (1985) appears similar but at a different time point of HIV infection. Thus, the role of CMV and antiviral agents in this neuropathy is not clear.

Autonomic Neuropathy

Late in HIV-1 infection a small number of patients develop an autonomic neuropathy that is clinically significant (Freeman et al. 1990). Patients present with postural hypotension, bowel and bladder dysfunction, impotence, sweating abnormalities, presyncope, and sudden arrhythmias, with a risk of death. Numerous factors may contribute to these symptoms, but often these symptoms are due to small fiber peripheral neuropathy. Extensive autonomic testing revealed both parasympathetic and sympathetic dysfunction in 50 % of patients (Cohen and Laudenslager 1989). Treatment is purely symptomatic, with the use of agents such as fludrocortisone for stabilization of blood pressure.

Toxic Polyneuropathies

A painful peripheral neuropathy has been associated with the use of several dideoxynucleoside analogues in the treatment of HIV-1 infection. In phase I trials of ddI this painful peripheral neuropathy has been the major dose-limiting side effect. The syndrome is characterized by burning pain and tingling in the feet and legs, starting 8–27 weeks after initiation of ddI treatment. These neuropathic symptoms have generally not been associated with significant abnormalities in nerve-conduction studies. Some patients have reported marked improvement in symptoms within 1–2 weeks of discontinuing ddI. The neuropathy appears to be related to the total cumulative dose of ddI. In the series of Lambert et al. (1990), 7 of 22 patients who received a daily dose of ddI greater than 12 mg/kg developed neuropathy, while only 1 of 15 patients who received a lower dose did. Another study revealed a very low incidence of neuropathy in ddI users (Cooley et al. 1990).

ddC neuropathy is clinically similar to ddI neuropathy. This neuropathy is also dose related, and significant recovery occurs in most patients (Schaumburg et al. 1990). The findings in these ddI and ddC neuropathies are consistent with a distal axonopathy primarily affecting sensory fibers.

Myopathies

Several myopathies have been described in HIV-1 infected individuals. The most important are HIV-1 associated polymyositis and zidovudine-associated myopathy (Simpson and Wolfe 1991). Progressive proximal muscle weakness, often associated with myalgia, elevated serum creatine kinase (CK), myopathic EMG abnormalities, inflammatory infiltrates, and mitochondrial abnormalities (by electron microscopy) in muscle biopsy, may be present in both types, and no features discriminate clearly between them.

HIV-1 associated polymyositis (some authors prefer the term HIV-associated myopathy because not all patients satisfy the accepted diagnostic criteria for polymyositis) has been described in all stages of HIV-1 infection (Dalakas et al. 1986; Simpson and Bender 1988). Patients present with subacutely progressive proximal weakness and myalgia, most prominent in the thighs. The weakness involves the legs and neck flexors more than the arms. CK elevation is mild or moderate. Patients usually have myopathic EMG abnormalities, and 50 % may have nerve-conduction abnormalities indicating peripheral neuropathy (Simpson and Bender 1988). Pathological findings include non-inflammatory myofiber degeneration, myofiber necrosis with inflammatory infiltrates, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. The pathogenesis is unknown. A T-cell mediated and MHC-I restricted cytotoxic process may be the underlying mechanism (Dalakas 1991). HIV-1 associated polymyositis may respond to corticosteroids.

Zidovudine-associated myopathy occurs in a minority of patients who have been treated with zidovudine for at least 9–12 months. Muscle tenderness and

weakness are preceded by CK elevation. In this myopathy mitochondrial dysfunction, resulting from drug-induced inhibition of the mtDNA polymerase, has been suggested as the direct cause of the myopathy. The cumulative dose of zidovudine might be important (Gherardi et al. 1991). Pathologically ragged red fibers, indicative of abnormal mitochondria, coexist with inflammatory changes (Dalakas et al. 1990). Zidovudine-associated myopathy usually (but not always) responds to zidovudine withdrawal.

■ Other Neurologic Syndromes

Cerebrovascular Complications

Some patients with AIDS suffer transient ischemic attacks or strokes (Engstrom et al. 1989). Sometimes these cerebrovascular complications occur as the result of an underlying opportunistic infection or lymphoma; occasionally they are secondary to marantic endocarditis. In other cases the underlying condition is not known. In the pathogenesis anticardiolipin antibodies may play an ancillary role since they are fequently found in HIV-infected patients (Maclean et al. 1990). Treatment is not different from that in the non-HIV-infected patient.

Seizures

Seizures without an underlying opportunistic infection or tumor have been reported in HIV-1 infected individuals (Wong et al. 1990). Because of a high relapse rate it is recommended to start anticonvulsive medication after the first seizure (Holtzman et al. 1989).

Multiple Sclerosis-like Illness

A syndrome resembling multiple sclerosis, with a fulminating course and multiple recent plaques typical for multiple sclerosis, has been described in HIV-infected patients (Berger et al. 1989; Gray et al. 1991). The association between multiple slerosis-like illness and HIV infection may be fortuitous, but the occurrence may be related to HIV-1 infection. The pathogenesis is presumably an autoimmune mechanism since it occurs at the same time as, for example, thrombocytopenic purpura.

■ Diagnostic Approach and Differential Diagnosis

In the diagnosis approach to a neurological problem in HIV-1 infected individuals it is critical to appreciate the following factors:

- The degree of advancement of HIV-1 infection (or the level of immune compromise): some neurological complications occur early in HIV-1 infection, others occur late.
- The anatomical site of involvement: focal brain lesion or non focal disorder? Central nervous system disease or neuromuscular complication?
- Is there a single disease or are multiple levels of the neuraxis involved simultaneously?
- The prevalences of the neurological complications: some complications are common, others are rare (Table 1.1).

CT/MRI scanning and CSF examination are the most important tools in confirming a presumed diagnosis and excluding others. Usually lumbar puncture (if not contraindicated) follows CT/MRI scanning. Electrophysiological studies may be helpful in neuromuscular complications. Brain biopsy, muscle biopsy, neuropsychological examination, and EEG may give additional and sometimes essential information in specific problems.

The following list summarizes the neurological complications frequently associated with HIV infection:

Diffuse Brain Disease
- AIDS dementia complex
- Metabolic encephalopathies
- Diffuse encephalitis:
  - HIV-1 (acute HIV-1 encephalitis)
  - CMV
  - HSV
  - Toxoplasmosis (diffuse form)

Focal Brain Lesions
- Toxoplasmosis
- Lymphoma
- PML
- Candida abscess
- Cryptococcoma

- Tuberculoma
- Stroke
- Metastasis
- Others

Myelopathies
- Vacuolar myelopathy
- CMV polyradiculomyelopathy
- VZV radiculomyelopathy
- Lymphoma (epidural or intradural)
- HTLV-1 associated myelopathy

Meningitides
- Cryptococcal meningitis
- Aseptic meningitis (HIV-1)
- Meningitis lymphomatosa (non-Hodgkin lymphoma)
- Tuberculous meningitis
- *Listeria* meningitis
- Syphilitic meningitis

Neuromuscular Complications
Neuropathies
- HIV-1 associated predominantly sensory polyneuropathy (distal symmetrical polyneuropathy)
- Inflammatory demyelinating polyneuropathy (acute and chronic)
- Mononeuropathy multiplex
- Autonomic polyneuropathy
- Toxic neuropathies (ddI, ddC, isoniazid, etc.)
- CMV polyradiculomyelopathy

Myopathies
- HIV-1 associated polymyositis (HIV-associated myopathy)
- Zidovudine-associated myopathy
- HIV wasting syndrome

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Chapter 2

Diagnostic Imaging of Intracranial Manifestations of AIDS

H. Henkes, R. Jochens, J. Hierholzer, and U. Piepgras

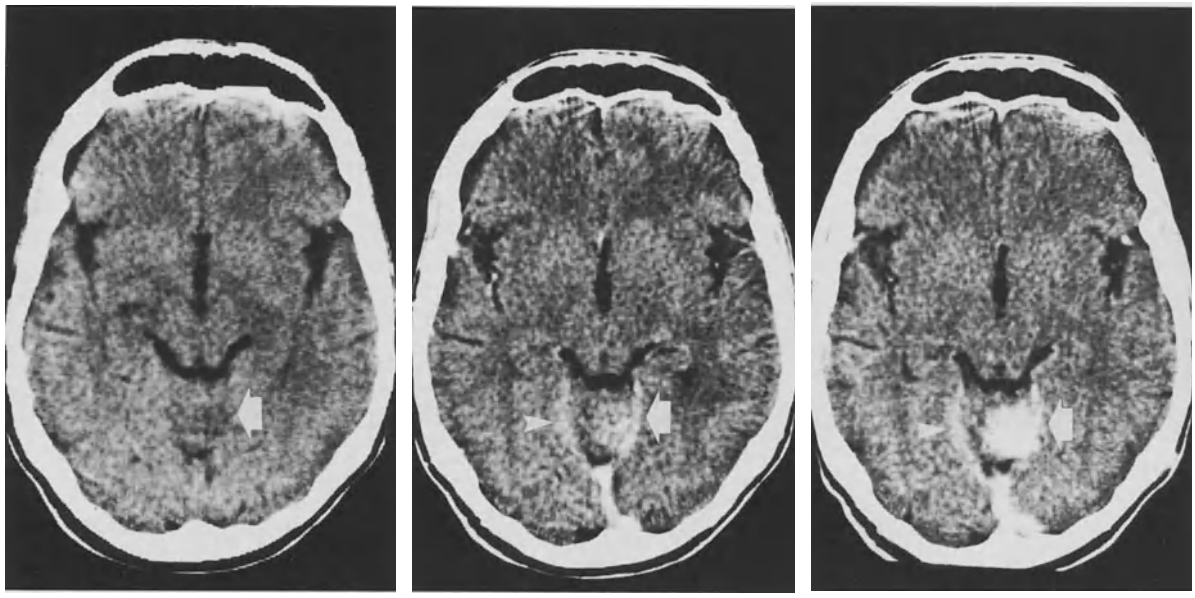
■ Introduction

The incidence of CNS manifestations of AIDS is considerably high. As early as 1984 Berger et al. reported on 186 patients, 11 % of whom presented with CNS abnormalities, and 33 % of whom showed neurological symptoms during the disease. Levy et al. (1985) evaluated the clinical history of 352 AIDS patients and detected neurological symptoms in 39 %. In about one quarter of these (10 %) they were the initial manifestation of the disease. Clinical studies probably underestimate the true frequency of CNS manifestations of AIDS, especially when they are obscured by life-threatening systemic, non-cerebral manifestations. This is supported by neuropathological data showing morphological changes of the brain, spinal cord, and surrounding tissues in 70 %–95 % of all autopsy cases (Gray et al. 1988; Iglesias et al. 1988; Lang et al. 1989). A systematic overview of CNS manifestations of AIDS, based on various etiologies, was given by Levy et al. (1985) and was subsequently modified by other authors (Kesselring 1986).

This chapter considers the diagnostic imaging of intracranial manifestations of AIDS, using computed tomography (CT) and magnetic resonance imaging (MRI). First we present various concepts of a systematic approach to lesion patterns; nonspecific changes (atrophy, signs of degenerative brain disease) are then discussed. Further topics are the sequelae of former insults, focal calcifications (e. g., in pediatric AIDS patients), and meningeal findings, putting emphasis on the findings in defined etiologies, especially cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), and CNS lymphoma.

■ CT and MRI: General Considerations

In the diagnostic imaging of the CNS, CT and MRI have gained a key role in the clinical work-up of patients with neoplastic, vascular, degenerative, or inflammatory brain disease. Neurophysiological examinations, CSF analysis, and angiography have become supplementary diagnostic tools. In AIDS patients with presumed or confirmed CNS manifestations CT and MRI are even more important. The disturbance of the immunological system decreases the diagnostic value of CSF analysis. EEG provides relevant functional data. In terms of localization and specificity, however, the information obtained is poor.



a–c

Fig. 2.1 a–c. Double dose, delayed (DDD) technique in CT, illustrated in the detection of a large toxoplasmotic lesion. **a** The unenhanced scan shows a hypodense lesion of the cerebellar vermis *(arrow)*. **b** On the scan, generated immediately after drip infusion of 100 cc iodinated contrast medium, a subtle increase in the density of this lesion can be seen *(arrow)*. **c** An even higher contrast between the contrast-enhancing lesion, normal brain tissue, and normally enhancing tentorium *(arrowhead)* is achieved on images obtained 60–90 min after infusion of 200 cc

Cranial CT is part of the basic examinations in HIV-infected persons (Fig. 2.1). In patients with full-blown AIDS, cranial CT evaluation should be carried out even if there are no cerebral symptoms (Pohle and Eichenlaub 1987; Rossi et al. 1990). Follow-up studies are mandatory in newly occurring or basically changed neurological symptoms and both during and after chemotherapy (Barber et al. 1990). In patients with stages I–III (Centers for Disease Control classification) a cranial CT study should be performed whenever a cerebral manifestation must be ruled out as a result of the following factors: (a) the patient's history (e. g., syncopes, questionable seizures, headache, memory or behavioral disturbances), (b) objective neurological findings (e. g., hemiparesis, cranial nerve palsy, visual failure), (c) diffuse or focal disturbances in the EEG, (d) pathological latencies of evoked potentials (EP), (e) CSF abnormalities, or (f) fever of unknown origin.

MRI is the imaging method with the highest sensitivity for parenchymal and meningeal intracranial lesions. Thus, if freely available, it is the imaging modality of choice in AIDS patients with cerebral or meningeal symptoms (Kupfer et al. 1990; Levy et al. 1986a). Some authors have recommended the complementary use of CT and MRI (Poser et al. 1988). If the capacities for MRI examinations are limited, and a selection of patients is necessary, we propose some obligatory indications for the performance of a MRI study, for example, (a) when a previous CT study (including contrast-enhanced scans) yielded a normal finding, but there are persisting and unexplained fever, neurological symptoms, or CSF, EEG, or EP findings indicate a possible intracranial lesion, and (b) when a previous CT study confirmed an intracranial lesion, but chemotherapy was not successful, and the stereotactic biopsy of a lesion is planned. On the other hand, the additional performance of an MRI examination does *not* appear necessary in the following cases: (a) when CT demonstrates a lesion that decreases under chemotherapy, and (b) when further or more aggressive treatment or diagnostic procedures are not possible because of the patient's poor general condition.

Patients with metallic or electromechanical implants (e. g., pace-makers, implanted pumps or ports) are not referable to high-field MRI. For some of these patients the strong magnetic field required for imaging can be hazardous. Furthermore, metallic parts disturb the homogeneity of the magnetic field, leading to image artifacts (Fig. 2.2). In patients with suspected or confirmed CNS manifestations of AIDS, a contrast-enhanced MRI examination is mandatory, even if

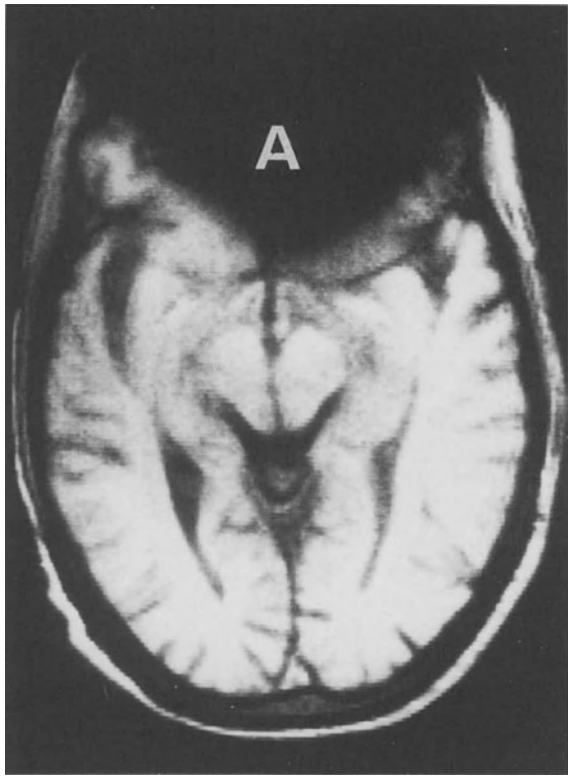


Fig. 2.2. Ferromagnetic artifact caused by a dental prosthesis. The wedge-shaped signal loss *(A)* prevents evaluation of the whole frontal region. (FLASH 90 °, 315/14)

there was no pathological contrast enhancement in a previous CT study. For investigational purposes, especially for the examination and follow-up studies of HIV-infected asymptomatic individuals, MRI proved to be very suitable since it is highly sensitive, and no health risks are known (Cohen et al. 1992; Dooneief et al. 1992; Goethe et al. 1989; McArthur et al. 1989; Post et al. 1992; Rosci et al. 1992; Sonnerborg et al. 1990). Excellent papers on the physics as well as on the clinical methods and basics of CT and MRI are available (CT: Kazner et al. 1989; Kretschmann and Weinrich 1991; Latchaw 1985; Lee and Rao 1987; Schultz 1985; Unsöld et al. 1982; Yock 1985; MRI: Horowitz 1989; Pomeranz 1989; Runge 1989; Sigal 1988).

For clinical purposes, a description and documentation of imaging findings with respect to the underlying etiology is indispensable. A schematic and basically morphological system for the description of findings is helpful for the differential diagnosis in patients with CNS lesions of unknown etiology. Bursztyn et al. (1984) published the results of a CT study carried out in 30 AIDS patients presenting with neurological and/or psychiatric symptoms. They proposed six basic types of morphologically defined CNS lesions with their respective differential diagnoses. Type 1 lesions are solitary or multiple ring-enhancing lesions, surrounded by edema causing limited mass effect. In most cases a toxoplasmotic focus can be expected. Type 2 lesions are nodular and homogeneously enhancing, caused either by toxoplasmosis or cerebral lymphoma. Type 3 lesions comprise irregular, confined, hypodense areas without contrast enhancement. These may be a correlate of PML. We have also observed this lesion pattern in terminal stage toxoplasmosis. The lack of contrast enhancement may be due to thrombosis of microvessels or to an almost complete immunological anergy in this agonal state. Type 4 lesions show multiple, small, hypodense, nonenhancing foci. This is a rather unspecific finding that can be observed in toxoplasmosis, *candida* infection, lymphoma, many other diseases, and in combined etiologies. Cortical atrophy is a type 5 pattern. Based on imaging data, brain atrophy is very frequent in AIDS patients, and it appears to be a dubious prognostic factor. Various findings such as ischemic or hemorrhagic infarcts, cerebral or sub- and epidural hemorrhage are described as type 6 lesions.

Attempts at establishing such a system of findings and their related differential diagnoses confront the fact that in immunocompromised hosts diseases of different etiologies can coexist not only in the same patient but even in a single focus (Catania et al. 1990; Enzensberger and Fischer 1987b; Farkash et al. 1986; Fischl et al. 1985; Grafe et al. 1990; Lang et al. 1989; Levy et al. 1983; Moskowitz et al. 1984b; Pepose et al. 1984; Zimmerman et al. 1987).

Systemic similar to that above have been proposed for the MRI of CNS manifestations of AIDS. Jarvik and Hesselink (1988a) distinguish four basic types, according to the results of T2-weighted MRI scans (T2-WI). Type A lesions are multiple and show a slightly increased signal intensity (e.g., in toxoplasmosis or PML). Type B lesions are large, bilateral, and confluent hyperintense white matter lesions, as observed, for instance, in cytomegalovirus (CMV) and HIV encephalitis. Type C refers to all variants of internal and/or external brain atrophy, due either to HIV encephalitis or to general physical wasting. From a systematic point of view, the enlargement of the ventricles as frequently observed in patients with cryptococcal meningitis belongs to this type. Type D lesions are solitary foci of increased signal intensity and are observed, for instance, in nonviral opportunistic infections. These are, of course, preliminary proposals, meant to help in cases in which various differential diagnoses must be considered. Since their

publication, the introduction of contrast-enhanced MRI (which has become a routine procedure) and the examinations of large numbers of AIDS patients have added substantially to our experience.

Several investigators have dealt with the diagnostic value of Gd-DTPA application in routine MR imaging of HIV-infected patients. Jensen and Brant-Zawadzki (1993) emphasized the primary role of T2-WI in the screening for brain pathology in AIDS patients. Tuite et al. (1993) evaluated data of 103 patients. In 16 of 82 patients who had normal unenhanced scans, pathologic contrast enhancement of meningeal, ependymal or parenchymal structures was observed. The absence of contrast enhancement supported a diagnosis of PML. Pathologic meningeal contrast enhancement in aseptic meningitis and enhancement of focal lesions due to toxoplasmosis or lymphoma near the CSF yielded significant information. The detection of multiple instead of solitary lesions helped in the differentiation of toxoplasmosis and lymphoma. The authors estimated that new information was obtained from Gd-DTPA application in 23% of their patients.

■ Nonspecific Changes

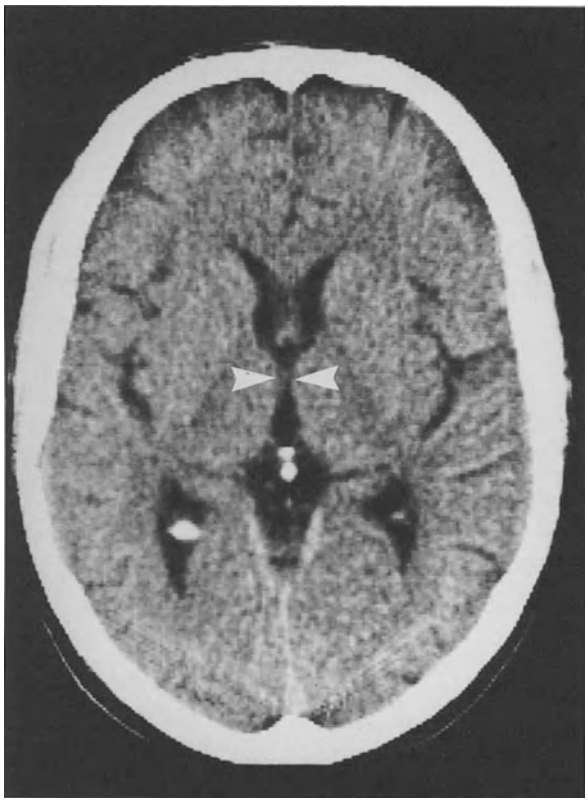
Atrophy

Brain atrophy or, more generally, enlargement of the intracranial CSF spaces, can frequently be observed in adult AIDS patients, especially at more advanced stages of the disease (Jakobsen et al. 1989; Moeller and Backmund 1990; Post et al. 1988; Raininko et al. 1992; Figs. 2.3, 2.4). In 40%–50% of AIDS patients, unselected with regard to psychiatric symptoms, a certain degree of brain atrophy is shown by CT or MRI (Bursztyn et al. 1984; Elovaare et al. 1990; Flowers et al. 1990). AIDS dementia is usually associated with brain atrophy which may be prominent in the caudate region (Dal Pan et al. 1992, Navia et al. 1986). Follow-up examinations and statistical analysis, however, demonstrated that the development of AIDS dementia is associated with white matter lesions on MRI, whereas there is no significant association with brain atrophy (Pedersen et al. 1991). The speed of information processing in HIV-infected persons is directly correlated with the severity of their brain atrophy (Levin et al. 1990). In AIDS patients with confirmed brain atrophy, the frequency of further intracranial lesions during their disease is greater than in AIDS patients with normal-sized CSF spaces (Levy et al. 1986b). Mundinger et al. (1992) calculated the prognosis of AIDS patients with respect to their initial imaging result. The mean survival time was 700±89 days in patients with initially normal CT or MRI findings, 326±65 days in patients with cerebral atrophy, 202±97 days in patients with focal lesions, and only 78±34 days in patients with both cerebral atrophy and focal lesions. In the series of Elovaara et al. (1990) 57% of the cognitively intact HIV-infected individuals showed slight brain atrophy and/or parenchymal lesions. However, in the patients with neurological symptoms and long-standing HIV infection, the most severe and the most frequent abnormalities were detected by CT and MRI.

Fig. 2.3a–d. Development of AIDS-associated brain atrophy. ▶ This 36-year-old man presented with Kaposi's sarcoma, mild psycho-organic syndrome, and without focal neurological deficits. The images (**a–d**) are from examinations performed over a 4-month period. The size of the lateral ventricles, third ventricle *(arrowheads)*, and external CSF spaces has increased considerably

The main cause of progressive brain atrophy in AIDS patients is considered to be subacute HIV encephalitis (synonyms: chronic AIDS encephalopathy, HIV encephalitis, HIV leukoencephalopathy; Budka et al. 1991). Chrysikopoulos et al. (1990) correlated imaging findings and neuropathological data of seven patients with encephalitis caused exclusively by HIV and found atrophy in five of them. In their total series of 24 patients with neuropathologically confirmed HIV encephalitis, 18 had supratentorial atrophy. In good correlation with the distribution of HIV-induced lesions, the central atrophy was more pronounced than the peripheral volume loss. In 16 of 18 patients progression of the atrophy was documented by follow-up studies. It is also our experience that diffuse white matter lesions precede atrophy in HIV encephalitis. Thus, brain atrophy is part of the late, or at least of the advanced, stages of HIV encephalopathy (Balakrishnan et al. 1990). As in other instances, the clinical significance of this finding is not clear.

The clinical courses of children with HIV infection vary considerably. Based on neuropathological data, Wiley et al. (1990) distinguished two categories of pediatric AIDS. The progressive type is characterized by the loss of previously acquired language and cognitive skills. The plateau type is accompanied by the failure to acquire additional developmental skills. The CT examinations of six children with a progressive course showed brain atrophy, increasing white matter hypo-



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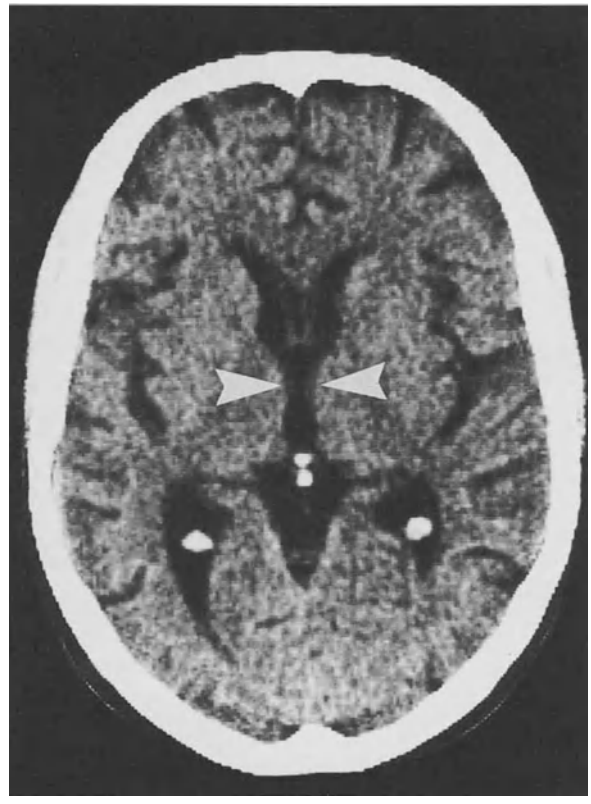

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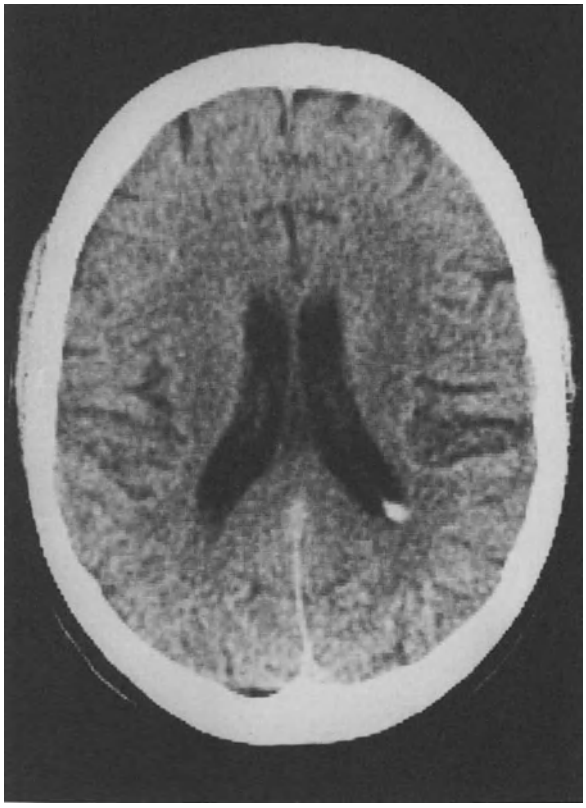

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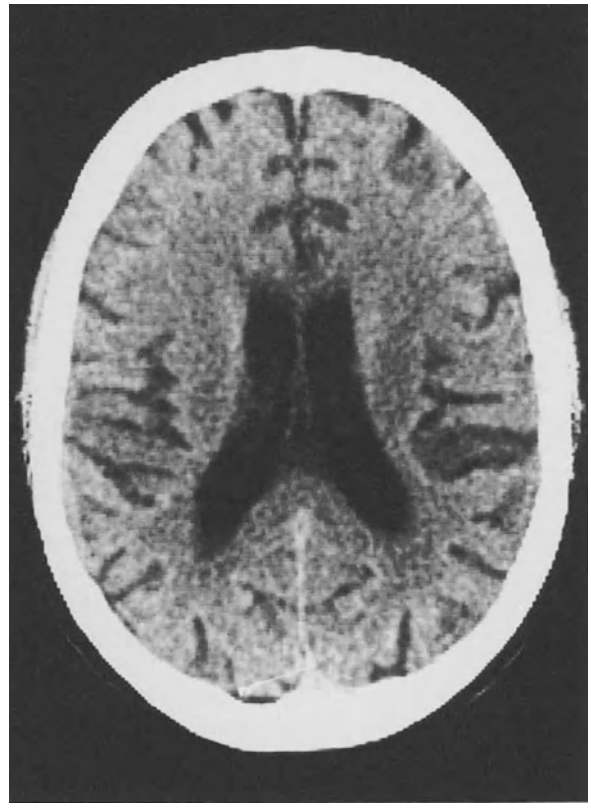

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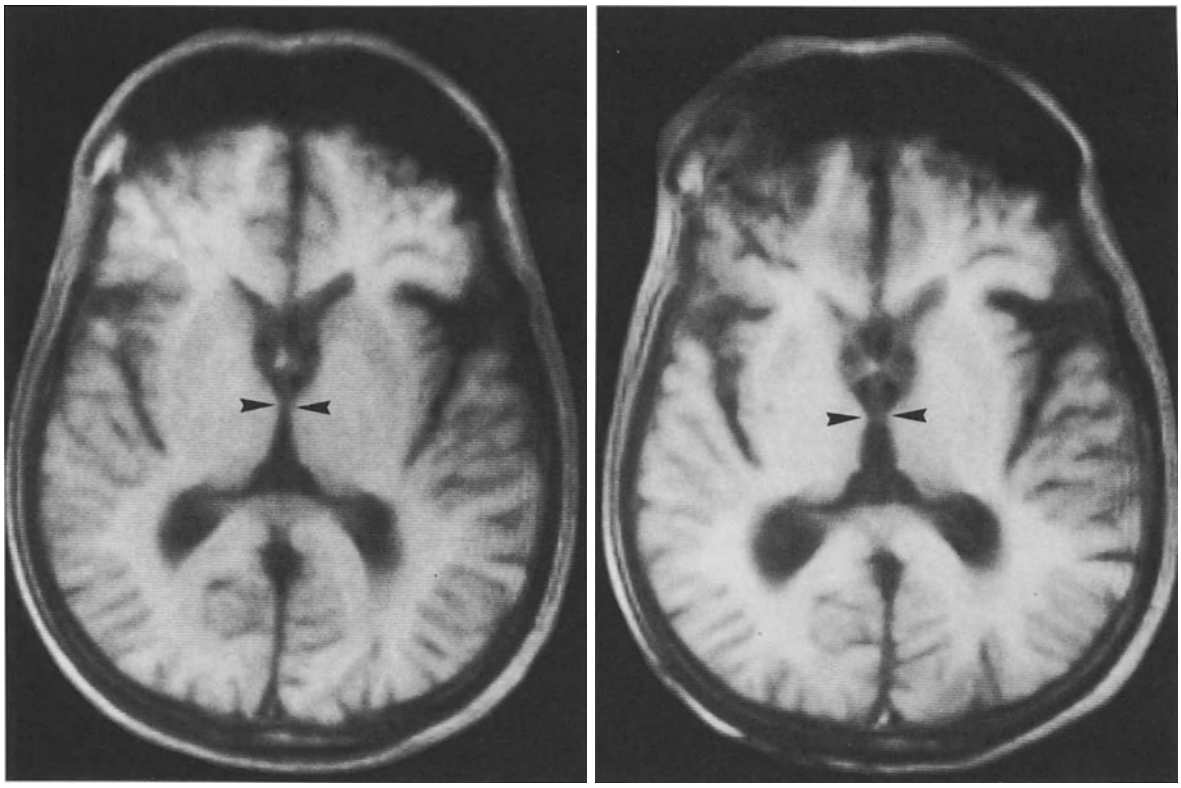


a b

Fig. 2.4a,b. Development of brain atrophy *(arrowheads)* in an AIDS patient with recurrent cerebral toxoplasmosis. The course over 16 months is shown. Despite prompt improvement of the cerebral toxoplasmosis after chemotherapy the patient developed severe dementia

density and calcifications of the basal ganglia. In the plateau group, CT findings were less obtrusive, consisting mainly of mild atrophy and faint calcifications. In children with HIV-induced encephalopathy, there was a decrease in brain atrophy after 6 months of zidovudine therapy, confirmed by CT follow-up studies and planimetric measurements (DeCarli et al. 1991).

Any assessment of brain atrophy shown by CT must consider clinical information as well as the clinical goal of the examination. Regarding the degree of brain atrophy an evaluation based on experience is sufficient in most cases. Several exact measures have been proposed. The Huckman number allows assessment of the internal CSF spaces. This is the sum of the largest and the smallest outer distance of the anterior horns of both lateral ventricles, and it is normally below 58 mm (Huckman et al. 1975). The outer CSF spaces can be assessed by counting the number of sulci that can be delineated in the first supraventricular plane of an axially performed study. More accurate data are produced by linear, planimetric, and volumetric measuring, which requires various technical prerequisites and can be very time consuming. Some of these parameters also are suitable for clinical purposes. Below, we will list some of these CSF space parameters with the methods of measuring and the normal values with 5–50–95 percentiles as far as these are known.

- *Size of the third ventricle:* to be measured at the greatest distance of the walls of the third ventricle; 1.7–3.3–6.6 mm (Gyldensted 1977).
- *Ventricle index:* distance of the choroid plexus divided by the greatest distance of the anterior horns of the lateral ventricles; 1.59±0.18 (Skødt et al. 1986).
- *Cella media index:* outer biparietal diameter divided by the greatest distance of the anterior horns of the lateral ventricles at the level of the cella media; 4.2–5.0–6.8 (Gyldensted 1977).
- *Evans ratio:* to be measured for each hemisphere separately; 2x maximum widths of the anterior horn of the lateral ventricle divided by the maximum inner skull width; left 0.21–0.27–0.32, right 0.2–0.26–0.3 (Gyldensted 1977).

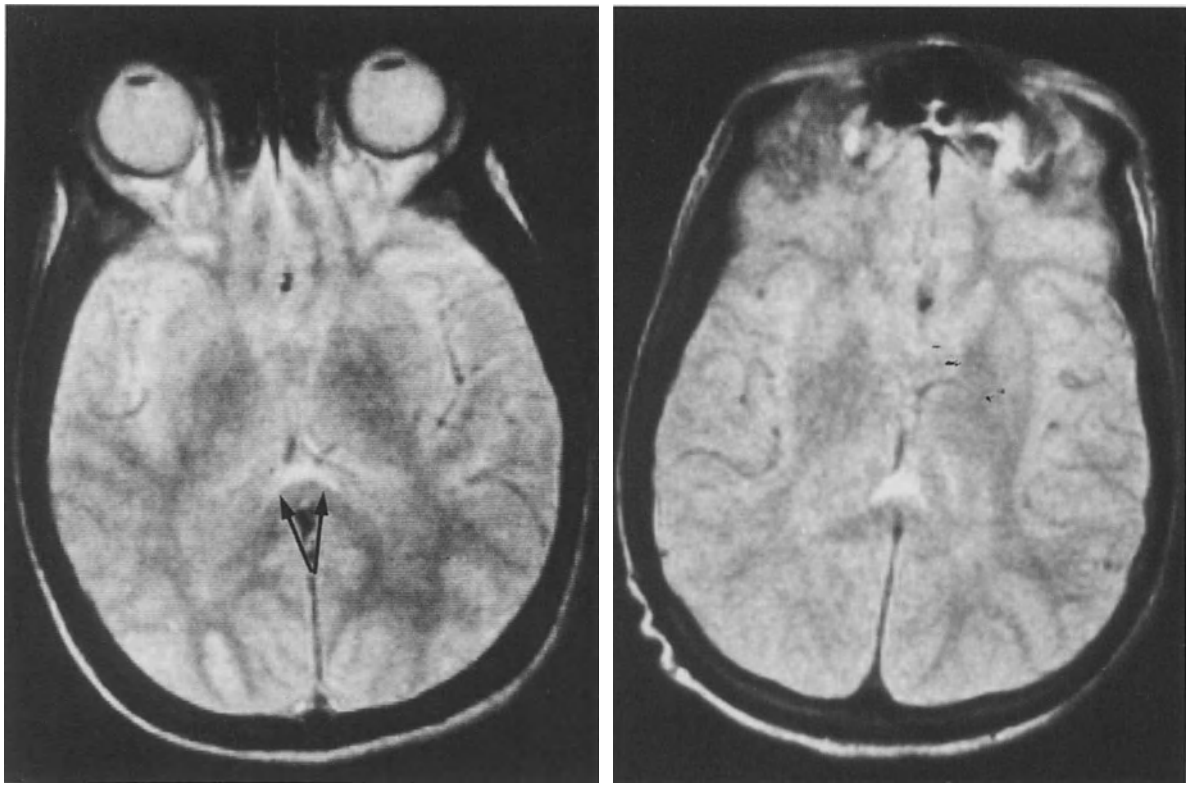
- *Mean width of four sulci:* the two broadest sulci of every hemisphere are measured at a level 16 mm above the lateral ventricles; 2.02±0.9 (Skødt et al. 1986).
- *Frontal width of the interhemispheric fissure:* a midsagittal line is drawn from the rostrum to the inner frontal surface of the skull, and the interhemispheric distance is then measured in the middle of this line; 3.8 mm (Schindler and Ludwig 1978).
- *Width of the Sylvian fissure:* measured at the greatest distance (Schindler and Ludwig 1978).
- *Ventricular area:* maximum area of the ventricles in the plane with the greatest extension of the ventricles, measured by planimetry, < 10 cm^2 (Hedde and Reischies 1986).

We refer to the literature for further computer-assisted quantitative methods of planimetry and volumetry (Brassow and Baumann 1978; Gyldensted 1977; Hacker and Artmann 1978; Haug 1977; Huckmann et al. 1975; Penn et al. 1978; Schindler and Ludwig 1978; Skødt et al. 1986; Synek and Reuben 1976).

CT is regarded as sufficient for the assessment of brain atrophy (Meese et al. 1976). The presence and the extension of brain atrophy are judged on the basis of T1-weighted (T1-WI) or proton-density (Pd-WI) MRI scans. Volumetric normal values derived from MRI studies have been published by Filipek et al. (1987). Direct coronal MRI images yield more reliable information concerning the depth of the parietal sulci. The parameters for quantification of brain atrophy can be applied to MRI as well as to CT data.

Handwerker et al. (1992) presented data from volumetric measurements of the CSF space in HIV-infected patients, based on computer analysis of T2-WI. They found a poor correlation of volumetric data with those values determined by conventional measurements and indices. The mean CSF volume was significantly larger in AIDS patients than in healthy volunteers but was not significantly increased in

Fig. 2.5 a, b. Increased signal intensity of the splenium of the corpus callosum as an unspecific, "degenerative" sign (*arrows*, **a**). We observed this finding in AIDS patients with various, most probably unrelated disorders. **a** A 22-year-old man with generalized seizures manifested after testing positive for HIV antibodies. **b** A 32-year-old patient with Kaposi's sarcoma and memory disturbance



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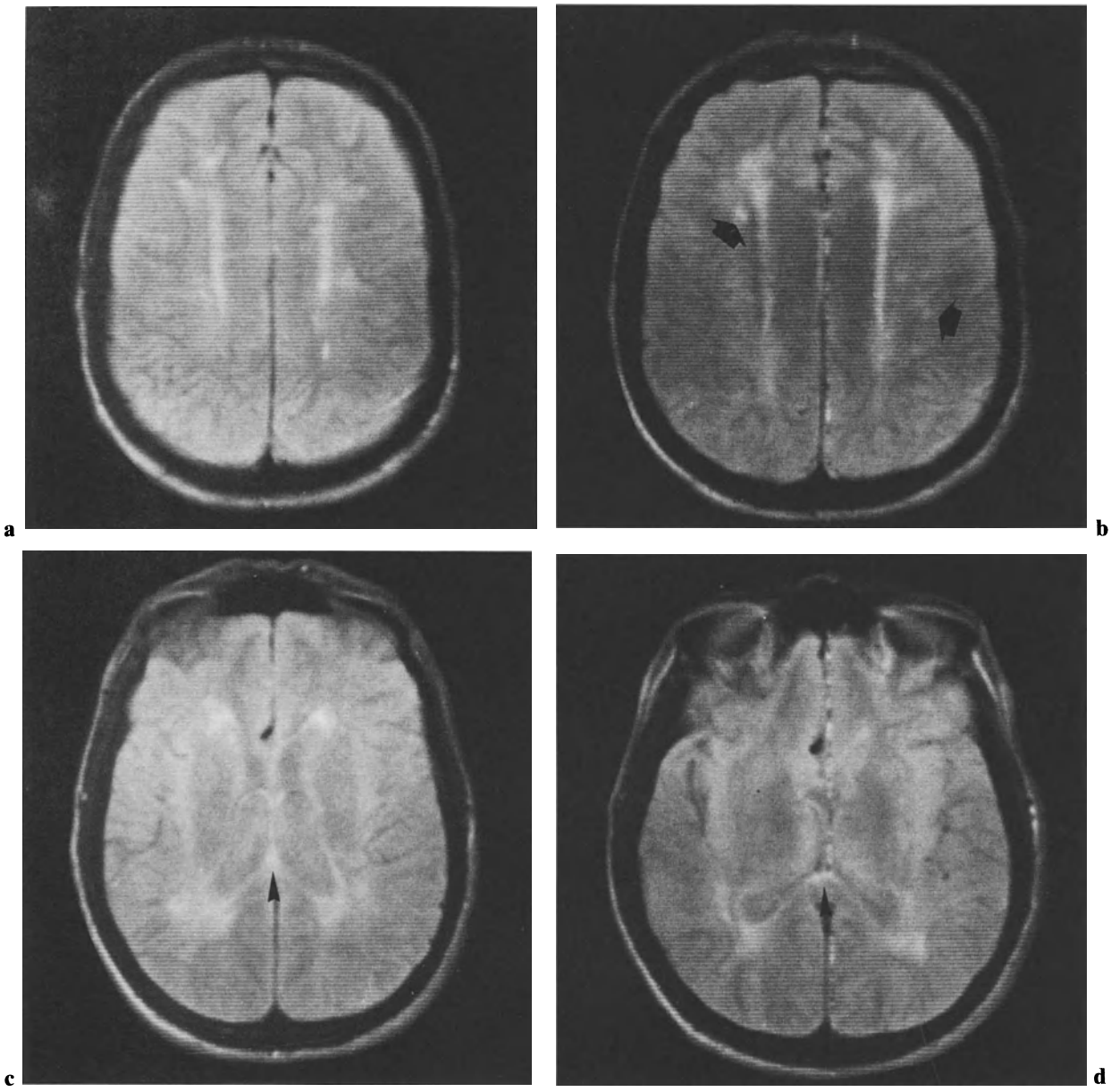


Fig. 2.6a–d. Multiple white matter lesions in AIDS. In this 32-year-old patient with dementia, but without any focal neurological deficit, multiple hyperintense foci in the centrum semiovale *(arrows)* and along the ventricular wall in a rimlike pattern can be observed. Note also in this case the increased signal intensity of the spleniúm corporis callosi *(arrowheads)*

asymptomatic HIV-infected patients or in those at the stage of AIDS related complex. During follow-up examinations, however, in both latter groups an increase of CSF volume was observed.

True brain atrophy shows an irreversible loss of neuronal and/or glial tissue. It may be impossible to distinguish between brain atrophy and reversible changes of the brain volume if no CT or MRI follow-up findings are available. The reversible decrease in brain volume, mimicking brain atrophy, has been described in chronic alcohol addicts (Artmann et al. 1981) and in patients suffering from anorexia nervosa (Enzmann and Lane 1977). The latter phenomenon, together with nonstandardized methods of measure-

ment and selection bias, may be responsible for the substantial variance in incidence and severity of brain atrophy in AIDS patients reported by different authors. Considering neuropathological data, brain atrophy seems even less common. Iglesias et al. (1988) observed signs of atrophy in only 7 % of all brains obtained from AIDS victims.

Gelman and Guinto (1992) found in 58% of their autopsied AIDS patients a CSF space greater than two standard deviations above the mean of the age-matched control subjects. Compared to antemortem CT scans, brain atrophy appeared less severe at autopsy. Presence and pattern, however, were detected with a certain consistency by both CT and neuropathological examination.

Degenerative Changes

On T2-WI, increased signal intensity of the white matter adjacent to the lateral ventricles is a common finding, especially in elderly patients (Bradley et al. 1984; Sze et al. 1985). Cerebrovascular insufficiency is a possible cause along with many other risk factors (Gerard and Weisberg 1986). Thus, in elderly HIV-infected patients, white matter foci can hardly be ascribed to a specific etiology, either to general factors or to viral infection or its sequelae (Freund-Levi et al. 1989; McArthur et al. 1990). Olsen et al. (1987, 1988) observed hyperintense white matter lesions in one third and Flowers et al. (1990) in two thirds of all examined AIDS patients. In 50 of these patients clinical examinations and/or brain biopsies revealed no signs of opportunistic or neoplastic causes for these foci. The white matter foci in AIDS patients are frequently attributed to the HIV infection itself (Post et al. 1988; Trotot et al. 1987). Post et al. (1992) reported on follow-up data obtained from asymptomatic and symptomatic HIV-infected individuals. Their most frequent finding were punctate white matter lesions, few in number and under 5 mm in diameter. A progression upon 1- to 2-year observation was rare, seen only in neurologically symptomatic patients and correlating with clinical deterioration. One of their patients, initially neurologically symptomatic and having white matter lesions, showed significant clinical improvement and almost total resolution of lesions under zidovudine and α-interferon therapy. The series of Reboulot et al. (1992) included a patient with spontaneous disappearance of extensive white matter lesions previously shown by MRI. Bornstein et al. (1992) performed MRI examinations on 243 HIV-positive and -negative homosexual or bisexual men. Based on T2-WI they observed a low incidence of hyperintense foci in all patient groups, which was slightly higher in patients with AIDS, and was not correlated with neuropsychological impairment.

We have also observed white matter lesions with high signal intensity on T2-WI in AIDS patients. Figure 2.5 shows a moderately T2-WI of a 22-year-old patient with an abnormally high signal intensity of the splenium corporis callosi Figure 2.6 shows the multiple, multilocated white matter lesions of a HIV-positive patient with a psycho-organic syndrome.

Scars and Sequelae of CNS Infections and Other Lesions

Previous cerebral infection may result in circumscribed parenchymal loss and focal calcifications seen on CT (Fig. 2.7; Davis et al. 1985; Elkin et al. 1985; Emerson et al. 1981; Wery et al. 1990; Whelan et al. 1983). Post et al. (1985) observed perilesional calcifications in 4 of 20 patients with cerebral toxoplasmosis 2.5–5.5 months after clinical onset and the initiation of chemotherapy. Such calcifications, however, do not necessarily confirm inactivity or definite healing of an inflammatory process. Especially a persisting contrast enhancement in the area of the former lesion indicates inflammatory activity.

Besides focal calcifications and parenchymal defects MRI allows the detection of glial scars. Often it fails to visualize calcifications, especially if the calcified foci are small and surrounded by tissue with high signal intensity (e.g., glial scars on T2-WI), or if the calcification is adjacent to structures with low signal intensity or signal void, such as bone or larger vessels. If the calcification is large enough in diameter to compensate for partial volume effects, a circumscribed reduction or even a complete extinction of signal results (Fig. 2.7; Holland et al. 1985; Schörner et al. 1991). Rarely, calcifications cause a shortening of T1-relaxation, thus appearing as hyperintense structures on T1-WI (Dell et al. 1988). In general, for the detection of focal calcifications CT is more suitable than MRI. In cases with lesions of uncertain etiology the confirmation of calcified parenchymal deposits is a clue to parasitic origin, such as toxoplasmosis, which makes a viral or nepolastic etiology less probable. In these cases, thin-slice, unenhanced CT scans are a helpful adjunct to standard examination procedures.

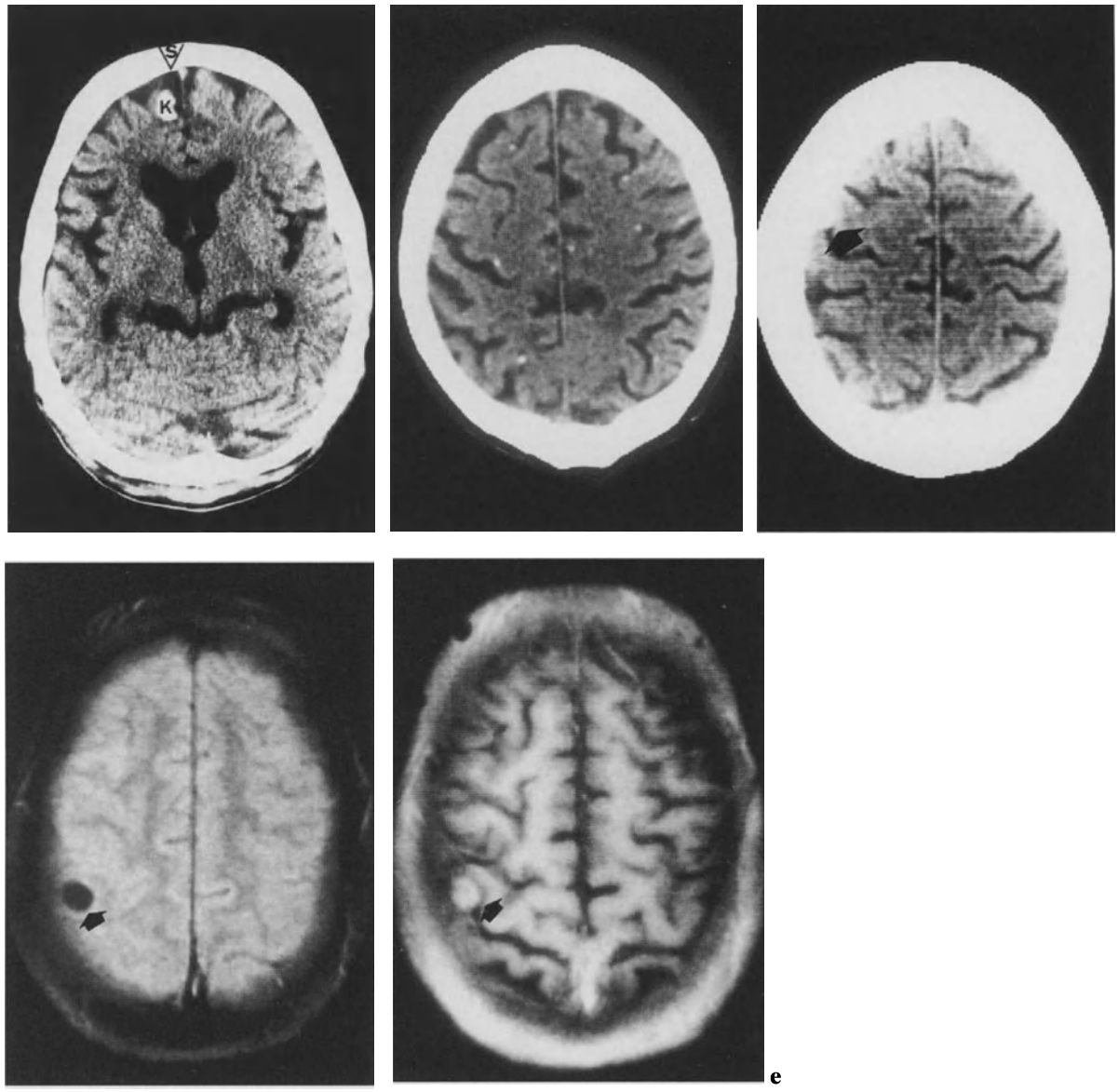
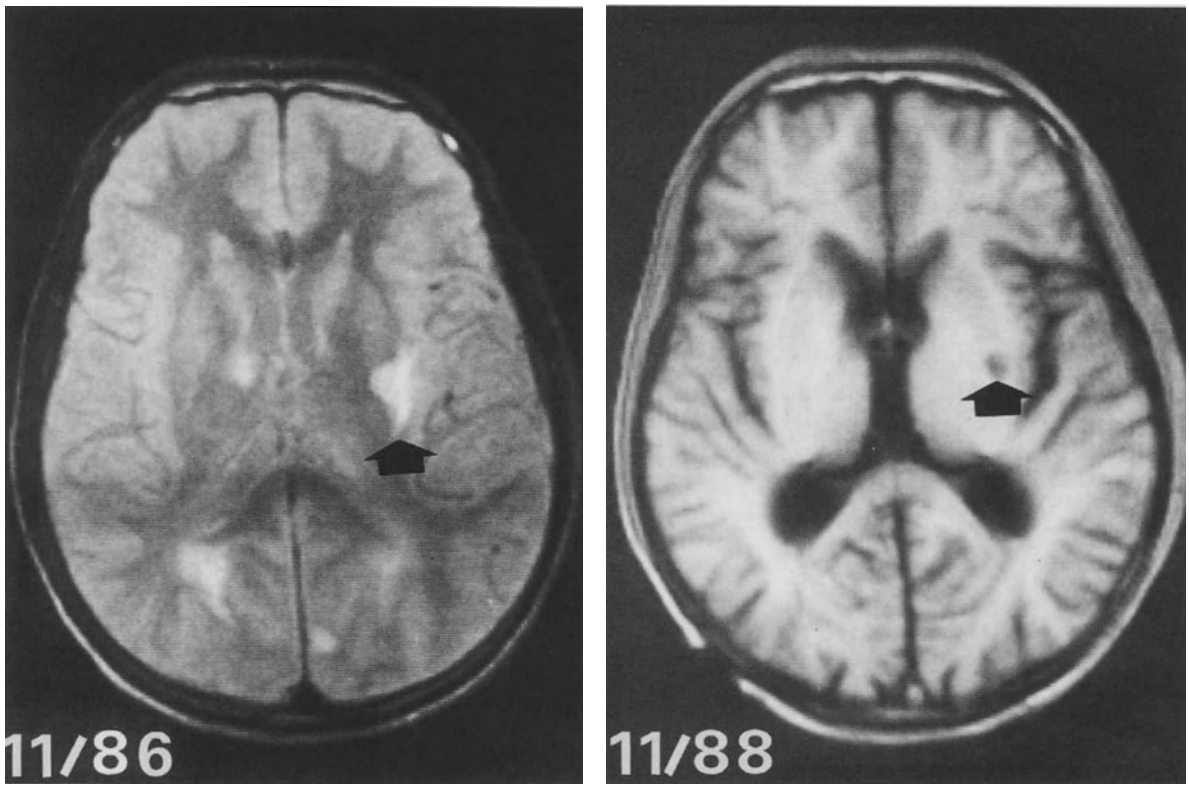


Fig. 2.7a–e. Focal calcifications as an example of the CT and MRI appearances of residual changes. **a** A patient who had been treated medically for a large frontal toxoplasmotic abscess several months previously showed a coarse calcification *(K)* adjacent to the gyral scar *(S)*. **b** Following disseminated cerebral toxoplasmosis, multiple, small calcified foci can be observed. **c** A hyperdense calcification can be seen adjacent to the inner surface of the skull *(arrow)*. **d** The corresponding T2-WI shows a round area without signal at the site of the calcified deposit *(arrow)*. **e** After intravenous administration of Gd-DTPA an increase in signal intensity can be seen on T1-WI *(arrow)*. This finding is due to a persisting disturbance of the blood-brain barrier. It is unclear at present whether focal calcifications can show a certain affinity to contrast materials such as Gd-DTPA

As in atrophy, short TR short TE, T1-WI are suitable to demonstrate parenchymal defects. Using this imaging modality, CSF appears with low signal intensity. Cystic lesions, enlargement of the ventricles, and superficial defects can be delineated (Fig. 2.8).

Most glial scars result in only a slight decrease in parenchymal X-ray attenuation. Even these minimal changes of the brain tissue, however, cause significant alterations of its magnetic properties. As in many other cases, MRI is more sensitive than CT. Various alterations in the area of the former lesion lead to a prolongation of T1 and T2 relaxation times. The finding is a



a b

Fig. 2.8 a, b. Substance loss and cystic defect at MRI. **a** T2-WI *(arrow)* shows cerebral toxoplasmosis. The lesion in the area of the left putamen led to a cystic substance loss. **b** T1-WI from an examination performed 2 years later *(arrow)* reveals the former lesion as an area of low signal intensity

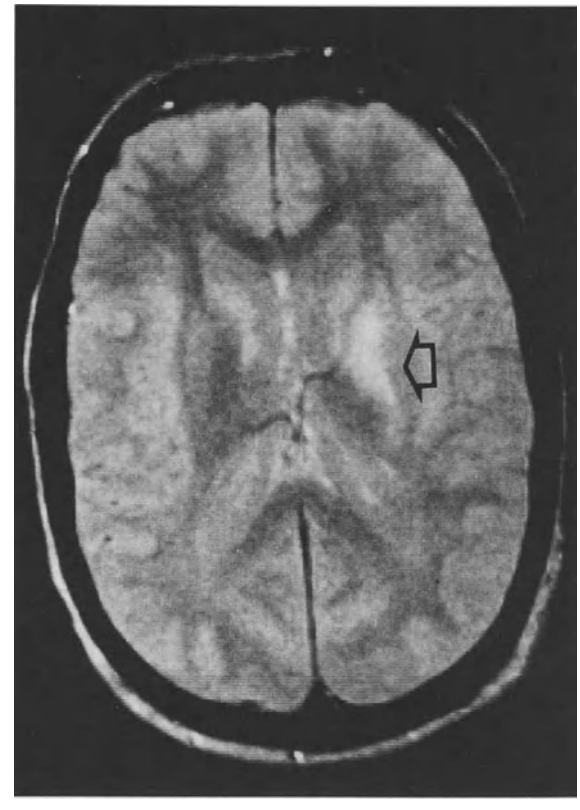


Fig. 2.9. MRI of a postinflammatory scar. Several months after successful medical treatment of cerebral toxoplasmosis. T2-WI demonstrates a residual hyperintense focus *(arrow)* between left putamen and globus pallidus. Active foci of different etiologies can have identical imaging characteristics, thus making the judgement of acuteness or inflammatory activity of such lesions based exclusively on T2-WI almost impossible ▶

more or less hyperintense focus on Pd- and T2-WI, often with only a slight difference in signal intensity from the surrounding tissue. If the differentiation from an acute process is not possible by previous studies or clinical data, a short-term follow-up examination is mandatory (Fig. 2.9).

Calcifications in Pediatric Neuro-AIDS Patients

In pediatric AIDS, CNS involvement is as frequent as in adults. Opportunistic infections of the brain, however, are less common. HIV-infected children tend to have severe manifestations of common diseases rather than opportunistic infections (Shaw and Cohen 1993). Cognitive functions are often impaired. The wide range of clinical symptoms in pediatric AIDS encephalopathy can be classified as normal neurological findings, static encephalopathy, or progressive encephalopathy (Ianetti et al. 1989).

An unspecific CT finding are focal calcifications in the basal ganglia, especially in the putamen and globus pallidum and in the thalamus and centrum semiovale. Kauffman et al. (1992) and Roy et al. (1992) conclude that cerebral atrophy, focal white matter lesions, and basal ganglia calcifications are the most common imaging findings in HIV-infected children. On ultrasound these calcifications appear as hyperechoic foci (Sica and Norton 1990). Belman et al. (1986) reported on 17 children suffering from full-blown AIDS with this pattern. They observed a significant increase in the calcifications as well as in the associated atrophy in the course of the disease. Neuropathological examination revealed a calcifying vasculopathy in four of the children. The authors proposed a connection between progressive encephalopathy and the basal ganglia calcifications. However, there is no linear correlation between progression of the destructive process and extension of the calcifications. Curless (1989) observed a child with a fatal, disseminated CMV infection. The initial CT examination revealed periventricular calcifications. A follow-up examination after clinical deterioration showed extensive edema surrounding the calcified foci, which may indicate reactivation of an intrauterine infection. Encha-Razavi et al. (1991) emphasize that in the evaluation of neuropathological findings in fetuses and neonates of HIV-infected mothers one must consider further maternal risk factors such as abuse of alcohol, nicotine, and drugs. Chamberlain et al. (1991) observed no apparent advantage of MRI over CT in the evaluation of children with AIDS.

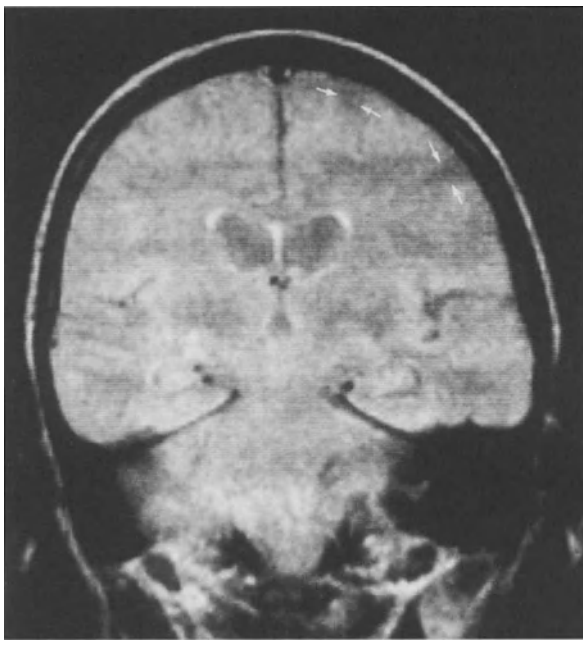
Meningeal Changes

Meningeal alterations and meningitis in AIDS patients are caused by opportunistic parasites and viruses, rarely by bacteria (Levy et al. 1985). Some authors also discuss HIV as a possible cause of meningitis (Enzensberger and Fischer 1987 a; Dal Canto 1989; Tucker 1989).

The clinical symptoms can be atypical in AIDS patients; neck stiffness and headache may be missing. CSF analysis may offer only vague clues. Only limited data are available from the literature about the diagnostic and especially the clinical value of MRI with meningeal lesions in AIDS. In most cases CT is not helpful or even fails to demonstrate the lesions, mainly because in CT direct visualization of structures adjacent to the skull is impaired by bone-hardening artifacts. When iodized contrast medium is used, the density of the thickened meninges increases, but the meningeal structures can distinguished even less from the skull. Some authors have described CT findings of meningeal lesions with mass effect (e.g., with subdural abscess formation) or with thickening of the meninges and resulting contrast enhancement (e.g., in tuberculosis; Bilaniuk et al. 1978; Rovira et al. 1980). Normal structures and discrete alterations, however, are generally missed by CT.

None of these limitations apply to MRI. Bone itself does not cause artifacts. Even unenhanced MRI allows visualization of meningeal structures in normal subjects (Davis et al. 1987; Han et al. 1984; Schörner et al. 1988; Tyrell et al. 1987). The subarachnoid space between the cortical surface and the skull appears dark on T1-WI. Within this space a linear structure is seen running parallel to the hemispherical surface. On unenhanced T1-WI this structure shows a relatively low signal intensity (Figs. 2.10 b). According to Tyrell et al. (1987) and in accordance with our own experience, this structure is the dura mater, at least the inner lamina. After contrast medium administration, a slight increase in signal intensity is observed (Fig. 2.10 c). Under normal conditions, the superficial subarachnoid space is homogeneous on T2-WI. Normal meninges cannot be delineated (Fig. 2.10 a).

Abnormal structures and abnormal signal intensities of meninges with tumorous or inflammatory changes can be observed in immunocompetent as well as in AIDS patients (McGeachie and Nelson 1989; Goldsher et al. 1990; Schörner et al. 1988; Tokumaru et al. 1990). In the majority of these cases unenhanced T1-WI have no diagnostic value. After Gd-DTPA administration a pathologically increased contrast enhancement occurs (Fig. 2.11 b). The correlated T2-WI may show a corresponding hyperintense rim partially covering the cortical surface (Fig. 2.11 a). Either imaging modality, contrast enhanced T1-WI or unenhanced T2-WI, can show the meningeal abnormality missed by the other one. This may be due to the fact



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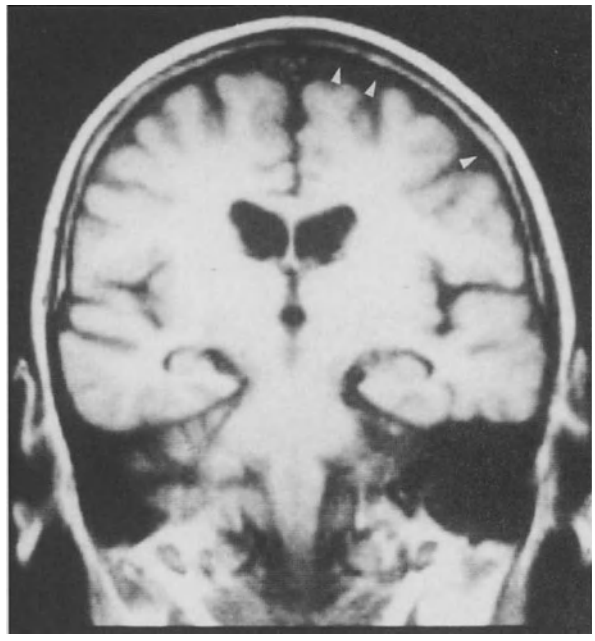

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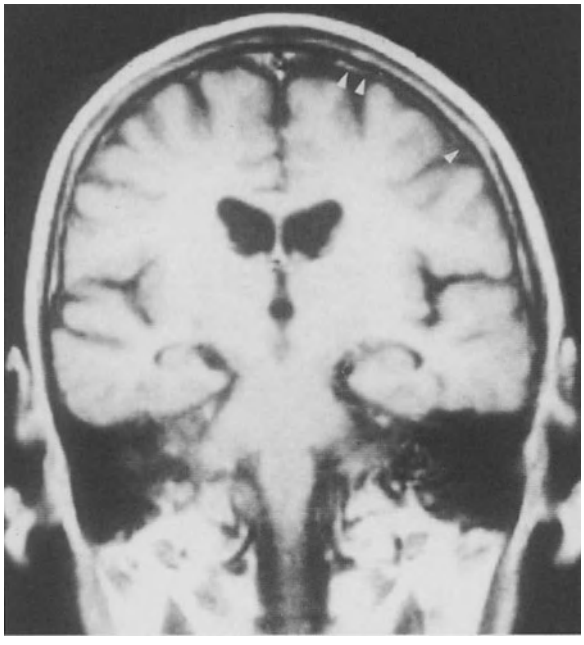
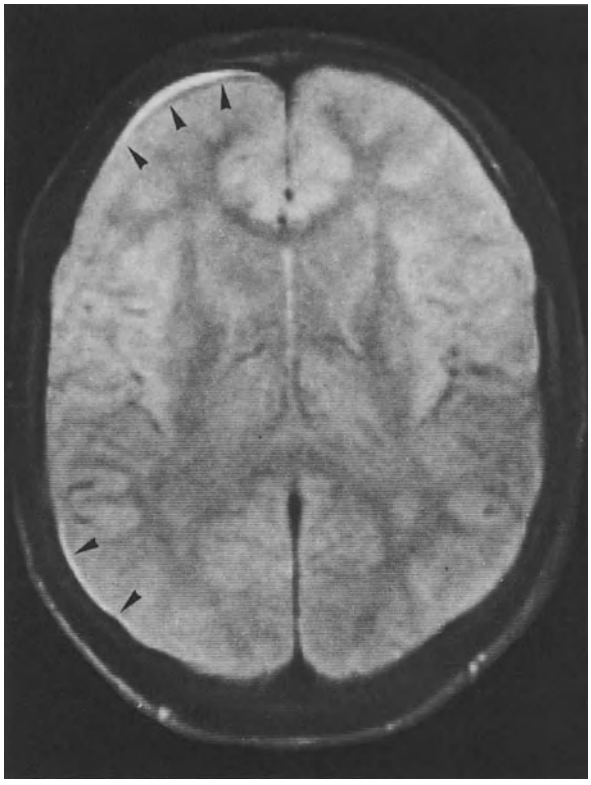


c

Fig. 2.10 a–c. MRI appearance of normal meninges. **a** On moderately T2-WI the CSF has a somewhat lower signal intensity than the brain tissue. Especially the gyri cannot be delineated clearly from the cortex. The space between cortex and inner surface of the skull appears homogeneous; meningeal structures are not visible. **b** On unenhanced T1-WI the external CSF space appears dark. In this space a linear structure running parallel to the inner surface of the skull can be differentiated. The signal intensity of this structure is equivalent to the general parenchymal signal intensity. **c** After administration of 0.1 mmol Gd-DTPA/kg BW an increase in the signal intensity of this meningeal structure is a regular and normal finding

that the thickening of the dura mater and the inflammatory exudation in the subarachnoid space can occur in isolation as well as in combination. Various reports stress the superiority of MRI in the diagnosis of meningeal diseases (Mathews et al. 1989). In an early study by our group, five of six patients with meningitis and with positive MRI examinations had negative CT scans (Schörner et al. 1988). A sound documentation of the frequency and clinical significance of an abnormal appearance of the meninges in AIDS patients is still lacking. Between 1987 and 1989 we prospectively examined 129 AIDS patients by CT and MRI. In seven of these we observed abnormal meningeal structures (Henkes et al. 1990).



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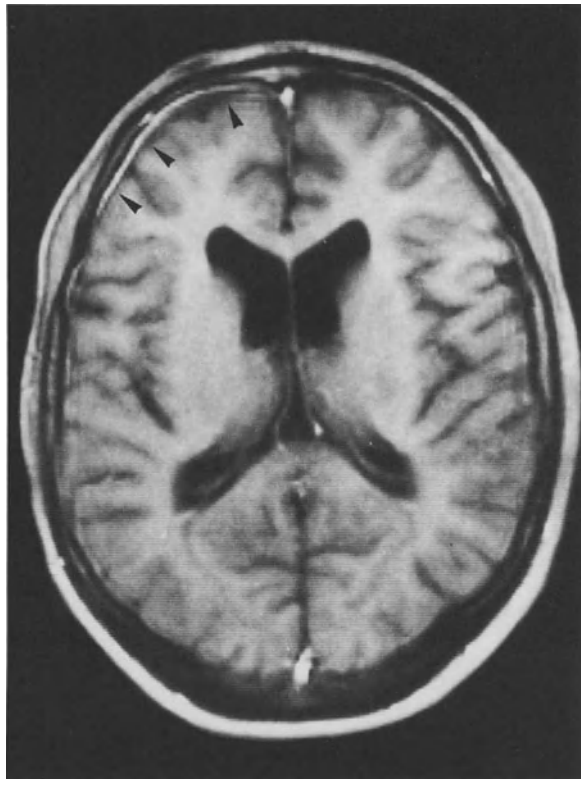

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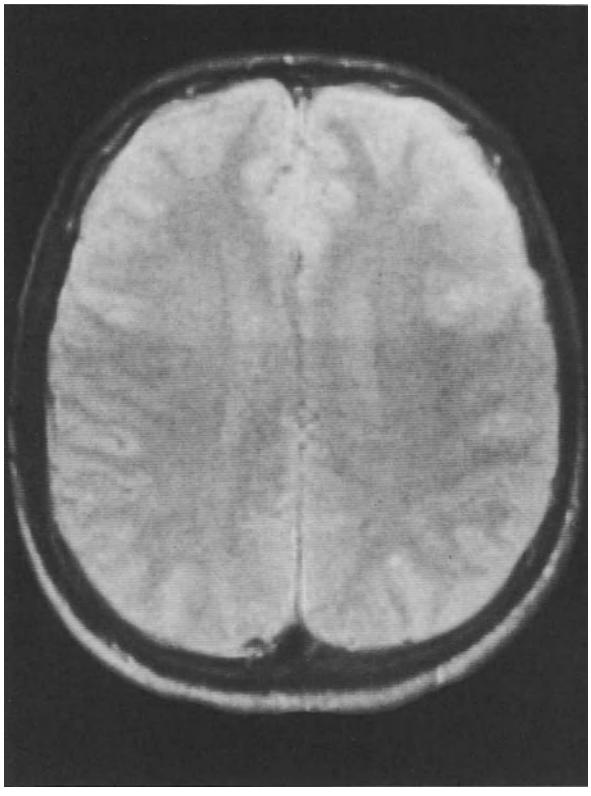

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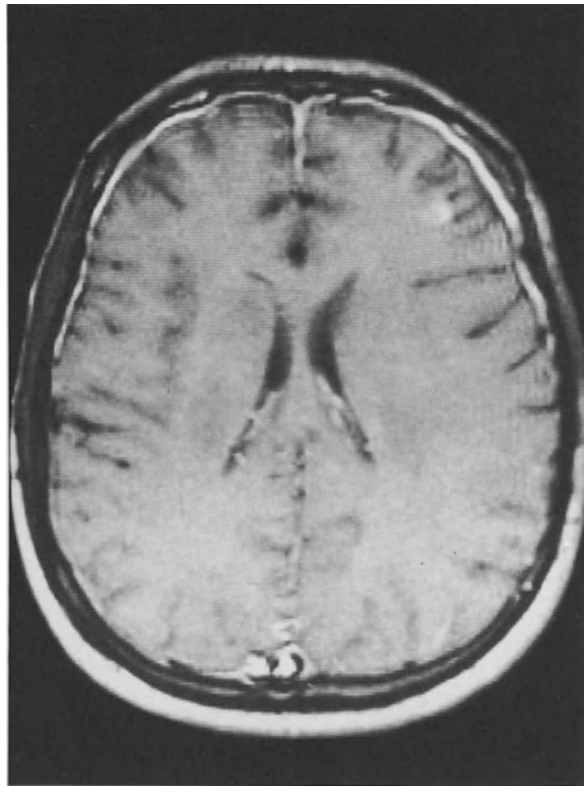


d

◀ **Fig. 2.11 a–d.** Inflammatory meningeal lesions. Over the right frontal cortex, also more discretely over the right parieto-occipital cortex, a rimlike, hyperintense structure *(arrowheads)* seen on T2-WI (**a**) and on contrast-enhanced T1-WI (**b**). This finding was not reproduceable on unenhanced or contrast-enhanced CT scans. The images are from an AIDS patient with severe dementia, headache, and CSF pleocytosis. **c** Meningeal changes can also be observed in patients with cerebral toxoplasmosis; on T2-WI, the affected meninges can be almost isointense to the CSF. **d** Only the contrast-enhanced T1-WI shows the thickening of the dura mater over the frontal cortex

■ CNS Infections

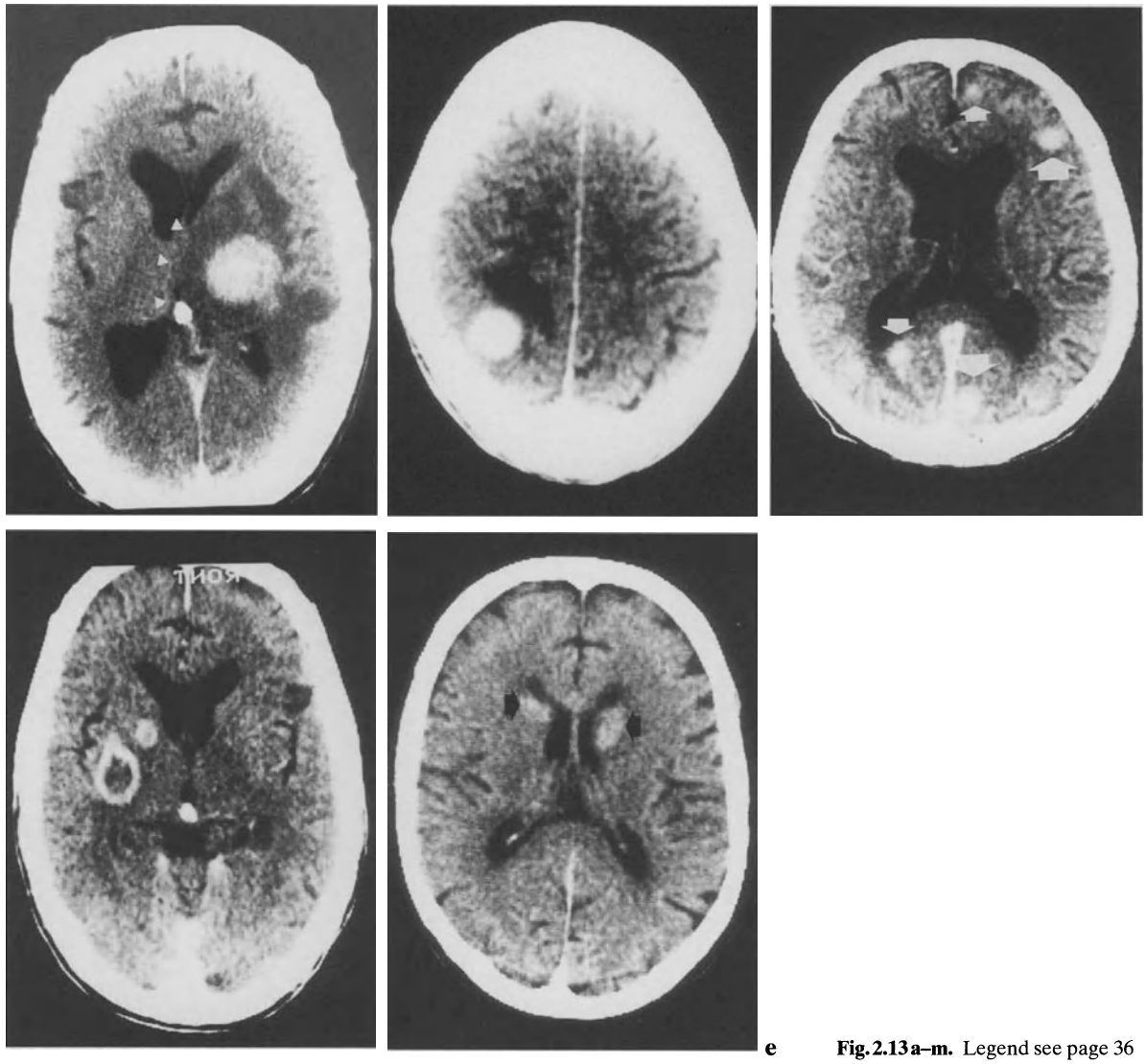
Parasitic Infections of the CNS

Toxoplasmosis

There are various estimates in the literature concerning the frequency of cerebral toxoplasmosis in AIDS patients, varying from 11% (Jordan et al. 1985) to more than 30% (Lang et al. 1989; Pohle and Eichenlaub 1987). Generally, it is the third most fequent opportunistic infection in AIDS patients. The probability of ever developing cerebral toxoplasmosis from the onset of AIDS is about 28% – about 26% within the first 2 years (Grant et al. 1990). After the first episode of CNS toxoplasmosis, the probability of a relapse is about 50% within the first year if no maintenance therapy is administered (Pedrol et al. 1990). In almost all cases the reactivation of a preexisting infection must be assumed. Thus, cultural and regional factors (e. g., eating habits) most probably play a major role in the prevalence of the infection. A wide spectrum of clinical symptoms can be expected, ranging from fever with headache to focal deficits and extending to coma after short prodromal phase (Carrazana et al. 1989, a, b; Enzensberger et al. 1985; Gonzales et al. 1992; Lüscher and Horber 1992; Nath et al. 1993; Noel et al. 1992; Porter and Sande 1992; Renold et al. 1992). Focal seizures are apparently more common in toxoplasmosis than in other cerebral manifestations of AIDS. The analysis of serum and CSF is generally not diagnostic and is particularly unsuitable for ruling out the disease (Horowitz et al. 1983). A negative basal titer for IgG antitoxoplasmotic antibody is a criterion against cerebral toxoplasmosis (Pedrol et al. 1990). EEG and EP can indicate a disturbance in CNS function. However, they do provide no information about the etiology or the exact extension of the underlying disease. Numerous authors recommend stereotactic or open brain biopsy (Alonso et al. 1984, Bedri et al. 1983; Bishburg et al. 1986; Fischl et al. 1985; Horowitz et al. 1983; Levy et al. 1983; Snider et al. 1983). In our experience, this procedure is a diagnostic necessity in only a few cases. It should be performed when at least 2 weeks of antitoxoplasmotic chemotherapy has not improved the patient's condition, and if no clinical clues concerning the etiology of the lesion are available (Anson et al. 1992; Pitchenik et al. 1983; Pohle and Eichenlaub 1987; Reparaz-Padros et al. 1991; Rodesch et al. 1989; Whelan et al. 1983). The mortality-morbidity rate for brain biopsy in AIDS patients has been estimated between 0% and 10% (Rossitch et al. 1990; Zimmer et al. 1992). Use of the polymerase chain reaction for examining the tissue specimen obtained by biopsy increases the sensitivity of this invasive procedure (Holliman et al. 1990). A biopsy prior to radiotherapy is mandatory if a CNS lymphoma is suspected.

In CT, cerebral toxoplasmotic lesions can be seen in a variety of different patterns (Fig. 2.12). They clearly show a predilection for the basal ganglia, thalamus, and corticomedullary junction (Fig. 2.12 a, b). Some authors have reported on solitary toxoplasmotic lesions in 50% of their cases (Moeller and Backmund 1991). Most frequently, in our experience, there are in both hemispheres multiple lesions, which are hypodense on unenhanced scans. After the administration of contrast medium, ring-shaped or nodular enhancement can be seen. The foci show local or general mass effect and are surrounded by edema. A gyral pattern of contrast enhancement is rarely observed. Atypical findings are the abscence of edema, mass effect, and even contrast enhancement (Bishburg et al. 1989; Ramsey and Geremia 1988). In patients with multiple lesions several patterns may coexist (Post et al. 1983). The enhancing properties of the lesions are, on the one hand, to some extent dependent on the immunological reactivity of the host. A strong immune reaction leads to a severe disturbance of the blood-brain barrier and to massive contrast enhancement (Gaston et al. 1985). On the other hand, contrast-enhancement indicates the acuteness of a lesion during the course of the disease. Both should regress under antitoxoplasmotic chemotherapy.

Further lesion patterns have been described in the literature. Hemorrhagic necroses can occur and are primarily hyperdense on unenhanced CT scans (Fig. 2.12 e; Casado-Naranjo et al. 1989; Christ et al. 1986; Moeller and Backmund 1991; Revel et al. 1992; Taccone et al. 1992; Wijdicks et al. 1991). Subependymal necrosis may result in periventricular contrast enhancement (Cohen and Koslow 1985). The choroid plexus can be affected (Bourgouin et al. 1992). Soli-



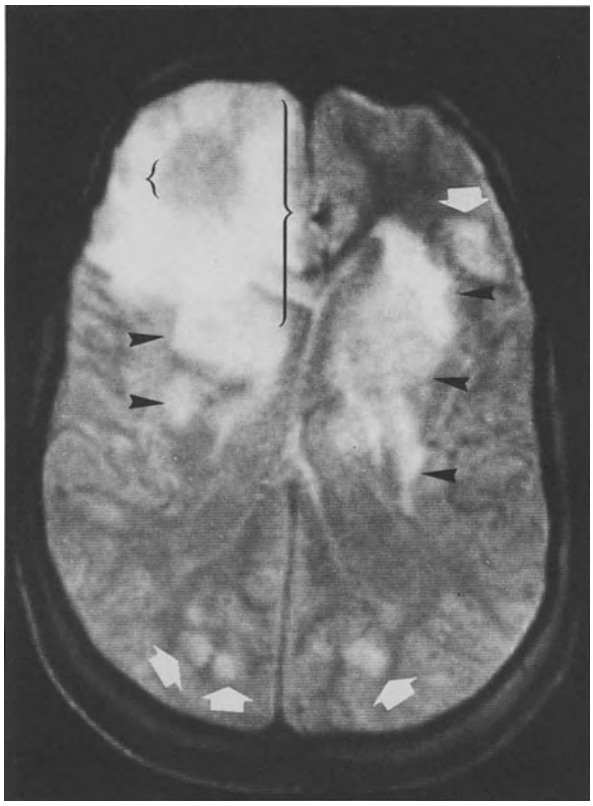
a–c

d **e**

Fig. 2.13a–m. Legend see page 36 ▶

Fig. 2.12a–e. CT appearance of cerebral toxoplasmosis: sites of predeliction, lesion patterns. Toxoplasmotic lesions may appear as large, tumorlike masses, especially in the region of the basal ganglia. **a** The lesion is surrounded by extensive perifocal edema and causes a considerable mass effect *(white arrowheads)*. **b,c** The corticomedullary junction is a second site of predilection for this type of lesion *(white arrows)*. **d** Similar to the appearance of bacterial abscesses, ring-enhancing lesions with a central necrotic compartment occur. Primary hyperdense, hemorrhagic lesions are atypical in toxoplasmosis. On the other hand, partially hemorrhagic parenchymal brain lesions in AIDS patients are most probably due to toxoplasmosis. **e** CT finding in a case with confirmed CNS toxoplasmosis. The head of the caudate nucleus is bilaterally hyperdense. During antitoxoplasmotic therapy the patient improved considerably; the hyperdensity resolved, as documented by follow-up CT examinations

tary midbrain toxoplasmosis involving the red nucleus and the rostral tegmentum of the pons was observed as the cause of ipsilateral ophthalmoparesis and contralateral ataxia and may lead to inferior olivary hypertrophy (Kure et al. 1989a). Diffuse toxoplasmotic panencephalitis is extremely rare. Lang et al. (1989) described multiple microglial nodules with bradyzoites and tachyzoites as the exclusive manifestation of cerebral toxoplasmosis. In our experience this type of manifestation is not detected by CT (Carrazana et al. 1989a; Levy et al. 1985; Pohle and Eichenlaub 1987). A regression of the toxoplasmotic foci can be expected from the second week after the initiation of



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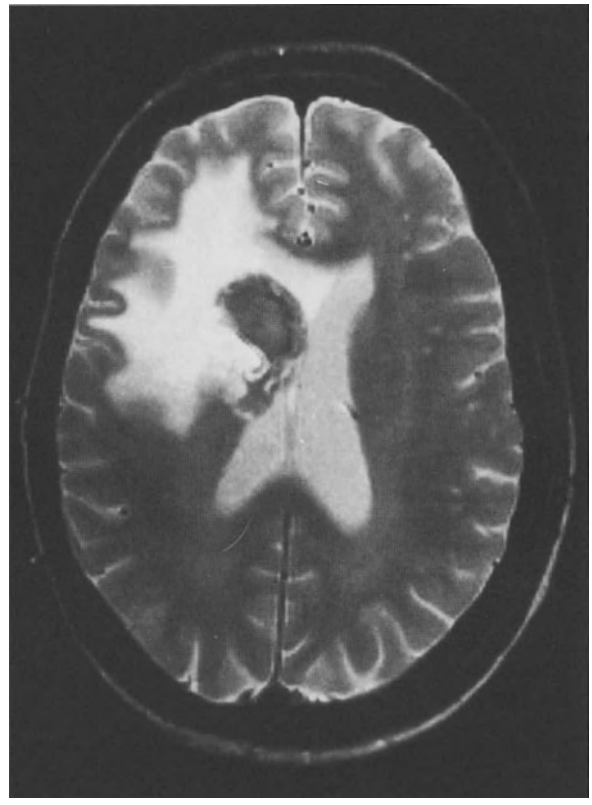

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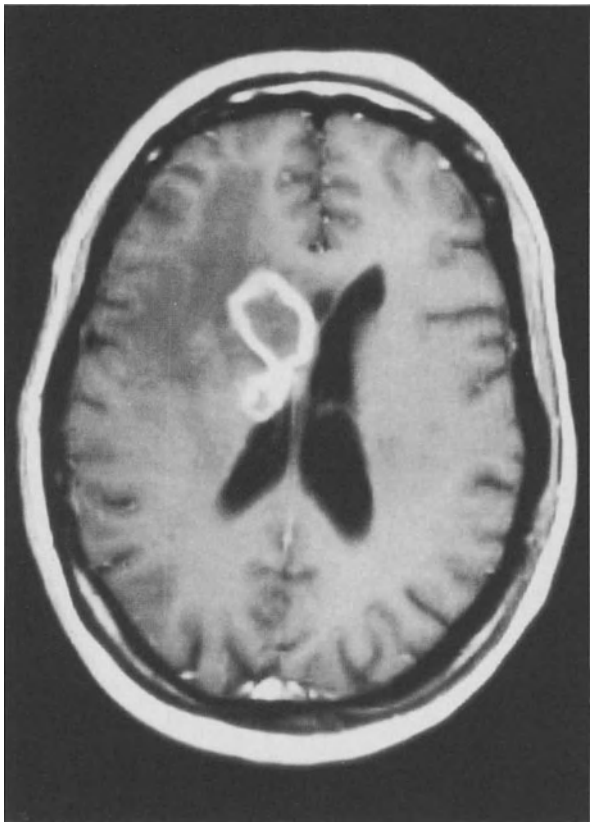

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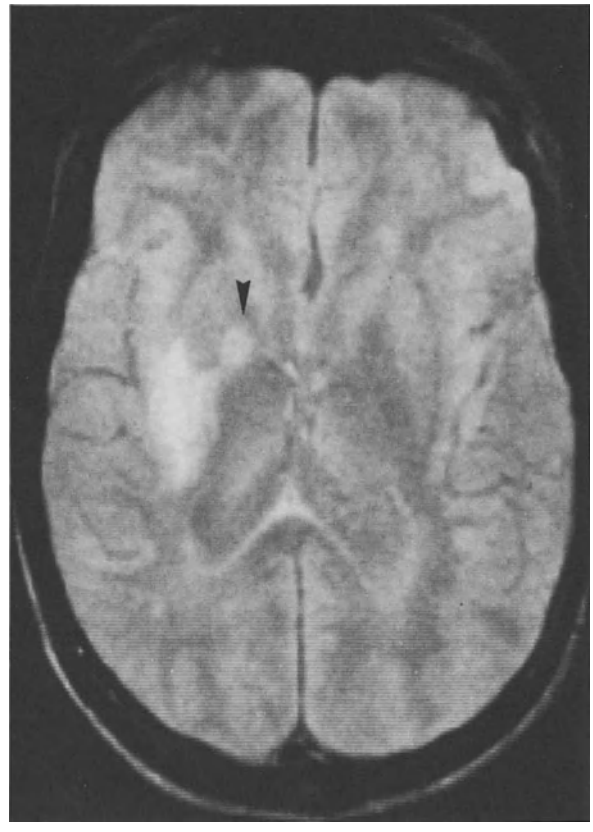

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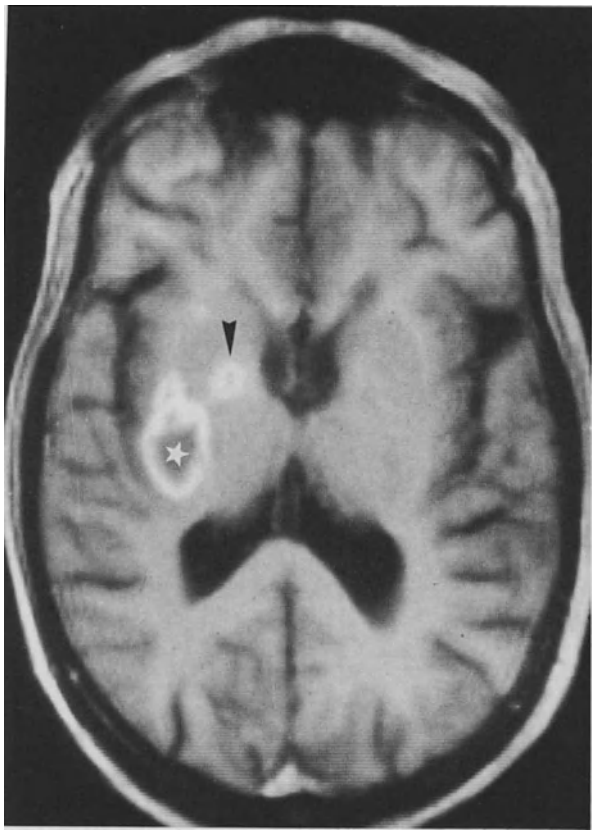
Fig. 2.13 a–d



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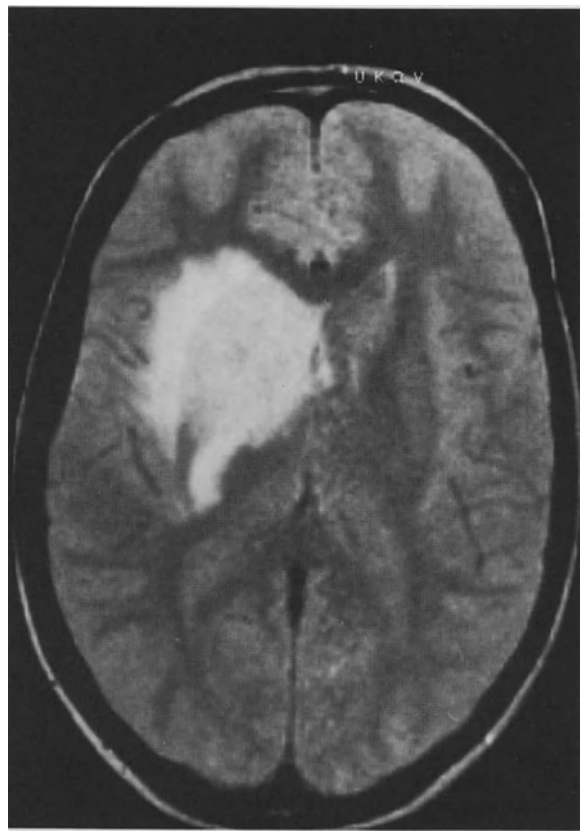

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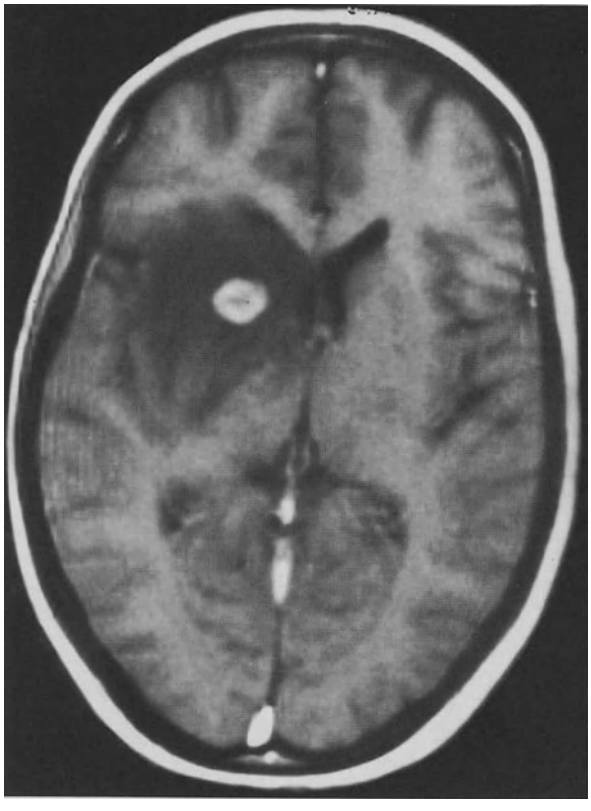

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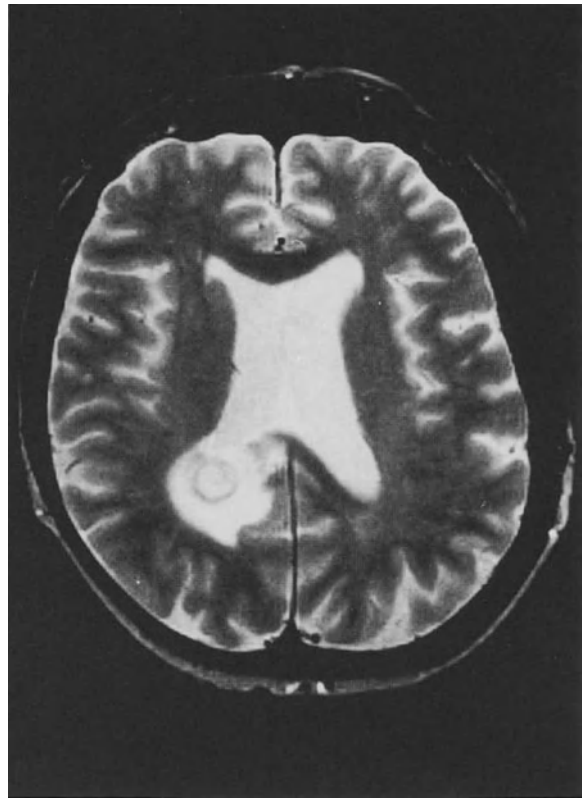

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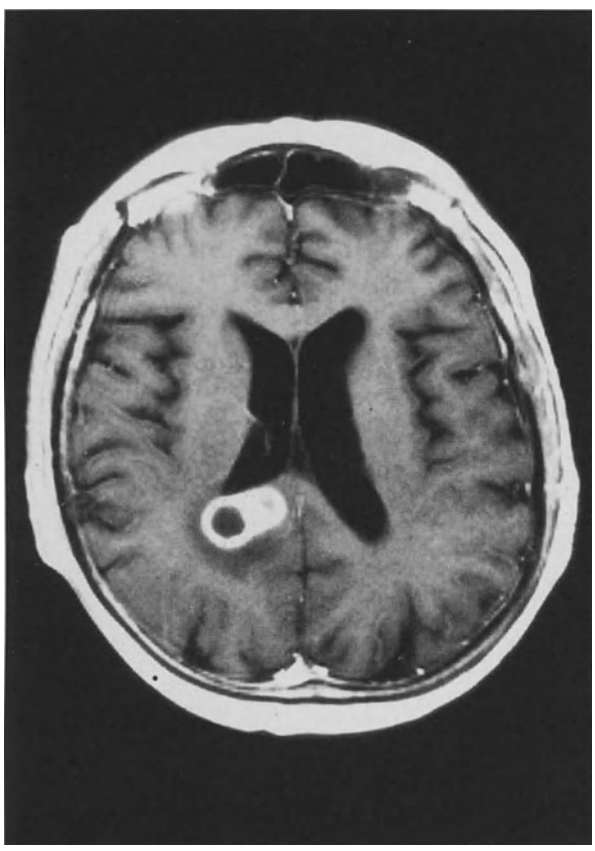
Fig. 2.13 e–h



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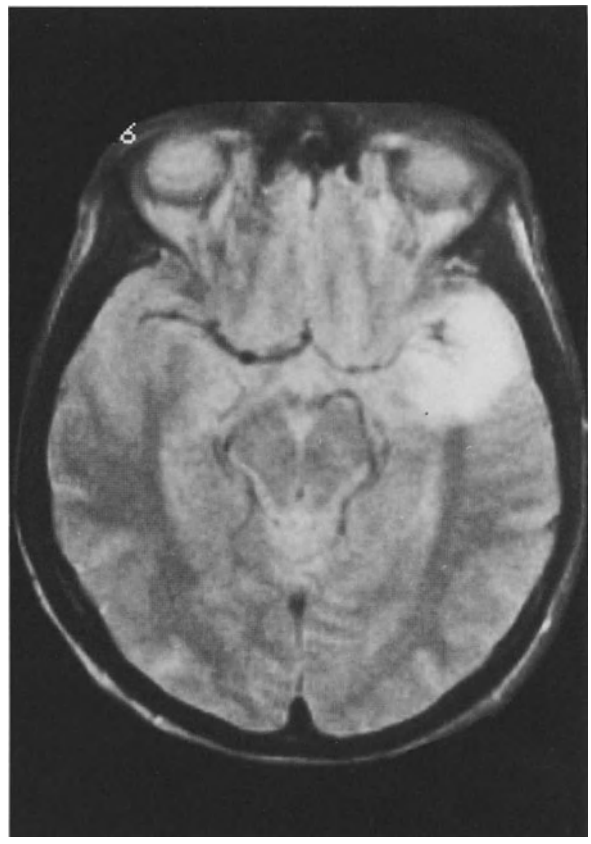

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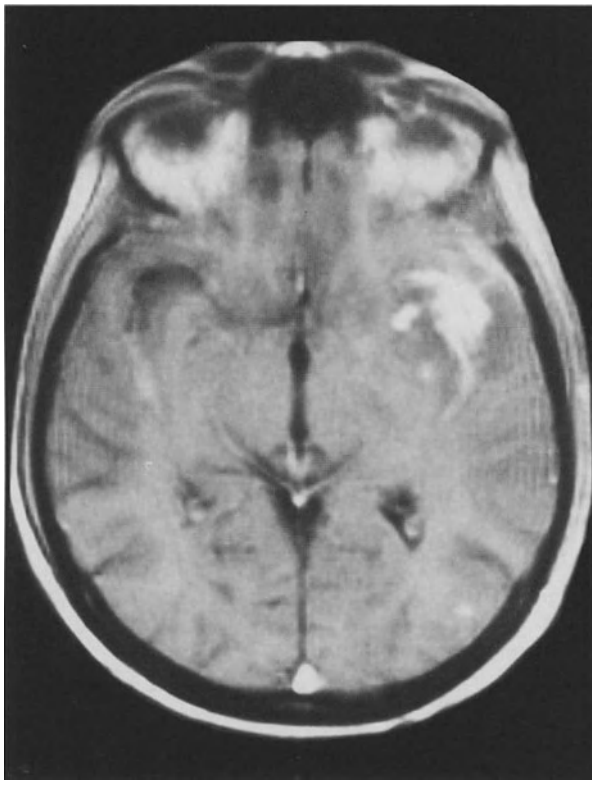

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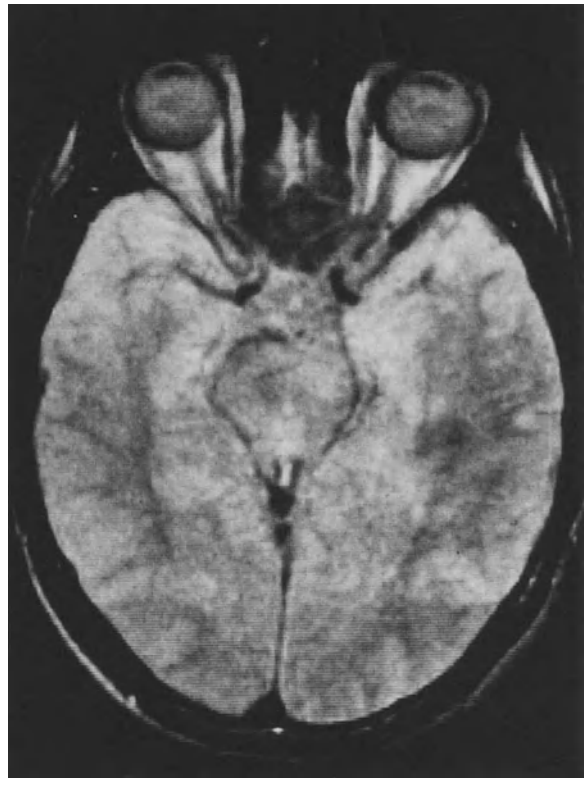

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Fig. 2.13i–l

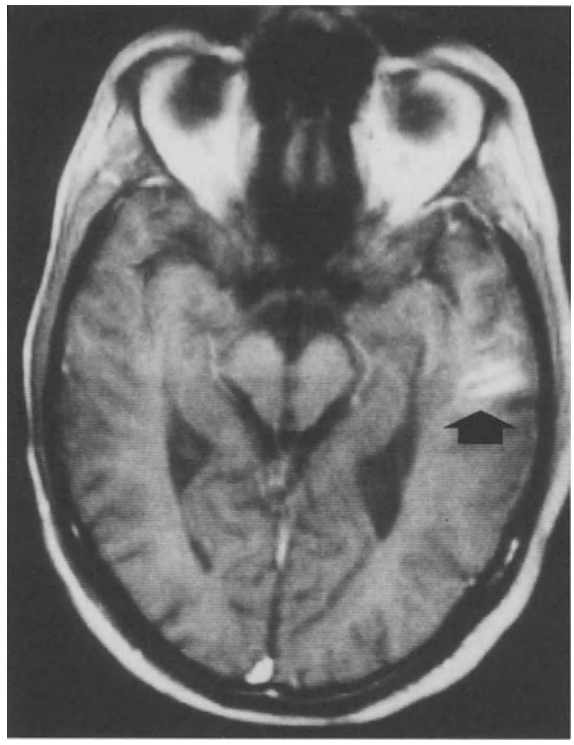


Fig. 2.13 m

Fig. 2.13 a–m. MRI appearance of cerebral toxoplasmosis; sites of predeliction, lesion patterns. **a** Multiple hyperintense lesions can be seen in the corticomedullary junction and the region of the basal ganglia of both hemispheres. Almost the whole left frontal lobe is affected by a large abscess *(small bracket)* and the perifocal edema *(large bracket)*. Note the considerable mass effect from this lesion. In some cases, the toxoplasmotic lesion cannot be distinguished from a necrotic tumor with a central mass, perifocal edema (**b**), and peripheral ring enhancement (**c**). T2-WI (**d**) are very sensitive for detecting toxoplasmotic lesions *(black arrowhead)*. These are depicted mostly as inhomogeneously hyperintense foci. The differentiation between lesion and perifocal edema is usually not possible. Gd-DTPA enhanced T1-WI are suitable for detecting areas with a disrupted blood-brain barrier. Thus a differentiation between edema and abscess is possible. **e** Ring-enhancing abscess; its central necrotic compartment *(asterisk)* and a small daughter abscess *(black arrowhead)* can be clearly delineated. In patients with preserved immunological reactivity, extensive edema (**f**) can be caused by relatively small focus (**g**). **h,i** The subependymal region is an infrequent site of toxoplasmotic lesions. **j,k** The concurrence of multiple etiologies can cause unusual patterns: a meningoencephalitic lesion of the left temporal region, the manifestation of toxoplasmosis and atypical mycobacteriosis. **l** So-called "isomagnetic lesions" are atypical MRI findings in cerebral toxoplasmosis: a normal T2-WI obtained after chemotherapy of an AIDS patient with confirmed cerebral toxoplasmosis. **m** The corresponding contrast-enhanced T1-WI revealed a residual focus with disrupted blood-brain barrier in the right temporal lobe *(black arrow)*. In such lesions, a local disturbance of the blood-brain barrier is present. However, the alteration is not sufficient to cause edema in an amount that allows detection by unenhanced T2-WI

medical treatment. The residues of toxoplasmotic foci are glial scars and pseudocystic substance loss. Coarse parenchymal calcifications are observed in about 30% of successfully treated cases (Moeller and Backmund 1991). Dina (1991) pointed out that a lesion pattern with subependymal spread, ventricular encasement, hyperdensity on unenhanced CT scans, and hypointensity on T2-WI of a focally enhancing mass most probably indicates a primary CNS lymphoma and is not well compatible with the diagnosis of a CNS toxoplasmosis.

Altogether, CT plays a central role in confirming or ruling out toxoplasmotic lesions in AIDS patients. A definite etiological diagnosis often requires follow-up CT examinations to demonstrate the therapeutic effect of antitoxoplasmotic treatment.

Similar criteria apply to MRI as to CT concerning the diagnosis of cerebral toxoplasmosis. MRI in most cases also shows multiple lesions in both hemispheres in the typical areas. Colliquated components of the "abscesses" and perifocal edema are hyperintense on T2-WI. Frequently a clear distinction between mass and edema is not possible, however (Fig. 2.13 a). Solid or coagulated necrotic components of the abscess like lesions appear as areas with low signal intensity in the center. This has been described as the "target sign" (Kupfer et al. 1990; Post et al. 1986 b). In the same patient, lesions with a hypointense center and homogeneously hyperintense lesions can coexist. The finding of a partially necrotic focus allows no conclusions regarding the acuteness or etiology of the lesion (Krestin et al. 1986; Kupfer et al. 1990; Post et al. 1986 b). The mass effect, best judged on T1- or Pd-WI, is determined mainly by the size of the lesion. It can be tremendous. In smaller or more peripheral lesions, however, it can almost be missing. After contrast medium administration, T1-WI shows ring-shaped, polycyclic or homogeneous nodular patterns of enhancement. Active toxoplasmotic lesions without contrast enhancement are extremely rare (e. g., in advanced stages of immunodeficiency). Bearing the above considerations in mind, we can regard the intensity of contrast enhancement as a criterion of disease activity. It therefore appears suitable for follow-up examinations during chemotherapy.

Many papers have focused on the higher diagnostic sensitivity of MRI compared to CT in the detection of toxoplasmotic lesions (Henkes et al. 1987; Krestin et al. 1986; Kupfer et al. 1990; Levy et al. 1986). A normal MRI finding, however, does not rule out diffuse toxoplasmosis. Arendt et al. (1991) observed two patients who presented clinically with dementia, fever, and basal ganglia dysfunction. The MRI examination was

normal in one and revealed minute basal ganglia lesions in the other. The autopsy showed widespread toxoplasmotic brain lesions in both patients. Due to the terminal breakdown of the immune system, an inflammatory tissue reaction to the pathogenic agent was almost missing.

If T2-WI shows multiple hyperintense lesions of different sizes and locations without mass effect or contrast enhancement, PML (see below) is one of the major differential diagnoses. Lesions of other etiologies (e. g., cerebral lymphoma) can coexist with toxoplasmotic "abscesses" but generally cannot be differentiated from them with sufficient certainty. The average size of toxoplasmotic foci tends to be smaller than that of lymphomas. Kupfer et al. (1990) discussed exclusive involvement of the white matter as an additional feature of primary CNS lymphomas.

An intramedullary manifestation of toxoplasmosis is rare. The neuropathological material of Lang et al. (1989) comprised three cases with toxoplasmosis of the spinal cord. Focally increased signal intensity on T2-WI and thickening of the spinal cord were observed (Mehren et al. 1988; Poon et al. 1992). So-called isomagnetic medullary lesions, i. e., lesions isointense in all sequences before administration of a paramagnetic contrast material but contrast enhancing, may be caused by toxoplasmosis (Kayser et al. 1990).

Nontoxoplasmotic Parasitoses

Other parasitic infections in AIDS patients, either opportunistic or coinciding, have been reported. Their clinical significance, however, is generally far less than that of toxoplasmosis. Del Castillo et al. (1990) from Argentina observed a tumorlike mass in an AIDS patient with severe hemophilia. At surgery the mass turned out to be caused by a *Trypanosoma cruzi* infection (Chagas' disease, American trypanosomiasis). The authors discussed whether the HIV infection is responsible for both the delayed reactivation of trypanosomiasis and the atypical tumorlike cerebral manifestation of the disease. In the cases published by Glückstein et al. (1992) and by Rosenberg et al. (1992) Chagas' disease occurred as a reactivated, opportunistic infection in AIDS. Despite the high frequency of *Pneumocystis carinii* pneumonia in AIDS patients, cerebral manifestation of this infection is extremely rare (Mayayo et al. 1990). As a cause of multifocal meningoencephalitis with multiple hypodense cerebral lesions, seen in an AIDS patient with a rapidly fatal course of the disease, Anzil et al. (1991) isolated the parasite *Leptomyxid ameba. Acanthamoeba* can give rise to thrombo-occlusive vasculitis with hemorrhagic and necrotizing parenchymal lesions (Gardner et al. 1991). The incidence and outcome of *Plasmodium falciparum* infection, either as "uncomplicated" or as cerebral malaria, do not seem to be affected by HIV (Leaver et al. 1990; Simooya et al. 1988). Neurocysticercosis has been reported in association with HIV infection (Thornton et al. 1992).

Viral Infections of the CNS

HIV Encephalitis

HIV encephalitis is basically a neuropathological diagnosis. HIV-1 or, rarely, HIV-2 (Livrozet et al. 1990; Schneider et al. 1990) are the presumed pathogenic agents; viral persistence in the brain is most probably a prerequisite (Ho et al. 1985; Kaiser et al. 1990). Other terms have been proposed, including (multifocal) giant cell encephalitis (MGCE), multinucleated cell encephalitis, and subacute encephalitis with multinucleated cells. The key neuropathological findings are multinucleated giant cells, rod cells, macrophages, lymphocytic infiltrates, focal necroses, and tubuloreticular cell inclusions (Mirra and Del Rio 1989). In order of decreasing frequency the white matter, subcortical gray matter, and cortex are affected (Budka et al. 1991). The predominant damage of cortical structures is rare (Gray et al. 1991 b). In cases with HIV myelopathy, degeneration of the internal capsule can be an associated finding (Rhodes et al. 1989).

HIV encephalitis is a *multifocal* process that can overlap with opportunistic infections as well as with *diffuse* variants of HIV-induced parenchymal damage (progressive diffuse leukoencephalopathy, PDL; see below). From a clinical point of view, the cognitive impairment is predominant. Three different clinical types of cerebral white matter disease in HIV-infected patients can be distinguished: a multiple sclerosis-like illness that precedes other HIV-associated symptoms, a similar disease which manifests concomitantly with the HIV infection, and a fulminating leukoencephalopathy that occurs during the early stages of HIV infection (Berger et al. 1992). Gray et al. (1991 a) reported two cases of a fulminating multiple sclerosis-like leukoencephalopathy in AIDS patients, with the CT appearance of multiple hypodense, nonenhancing lesions. Rosenhall et al. (1989) interpreted their own neurophysiological findings as evidence of an early but clinically silent dysfunction of the brain stem in-

duced by HIV. Disturbances of memory functions and of concentration, slowing, apathy, and social withdrawal are typical symptoms. In the final stage, dementia, akinetic mutism, pareses, long-tract signs, and incontinence are found (Navia et al. 1986). The mechanisms and substrates of tissue damage have been discussed extensively. Demyelination, formation of vacuoles, and increased vascular permeability are examples of the pathogenetic concepts (Artigas et al. 1989; De Girolami et al. 1990).

CT is not diagnostic in the MGCE variant of HIV encephalitis. In most cases with neuropathologically confirmed HIV encephalitis, CT shows only brain atrophy (Davenport et al. 1992). Post et al. (1988) reported on one case with a meningeal lesion, better shown by contrast-enhanced CT than by T2-WI. The authors interpreted the finding as a correlate of HIV meningitis.

Beside the nonspecific finding of brain atrophy, patchy and multifocal white matter abnormalities are a correlate of MGCE in MRI (De Gans and Portegies 1989; Fig. 2.14). A direct comparison of neuropathological and MRI findings, however, demonstrated the poor sensitivity of MRI in detecting microglial nodules, diffuse white matter gliosis, and lesions located near CSF spaces (Grafe et al. 1990; Hawkins et al. 1992). In some cases, a local accentuation of tissue alteration with corresponding clinical symptoms and focal deficits can be observed. A severe loss of Purkinje's cells, appearing as hyperintense lesions of the cerebellum on T2-WI, causes a subacute cerebellar syndrome (Graus et al. 1990). The subcortical gray matter (e. g., the putamina) can be affected symmetrically (Chrysikopoulos et al. 1990; Kodama et al. 1991). Holmes et al. (1992) discuss whether central pontine myelinolysis can be induced by HIV. Lang et al. (1992) attribute a giant intracranial aneurysm either to the HIV infection or to the administration of zidovudine in high doses. In a rare case of pediatric AIDS presenting with ptosis, nystagmus, and sixth-nerve palsy, MRI was superior to CT in revealing the brain stem lesions, which at autopsy proved to be HIV-induced necrotizing encephalitis and vasculitis (Raphael et al. 1989). Necrotic HIV leukoencephalitis was also reported as the cause of space-occupying lesions (Carcaba et al. 1991). Berger et al. (1992) described the findings in a patient with relapsing and remitting focal HIV-associated leukoencephalopathy. In this case with a multiple sclerosis-like course of the disease, MRI follow-up examinations revealed the disappearance of some cerebral lesions and the progression of others during prednisone and zidovudine therapy. Zenz et al. (1992) treated a child suffering from HIV encephalopathy with zidovudine. A regression of white matter lesions was shown by MRI seven months after the onset of chemotherapy.

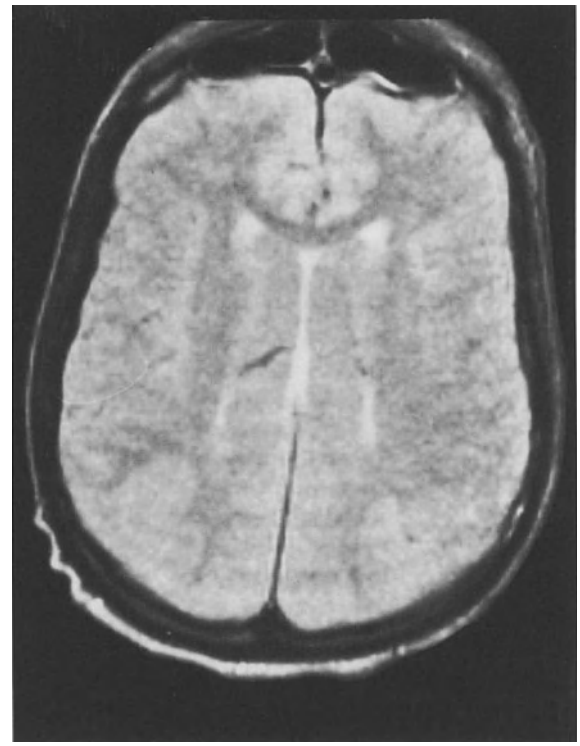
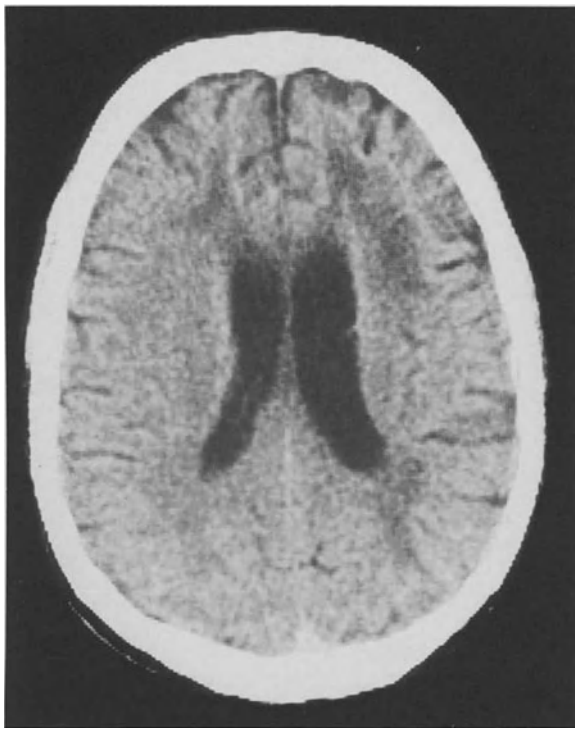


Fig. 2.14. Periventricular white matter lesions in a 28-year-old, demented AIDS patient

Proton MR spectroscopy is a potentially useful method for detecting CNS involvement in AIDS patients. In patients with AIDS dementia, reduced levels of N-acetyl aspartate relative to creatine and elevations in choline containing compounds were demonstrated (Jarvik et al. 1993; Menon et al. 1992).

Progressive Diffuse Leukoencephalopathy

PDL is a CNS manifestation of AIDS that is often not recognized clinically. The exact incidence rate is not known. Kleihues et al. (1985) introduced the term and reported on two cases, based on neuropathological data. In the transpose article published by Lang et al. (1989), PDL was observed in 10 % of neuropathologically examined brains obtained from AIDS patients. Thus, PDL seems to be more frequent than MGCE. The leading symptom is dementia, together with progressive paraparesis or other focal deficits. The process is located primarily in the frontal white matter and centrum semiovale. It is associated with a de-



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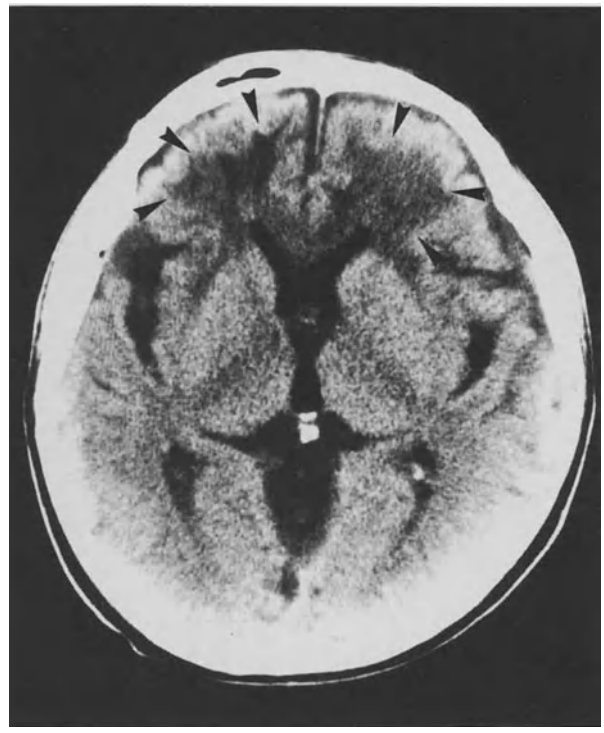

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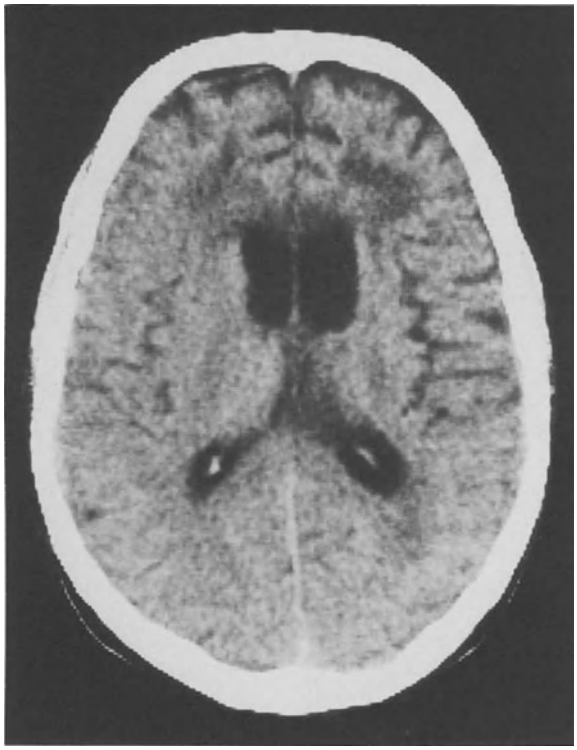
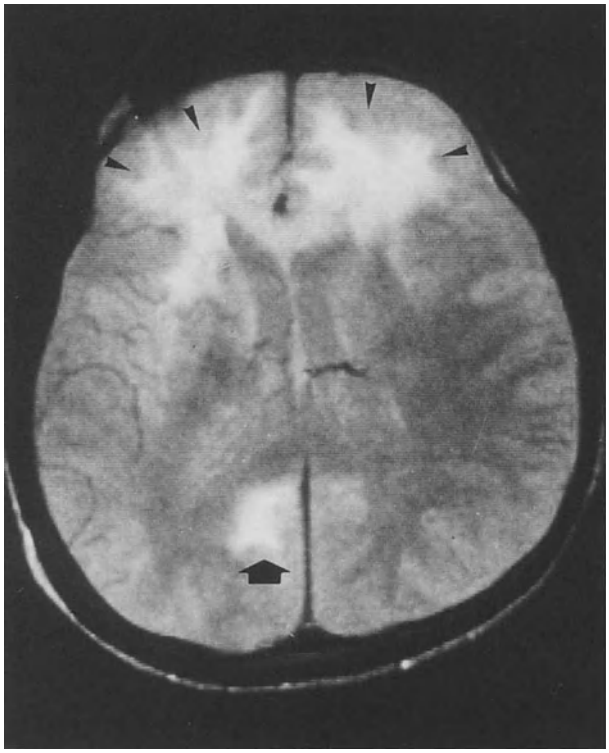


c

Fig. 2.15 a–c. CT appearance of progressive diffuse leukoencephalopathy. The key findings in PDL are confluent, hypodense areas of both frontal lobes (*black arrowheads,* **b**). Similar to PML lesions, these areas are neither contrast enhancing, nor do they cause mass effect. PDL can be accompanied by an almost normal width of ventricles and sulci (**a**) as well as by internal or external brain atrophy of various degrees (**b, c**). Clinically a profound psycho-organic syndrome or dementia is present

scending wallerian degeneration of the pyramid tract. The subcortical U fibers are spared. Concerning the etiology and the pathogenesis of the disease, various agents such as papovavirus, CMV, and HIV or an interaction of several viruses have been the subject of discussion. PDL is now regarded as a morphological variant of HIV leukoencephalopathy. Artigas et al. (1989) described diffuse demyelination, infiltration of macrophages, and formation of vacuoles as morphological correlates of what appears as the PDL pattern on CT and especially on MRI images. PDL may coincide with vacuolar myelopathy (Maier et al. 1989). In the neuropathology-based nomenclature, PDL is listed under the degenerative type and diffuse diseases of the white matter. The proposed general name is HIV leukoencephalopathy (Budka et al. 1991).



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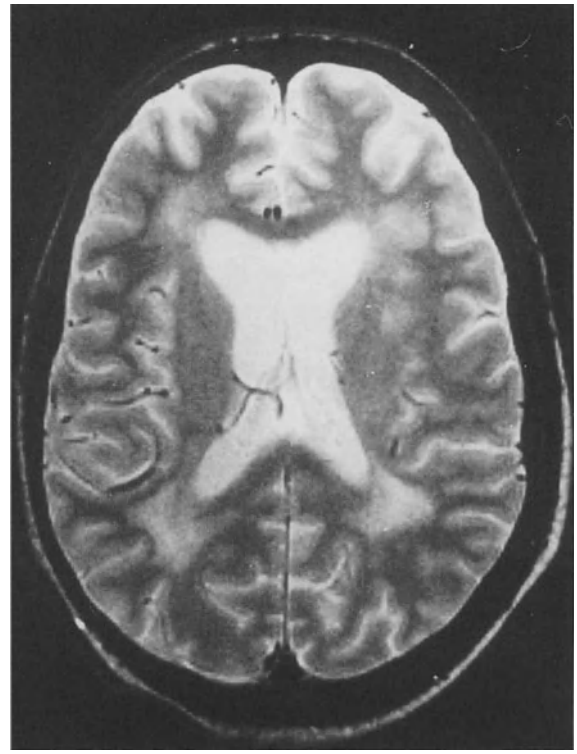

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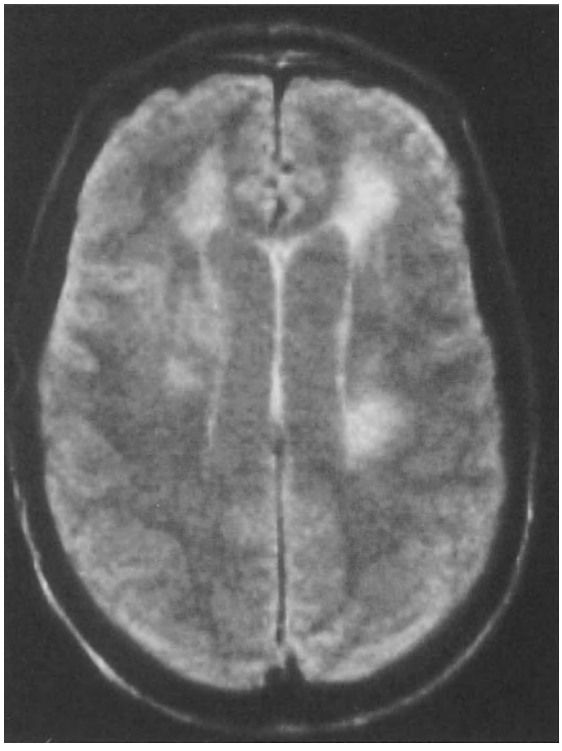

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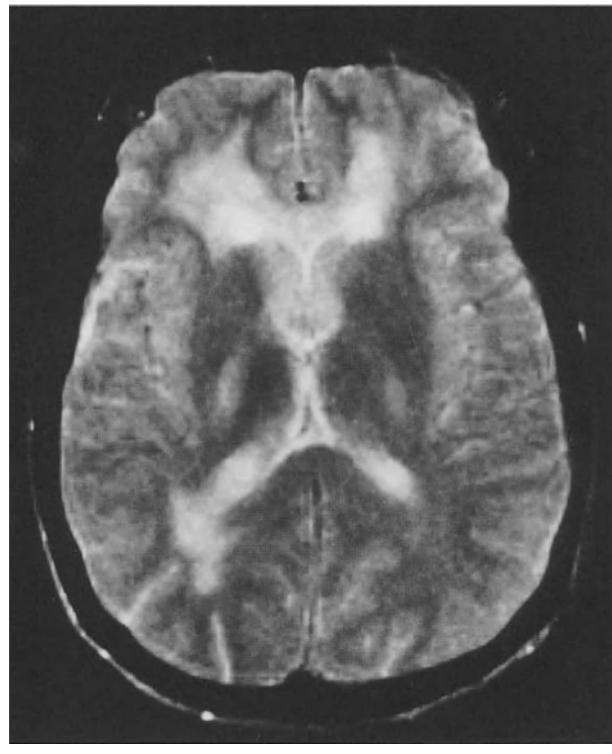

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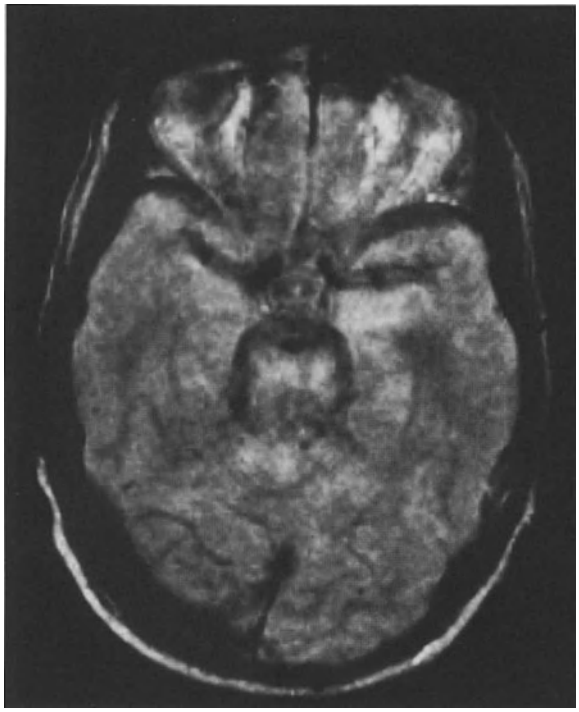

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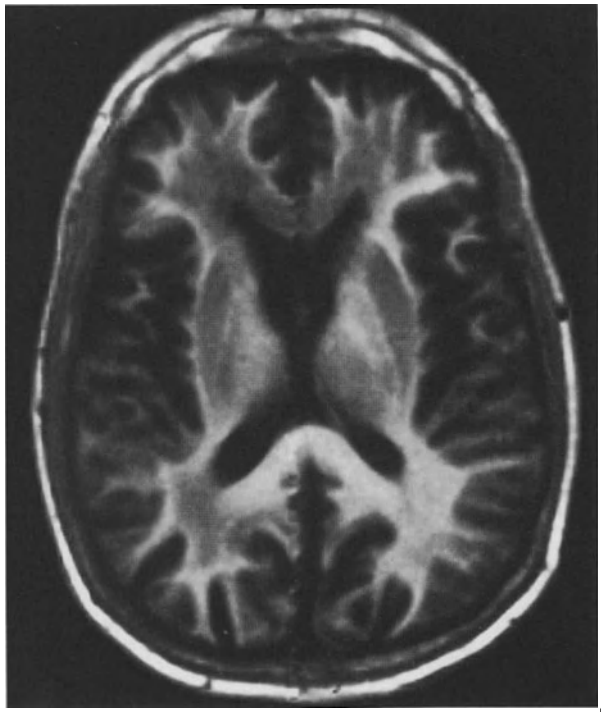


f

▲
◀ **Fig. 2.16 a–f.** MRI appearance of progressive diffuse leukoencephalopathy. The pattern has basically the same distribution as known from CT. As expected, the affected frontal white matter is hyperintense on T2-WI (**a–e**) and hypointense on T1-WI (**f**). Additional sites of demyelination, for example, in the occipital lobe (**a, b**) or along the internal capsule (**d**) are frequently detected by T2-WI. In patients with PDL, MRI frequently shows an increased signal intensity of the brain stem (**e**). This finding corresponds to wallerian degeneration of the descending tracts. A further feature of the PDL pattern is the sparing of the subcortical U fibers. This can be seen very clearly on heavily T1-weighted inversion recovery images (**f**)

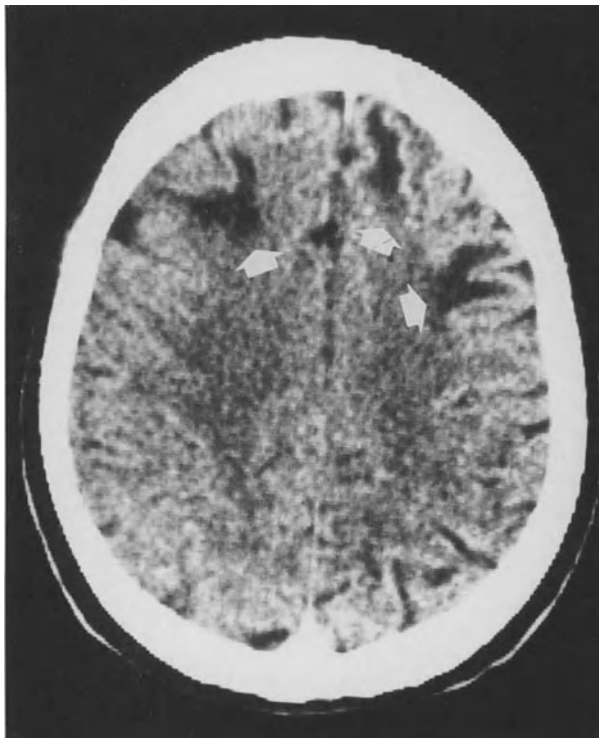
Further, anecdotal reports can be found in the literature (Helweg-Larsen et al. 1986; Levy et al. 1985, 1986 b; Snider et al. 1983; Vago et al. 1990). The CT appearance of PDL is quite characteristic (Fig. 2.15). In both frontal lobes the white matter shows confluent areas of reduced density. The lesion appears homogeneous, is strictly confined to the white matter, and shows no mass effect or contrast enhancement. In the early stages of the disease, diagnostic difficulties can be due to the fact that even under normal circumstances the white matter is of a slightly lower density compared to the cortex. In PDL this contrast is increased. As far as follow-up data are available, the white matter hypodensity seems to be progressive in the course of the disease. Thus, repeated examinations may facilitate the diagnosis.

In one patient of the series of Levy et al. (1985) MRI revealed a "prolongation of T2 relaxation time bifrontally – compatible with edema or inflammatory," as the authors concluded. They were probably the first to describe the MRI appearance of PDL in AIDS (Budka et al. 1988; Helweg-Larsen et al. 1986).

For detecting the bilateral and confluent lesions of PDL by means of diagnostic imaging, MRI is superior to CT because of the inversion of contrast between gray and white matter. On T2-WI the normal white matter is slightly hypointense to the cortex. Demyelinated lesions, however, are hyperintense to the cortex and white matter on T2-WI (Fig. 2.16). Thus a qualitative, not a quantitative change as in CT, develops. The correlation of neuropathological and imaging findings has shown that both CT and MRI fail to detect morphological sequelae of the cerebral HIV infection, such as diffuse microglial nodules, or to show the true extension of the HIV-induced parenchymal damage (Chrysikopoulos et al. 1990; Grafe et al. 1990).

Progressive Multifocal Leukoencephalopathy

PML shows a certain predilection for the parietal region. The cerebellum and temporal lobe are also frequently affected. DNA-containing viruses (JC, SV40, and BK viruses) have proven to be the pathogen



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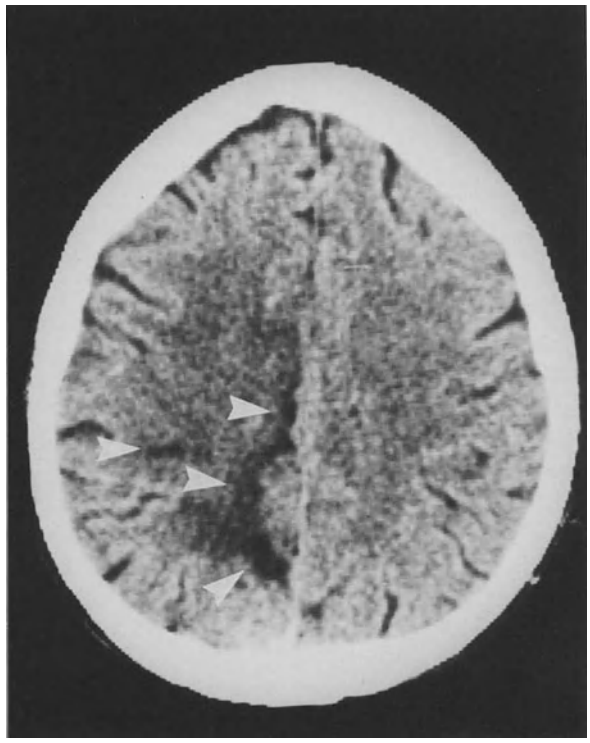

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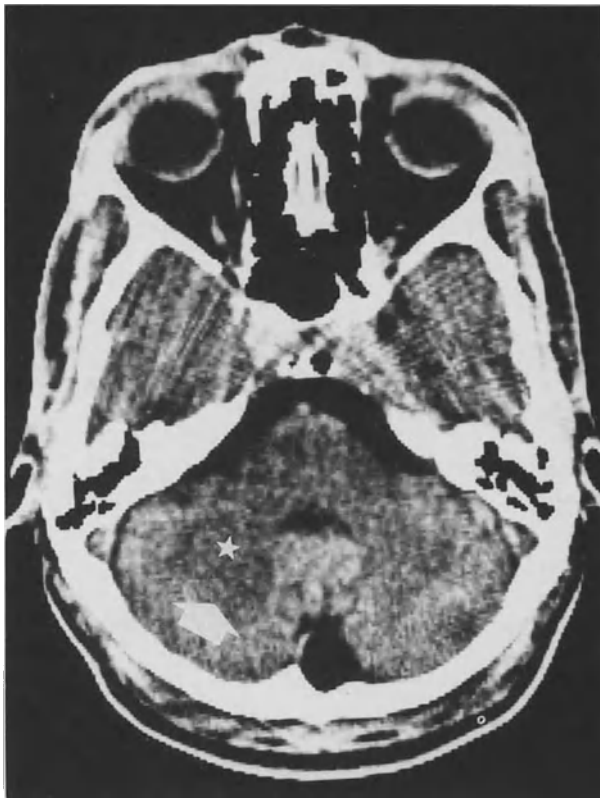

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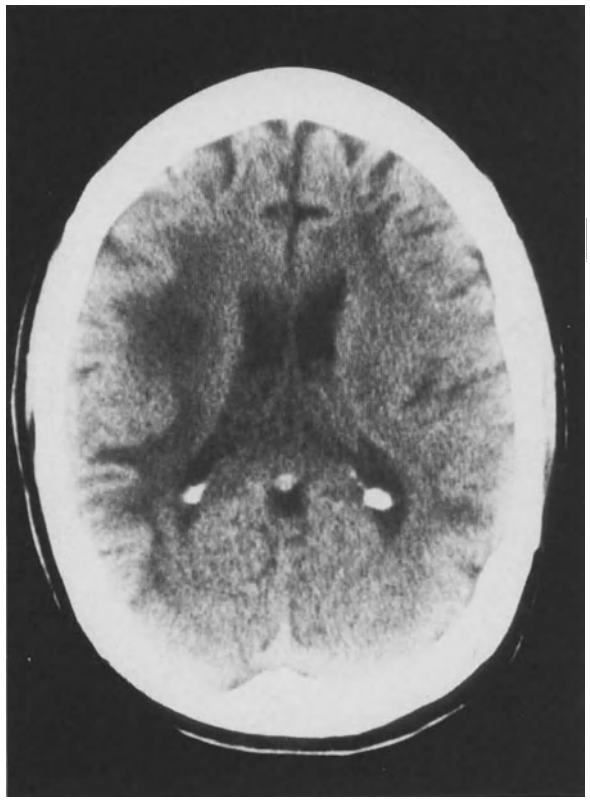


d

(Stoner et al. 1986). After the onset of clinical symptoms the mean survival time is as short as 4 months. There are some reports of clinical courses of more than 20 months, even with phases of neurological improvement (Berger et al. 1987; Hansman Whiteman et al. 1993). The foci of demyelination in PML appear hypodense (10–30 HU) on CT, without mass effect or contrast enhancement (Carrol et al. 1977). They are located in the white matter, involve the U fibers, and are not confined to the typical territories of vascular supply (Fig. 2.17).

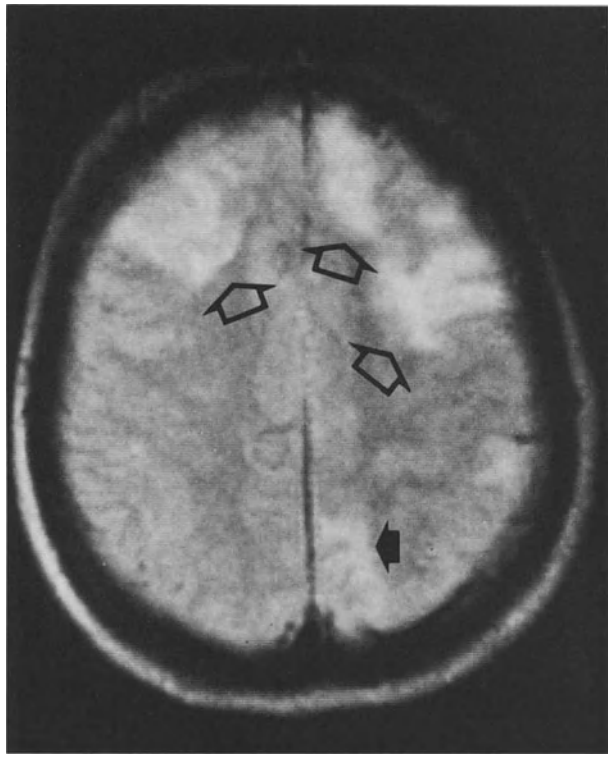
In the initial stage the lesions can be missed by CT. Gray et al. (1992) observed a patient with multiple, disseminated small PML foci limited to U fibers, whose CT was normal. Thus, short- or medium-term follow-up examinations may be necessary (Krupp et al. 1984). In the imaging findings of PML there seems to be no significant difference between HIV-negative and AIDS patients (Bernick and Gregorius 1984; Blum et al. 1985; Carrol et al. 1977; Ho et al. 1984; Koeppen and Lehmann 1987; Krupp et al. 1984; Trotot et al. 1990; Voutsinas 1987). It is discussed whether a massive HIV coinfection in PML lesions contributes to the occasionally necrotizing character of these foci (Budka 1990; Schmidbauer et al. 1990). In cases with space-occupying PML lesions, a coinciding toxoplasmosis or lymphoma must be suspected (Tosch et al. 1990).

Guilleux et al. (1986) described the MRI findings in PML seen in HIV-negative patients. They observed an increased T1 relaxation time (low signal intensity on T1-WI), shortened T2 relaxation time (high signal intensity on T2-WI), involvement of the white matter, asymmetrical distribution, no predilection for the periventricular regions, and no mass effect (Fig. 2.18). Levy et al. (1986b) published the case report of a patient suffering from AIDS and Hodgkin's disease. There, CT demonstrated hypodense lesions of both parietal lobes, thalamus, mesencephalon, and pons. Concerning the extension of the lesions, however, there was a higher correlation of MRI findings with neuropathological results at autopsy. The severe involvement of gray matter structures was a prominent feature in this patient. The MRI examinations of eight AIDS patients with confirmed PML were evaluated retrospectively by Mark et al. (1988); T2-WI showed hyperintense lesions in all patients, in six of them at multiple sites. They, too, regularly found gray matter involvement. In two patients it was even the only site of manifestation. In three patients they observed areas with high signal intensity on T1-WI, interpreting these as hemorrhage. In two patients an area of low signal intensity within the focus could be seen on T2-WI. The finding correlated with solid necrotic components of the lesions.

Sze (1988) and Hansman Witeman et al. (1993) emphasized the fact that in 10% of all cases the PML lesions are exclusively located in the posterior fossa. The study published by the latter authors comprised 47 patients. In 21 of those patients, "scalloped" appearance of the cortex indicated U fiber involvement. The lesions of the basal ganglia and thalamus represented extension of lesions from adjacent structures (e.g., internal capsule) or indicated involvement of small myelinated fibers coursing through basal ganglia and thalamus. Exceptional faint contrast enhancement of the lesions was observed by these and other investigators (Enting et al. 1992). Atypical findings such as mass effect generally indicate a concomitant opportunistic disease (e.g., toxoplasmosis) or cerebral lymphoma (De Gans and Portegies 1989). In patients with PML in whom CT fails to detect the lesions, MRI-guided stereotactic brain biopsy may prove a helpful method (Chappell et al. 1992; Levy et al. 1992; Zimmer et al. 1992). As to the clinical aspects or the diagnostic imaging findings of PML, numerous other contributions are available (Berger et al. 1987; De La Paz et al. 1986; Garrote et al. 1990; Ho et al. 1984; Jarvik et al. 1988a; Jürgens et al. 1986; Karahalios et al. 1992; Krestin et al. 1986; Rodriguez et al. 1991; Singer et al. 1993).

◀ **Fig. 2.17a–d.** CT appearance of progressive multifocal leukoencephalopathy. The disease is characterized by multiple demyelinating lesions, typically manifested at various brain regions. On CT these lesions appear hypodense, without contrast enhancement or mass effect. Typical PML lesions are shown in frontal (*arrows,* **a**), parietal (*arrowheads,* **b**) and cerebellar (*arrow* and *asterisk,* **c**) locations. In advanced stages, confluence of the lesions can occur (**d**). PML lesions are asymmetrical, show only rarely a frontal accentuation, and never spare the subcortical U fibers

Fig. 2.18a–h. MRI appearance of progressive multifocal ▶▶ leukoencephalopathy. T2-WI (**a,b,c**) show hyperintense lesions corresponding to the CT findings in Fig. 2.17a–c. The higher contrast resolution of MRI increases the sensitivity of this method. Thus sometimes additional lesions become visible (see Fig. 2.17a, and **a**). On T1-WI (**d,f**) the demyelinated foci show low signal intensity *(white arrow);* the cortex is spared *(white arrowheads).* Note that the lesions reach the cortex; the subcortical U fibers are not spared as in PDL (**e,f**). In PML foci of the temporal lobe *(black arrows),* coronal MRI images are very helpful and advantageous to axial scans (**g,h**)



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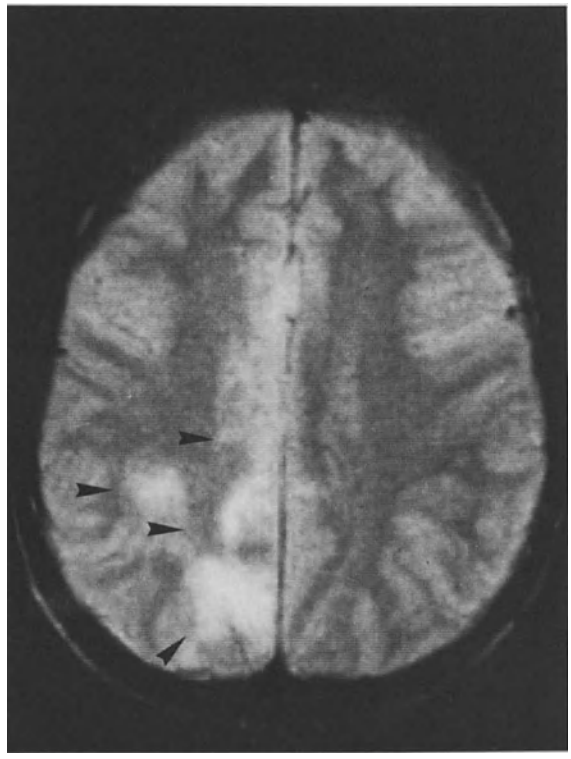

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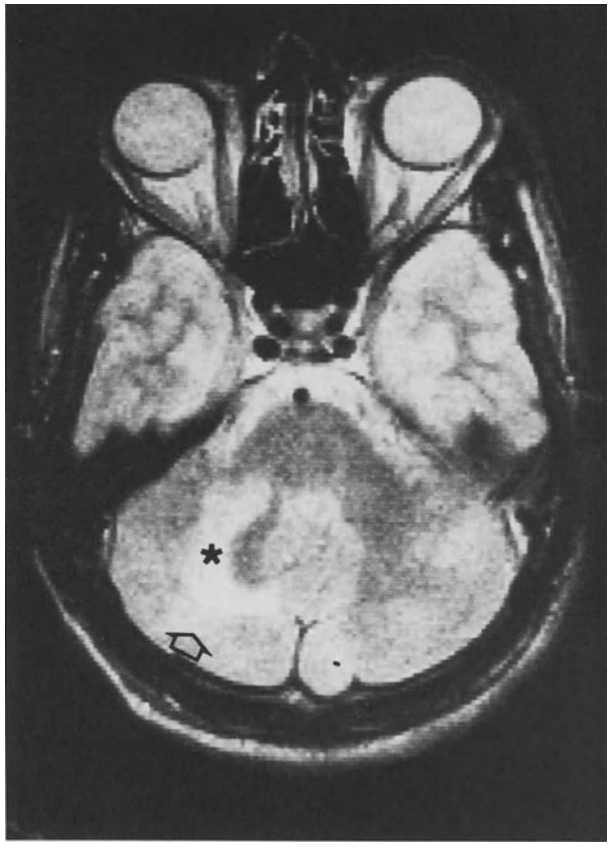

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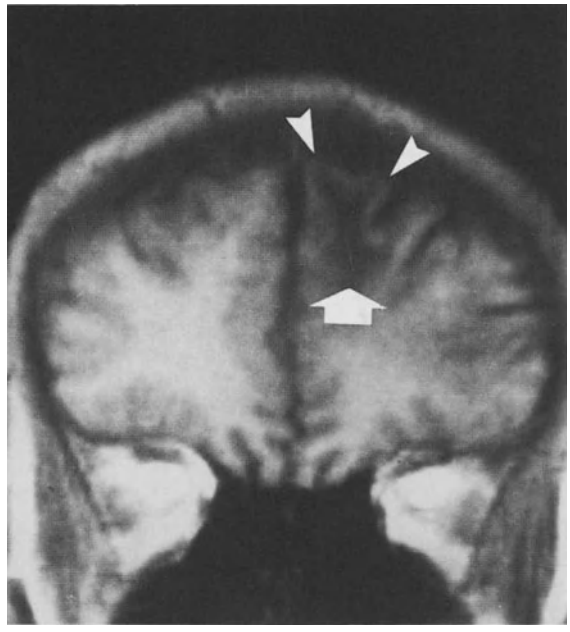

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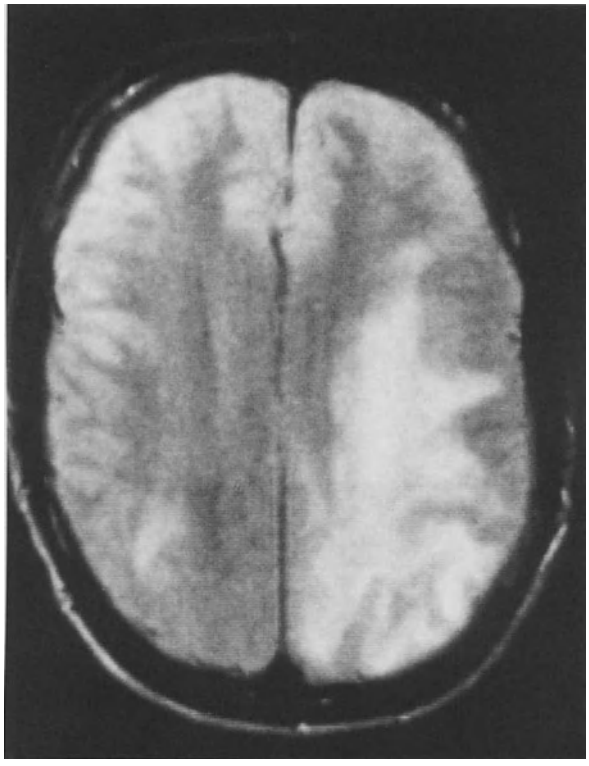
Fig. 2.18 a–d



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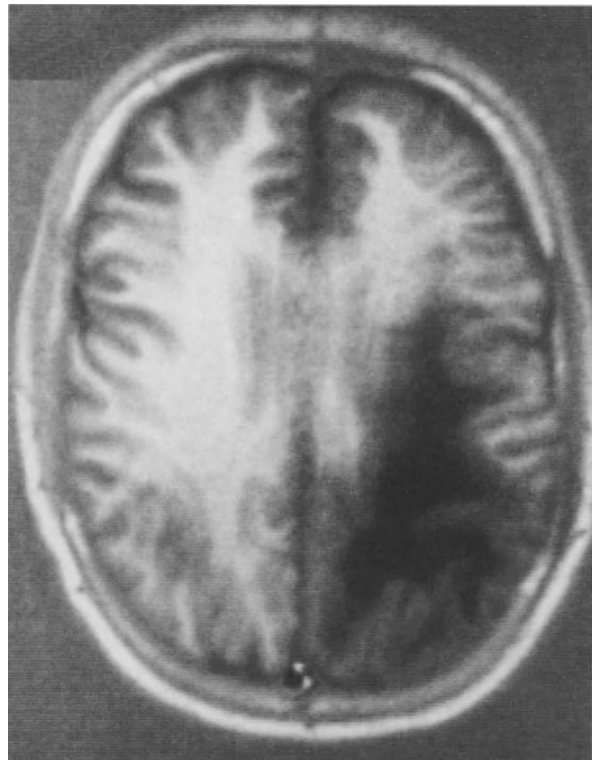

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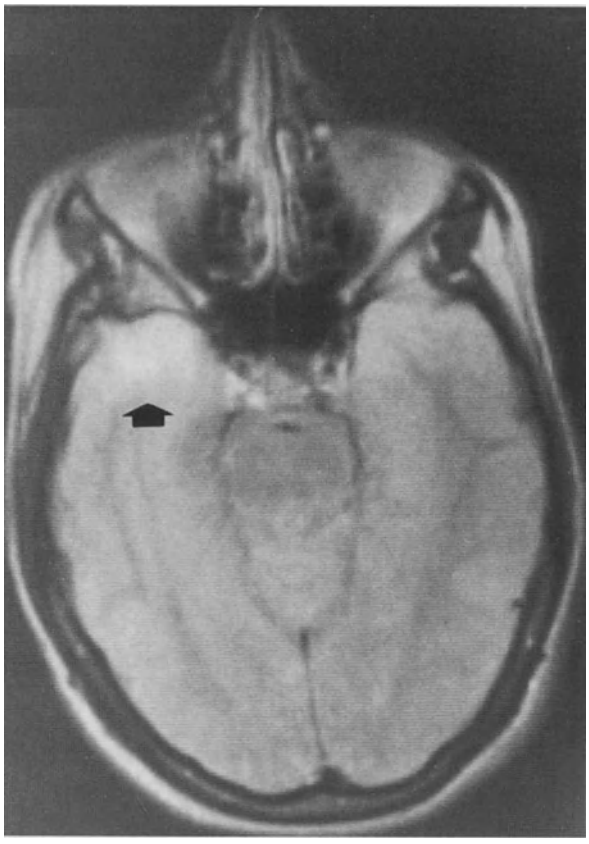

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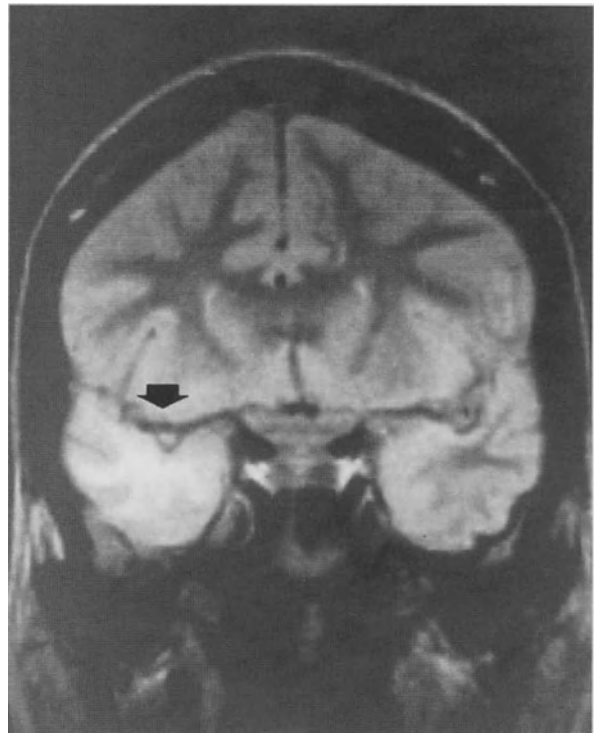


h

Fig. 2.18 e–h

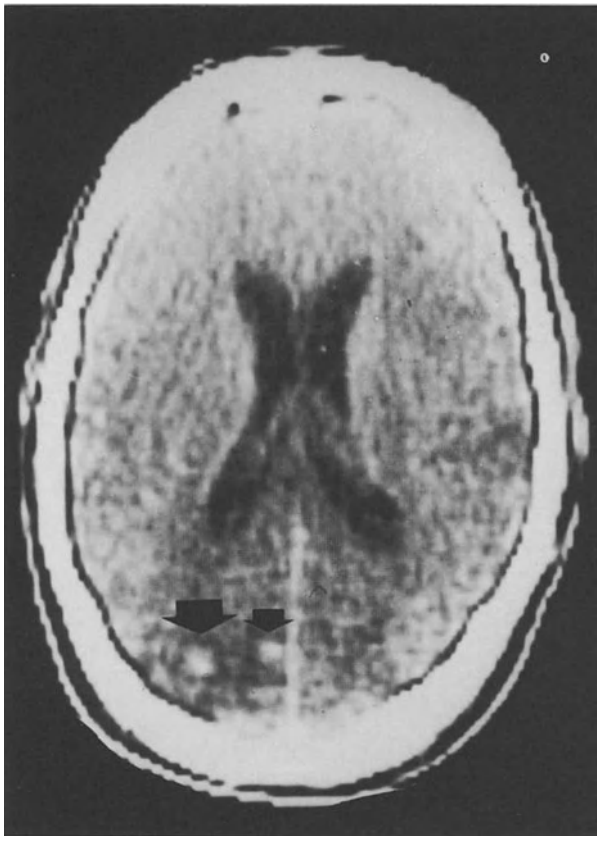
Other Viral Meningoencephalitides

Cytomegalovirus Encephalitis

In AIDS, systemic infection with CMV is a frequent phenomenon (Levy et al. 1985; Petito et al. 1986; Post et al. 1986 a; Snider et al. 1983; Wiley et al. 1986; Vinters et al. 1989). In the neuropathological material of Lang et al. (1989) 10 % of patients had cerebral lesions caused by CMV. Hawley et al. (1983) described a patient who showed no clinical symptoms of encephalitis but at autopsy had CMV particles in the periventricular region. In the series of Snider et al. (1983) CT showed white matter lesions in two patients with neuropathologically confirmed CMV encephalitis. The propensity of CMV to cause (sub-) ependymal lesions and to affect the brain stem and medulla oblongata has been emphasized (Fuller et al. 1989; Lang et al. 1989; Vinters et al. 1989). The spinal cord is another site of manifestation of the opportunistic CMV infection in AIDS (Lang et al. 1989). The CMV may damage endothelial cells, which leads to vascular occlusion and parenchymal infarcts (Grafe et al. 1990).

Levy et al. (1984) reported the CT findings of an AIDS patient who in addition to cerebral toxoplasmosis developed two small ring-shaped and contrast-enhancing lesions of the cerebellum. As confirmed by the neuropathological examination, these lesions were caused by CMV. Moskowitz et al. (1984 a) published the reports of three AIDS patients who died from CMV encephalitis and myelitis. CT was not diagnostic; the neuropathological examination demonstrated involvement of the hypothalamus, myelon, and spinal nerve roots. Edwards et al. (1985) cultivated CMV from the CSF of an AIDS patient. The CT examination of this patient showed a contrast-en-

Fig. 2.19 a, b. CT appearance of CMV encephalitis. These contrast-enhanced EMI CT 1010 scans were obtained from a hemophilic AIDS patient who presented with grand mal epilepsy and symptoms of increased intracranial pressure. Multiple round, intensively contrast-enhancing lesions with perifocal edema can be seen *(arrows)*. From a morphological point of view this pattern is indistinguisable from cerebral toxoplasmosis. (These images are reproduced despite their poor quality to illustrate the findings in this rare condition)



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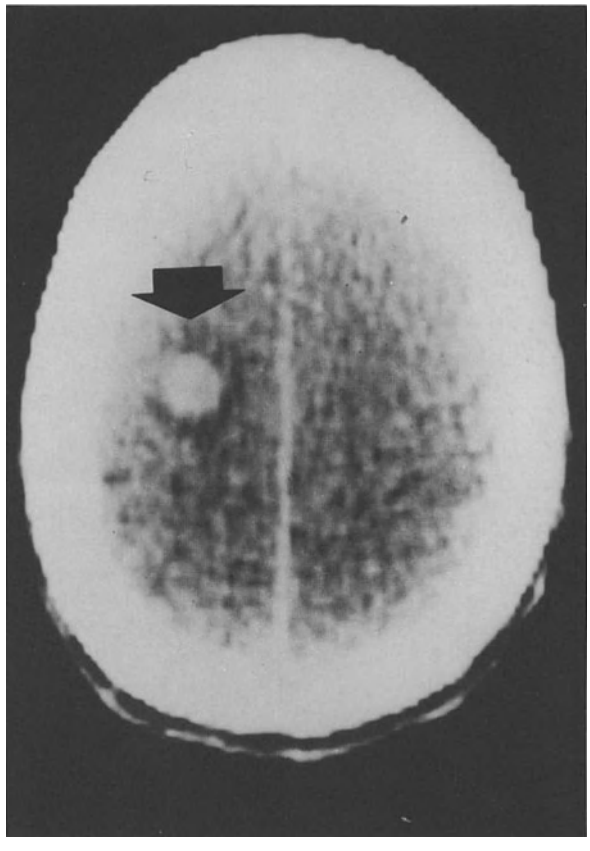

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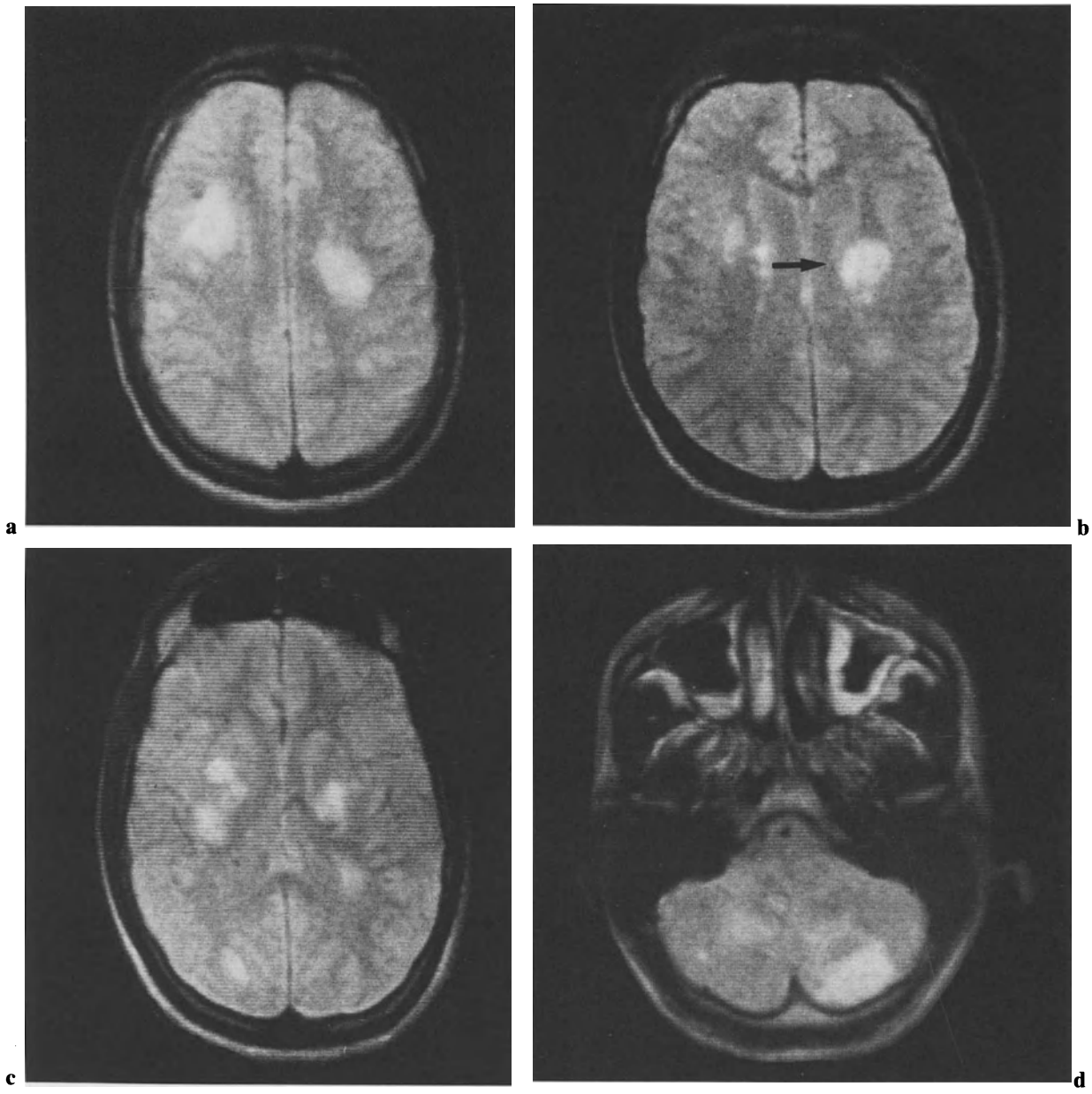


hancing lesion. The CMV infection, however, cannot be regarded as the proven cause of this focal process. Post et al. (1986a) in retrospect evaluated the CT examinations of ten patients with histopathologically confirmed CMV encephalitis. In only three of these patients did CT reveal lesions that could be ascribed to the CMV infection. In detail, a diffuse subependymal contrast enhancement, bilateral hypodensity of the centrum semiovale, and small contrast-enhancing foci in the cortex were observed. In three other patients with clinically manifest CMV encephalitis CT showed cerebral atrophy but no other correlates of

Fig. 2.20a–d. MRI appearance of CMV encephalitis. T2-WI corresponding to the CT scans in Fig. 2.19 show multiple hyperintense lesions in both hemispheres and in the cerebellum. Local mass effect is obvious (*black arrow,* **b**). At autopsy these lesions proved necrotic and hemorrhagic. In findings similar to this case, and progressing during antitoxoplasmotic chemotherapy, rare etiologies instead of toxoplasmosis must be taken into consideration

the generalized involvement of the brain. In four patients in whom CMV encephalitis was associated with a second etiology, the CT findings were dominated by the sequelae of toxoplasmosis or by the sequelae of a preceding biopsy. In one patient of the biopsy series of Anson et al. (1992) CT showed diffuse atrophy, periventricular lucencies and a hypodense temporal lobe lesion which at autopsy turned out as the correlate of a necrotizing CMV encephalitis. Fig. 2.19 shows the CT findings of a hemophilic AIDS patient in whom the foci were primarily hemorrhagic. Correlates of tissue damage that could directly be attributed to the CMV infection cannot be detected.

On MRI, Krestin et al. (1986) observed brain atrophy and periventricular areas of high signal intensity in a patient with confirmed CMV encephalitis. Neither in this case were lesions detectable that could be directly attributed to this specific etiology. The cohort studied by Post et al. (1986a) included two patients with clinically suspected CMV encephalitis in whom MRI revealed white matter lesions while the corresponding CT was inconspicuous. Bilateral, confluent lesions with high signal intensity on T2-WI were described by Jarvik et al. (1988a) in an AIDS patient with confirmed CMV encephalitis. Berthoty et al. (1988) performed postmortem MRI examinations on formalin-fixed brains of patients who had suffered from AIDS dementia. Foci with increased signal intensity on T2-WI, located in basal ganglia, brain stem, and cerebellum, proved to be CMV-associated infarctions. Both smaller CMV-associated lesions and micro glia nodules, however, were missed by MRI. MRI images of a hemophilic AIDS patient with neuropathologically confirmed hemorrhagic CMV encephalitis are shown in Fig. 2.20.

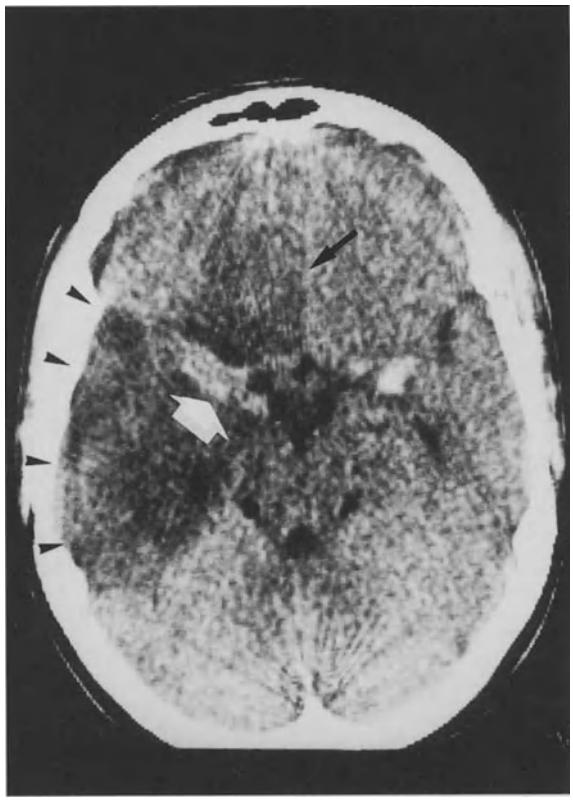


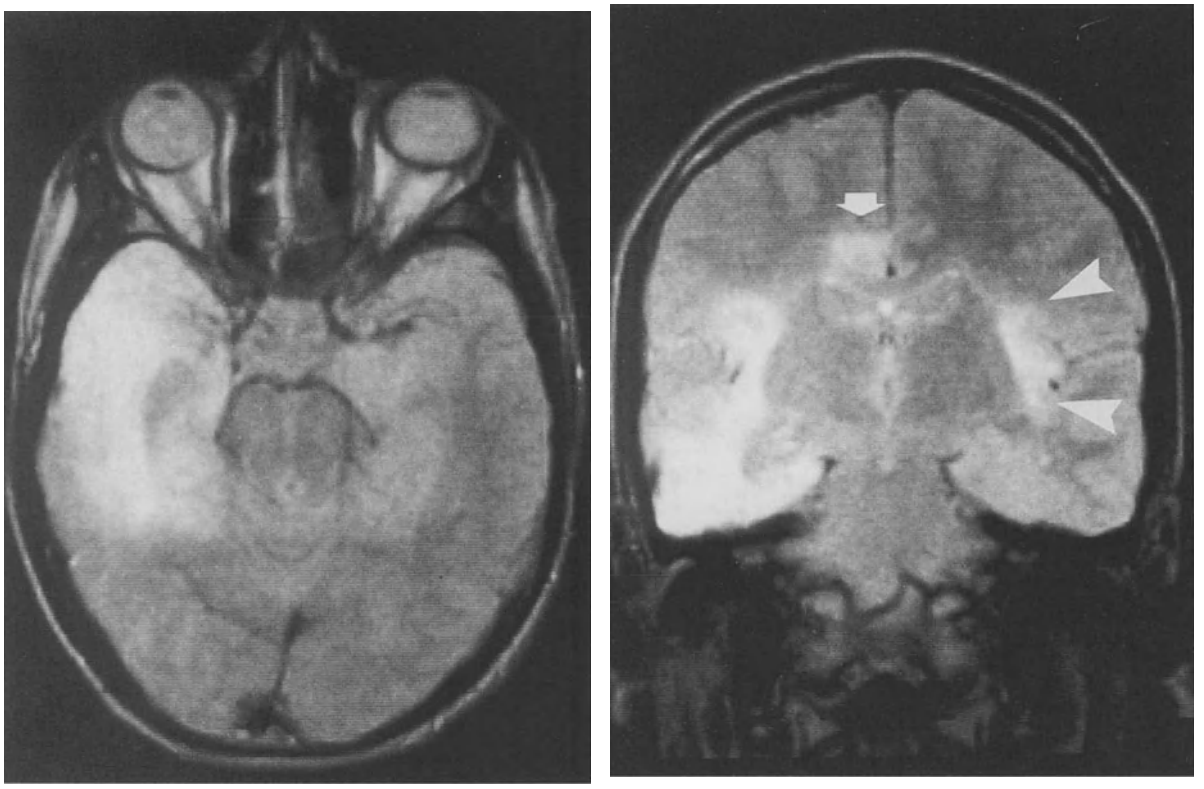
Fig. 2.21. CT appearance of herpes simplex virus encephalitis in a non-HIV-infected patient. Hypodense areas can be seen in the right temporal lobe and frontobasal cortex. Note the typical hemorrhagic component, seen here as a hyperdense area in the right temporomesial region *(white arrow)*

Herpes Simplex Virus Encephalitis

Herpes simplex virus encephalitis (HSVE), almost always caused by HSV type 1, is the most frequent sporadic encephalitis. In the immunocompetent host, hemorrhagic and necrotizing lesions of the temporomesial, cingulate, and frontobasal gyri are typical findings. HSVE is an infrequent secondary CNS manifestation of AIDS (Dix et al. 1985; Fischer and Enzensberger 1987; Pitlik et al. 1983). Ventriculoencephalitis and optic nerve neuritis in AIDS due to simultaneous infection by HSV and CMV have been described (Morgello et al. 1987; Zimmer et al. 1991). At present it is not clearly understood how the course of the disease is influenced by the accompanying disturbance of cellular immunity.

Kaufmann et al. (1979) published the CT findings of eight non-AIDS patients suffering from HSVE. In the initial phase of HSVE, CT frequently fails to detect any abnormality. Four to five days after the clinical onset of the disease they find hypodense, mostly unilateral lesions, with variable contrast enhancement and mass effect, sometimes with hyperdense, hemorrhagic compartments (Fig. 2.21; Davis et al. 1978; Rodiek and Backmund 1984). Diagnostic imaging in HSVE is crucial for the initiation of antiviral chemotherapy and for the evaluation of its therapeutic effects. In an AIDS patient with HSVE from HSV type 2 reported by Levy et al. (1986a), CT demonstrated bilateral, hypodense, contrast-enhancing lesions of the temporal lobe. Chappell et al. (1992) published the CT scan of an AIDS patient with HSV cerebritis which was diagnosed by stereotactic biopsy.

In the articles of Jarvik et al. (1988a) and Dix et al. (1985) there are no exact and detailed descriptions concerning the nature of MRI findings in patients with



a b

Fig. 2.22 a, b. MRI appearance of herpes simplex virus encephalitis; same patient as in Fig. 2.20. T2-WI in the axial (**a**) and the coronal (**b**) plane. The right temporal lobe appears entirely hyperintense, due mainly to increased water content caused by inflammatory tissue damage. The coronal plane clearly illustrates the pathognomonic limbic spread, with involvement of the ipsilateral cingulate gyrus (arrow) and the contralateral isle of Reil (arrowheads)

HSVE. In our AIDS patients HSVE was neither clinically manifest nor confirmed by CSF analysis or biopsy. It is known from experience with HIV seronegative patients that MRI is superior to CT because of its capacity to demonstrate bitemporal lesions and to visualize the spread of the process along the structures of the limbic system (Fig. 22). Hemorrhagic compartments of such lesions appear hyperintense on T1-WI.

Epstein-Barr Virus Infection

Epstein-Barr virus (EBV) is a gamma-herpesvirus that is endemic to humans. EBV is the cause of infectious mononucleosis and meningoencephalitis may occur in conjunction with it. A tropism of EBV for neuronal cells is not confirmed. Most probably, EBV-infected lymphocytes infiltrate the CNS. They are the direct cause of dysfunction or induce an inflammatory reaction. In AIDS patients EBV has been detected in primary CNS lymphomas. EBV probably plays a causative role in the pathogenesis of these tumors. A relationship between the degree of EBV content of the tumor cells and the patient's length of survival was not found (Bashir et al. 1989; Murray et al. 1987; Rosenberg et al. 1986). MRI findings in non-AIDS patients with disseminated or cerebellar encephalitis due to EBV were published (Klockgether et al. 1993; Shoji et al. 1992). We could not find corresponding data concerning EBV meningoencephalitis in AIDS patients.

Varicella Zoster Virus

CNS diseases induced by varicella zoster virus (VZV) include leukoencephalopathy, vasculopathy, encephalomyelitis, zoster ophthalmicus, and trigeminal encephalitis (Gilden et al. 1988; Morgello et al. 1988; Petito et al. 1986; Rosenblum 1989; Rostad et al. 1989; Ryder et al. 1986; Sandor et al. 1984). Edema, perivas-

cular and meningeal inflammation, demyelination, vascular occlusion, parenchymal hemorrhage, and necroses – and their characteristic correlates in CT and MRI – can be observed (De Girolami et al. 1990). Li et al. (1993) observed Gd-DTPA enhancement within the internal auditory canal, in the region of the facial nerve, and in the labyrinth in a HIV-infected patient with Ramsay-Hunt syndrome.

Bacterial Infections of the Brain and Meninges

Bacterial infections are of minor importance in AIDS patients. An etiological and specific diagnosis is generally not possible by means of diagnostic imaging. Especially in cases with lesions that prove refractory to antitoxoplasmotic therapy, bacterial infections must be included in differential diagnostic considerations (Post et al. 1983).

CNS Tuberculosis

Tuberculosis in HIV-infected individuals is in most cases due to reactivation (Johnson and Chaisson 1991). In AIDS patients, intracranial tuberulomas are well-known but comparatively rare mass lesions (Bishburg et al. 1986). They can be expected in 1 % of all patients with full-blown AIDS and comprise about 10 % of their extrapulmonary tuberculous manifestations. A definitive diagnosis can be obtained by open or stereotactic brain biopsy. In patients in whom biopsy is contraindicated, either because of the location of their lesion or of other factors (e.g., thrombocytopenia), the disappearance of their lesions after adequate antituberculous medications is considered as a confirmation of the diagnosis (Abós et al. 1991). An intracranial tuberculoma can be the initial clinical manifestation of AIDS. It is remarkable, however, that in patients with AIDS and extrapulmonary tuberculosis CNS toxoplasmosis is more frequent than intracranial tuberculoma. HIV-infected patients with tuberculosis are at an increased risk for meningitis but the outcome of this disease is not changed (Berenguer et al. 1992). Patients with intracranial tuberculoma present with subacute focal neurological deficits or, less frequently, with focal seizures. Fever and positive tuberculin skin test are rare; the CSF can be normal.

Various authors have reported on CT findings in intracranial tuberculous manifestations such as tuberculoma, abscesses, and meningitis (Giampalmo et al. 1989; Post et al. 1983; Villoria et al. 1992). Whelan and Stern (1981) differentiated various lesion patterns of intracranial tuberculoma in AIDS patients. On unenhanced scans these lesions were iso- or slightly hyperdense, showed no calcifications, and enhanced after contrast medium in a nodular or ring-shaped pattern (Fig. 2.23). They were surrounded by perifocal edema, and contrast enhancement was also seen in the adjacent meninges (Welchman 1979). In tuberculous meningitis, CT and MRI can produce false-negative results (Bouslama et al. 1991). Post et al. (1983) emphasized that in one of their patients multiple contrast-enhancing tuberulomas could not be distinguished from toxoplasmotic lesions. In the case reported by Fischl et al. (1985), toxoplasmotic and tuberculous lesions were both present. There were no evident criteria to differentiate the two etiologies by means of CT. Abós et al. (1991) discussed primary hyperdensity on unenhanced CT scans as a specific sign for intracranial tuberculoma. They observed no such appearance in toxoplasmotic lesions. In our experience, however, hyperdensity due to hemorrhage can also be found in toxoplasmotic foci. A higher frequency of CNS tuberculosis in the subgroup of HIV-infected drug addicts was concluded by Bishburg et al. (1986). Cerebral manifestations of *Mycobacterium avium intracellulare* infection are rare (Fauci 1985; Gray et al. 1991c; Greene et al. 1982; Snider et al. 1983).

Other Bacterial Meningoencephalitides

The infrequency of bacterial meningoencephalitides in AIDS patients has been attributed to the fact that mainly the cellular immunity is impaired (Sze et al. 1987). Anecdotal reports can be found concerning infection by *Escherichia coli* (Berger et al. 1984), *Actinomyces israeli, Salmonella* (Adair et al. 1987; Bishburg et al. 1989; Fraimow et al. 1990; Holtz et al. 1985; Pitlik et al. 1983), and *Listeria monocytogenes* (Berenguer et al. 1991; Goud et al. 1986; Patey et al. 1989; Thiel et al. 1986). Kim et al. (1991) observed six AIDS patients; Marin-Casanova et al. (1991) and Idemyor and Cherubin (1992) observed one AIDS patient with nocardiosis, which was fatal in five of them. In the study of Post et al. (1985) one patient suffered from *E. coli* meningitis while CT examination showed normal findings. Extracerebral bacterial infections may be the origin of intracranial metastatic abscesses (Lang et al. 1989).

AIDS patients are also at risk for meningeal, parenchymal, and vascular manifestations of *Treponema pallidum* infection (Berry et al. 1987; Fernández-

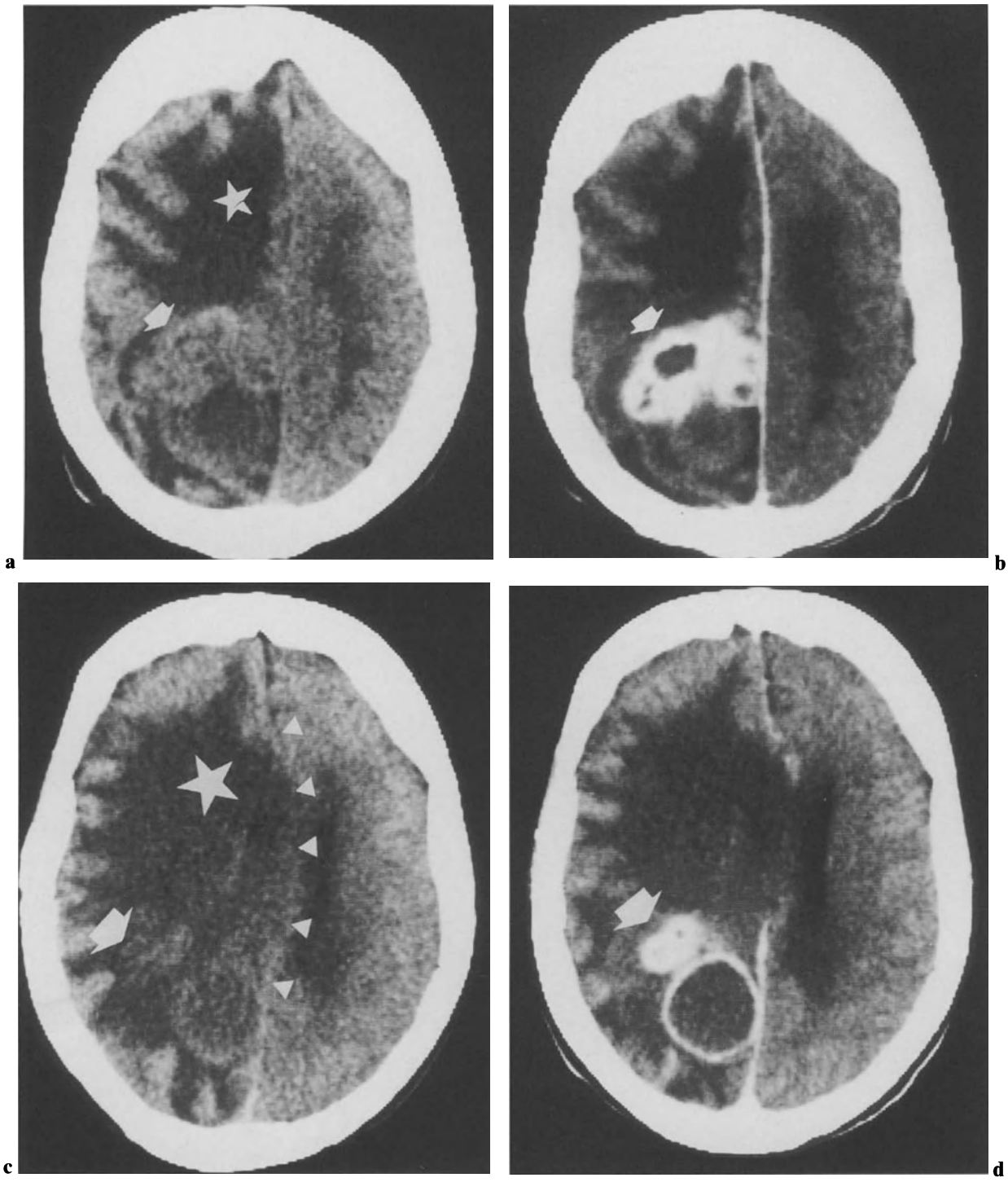
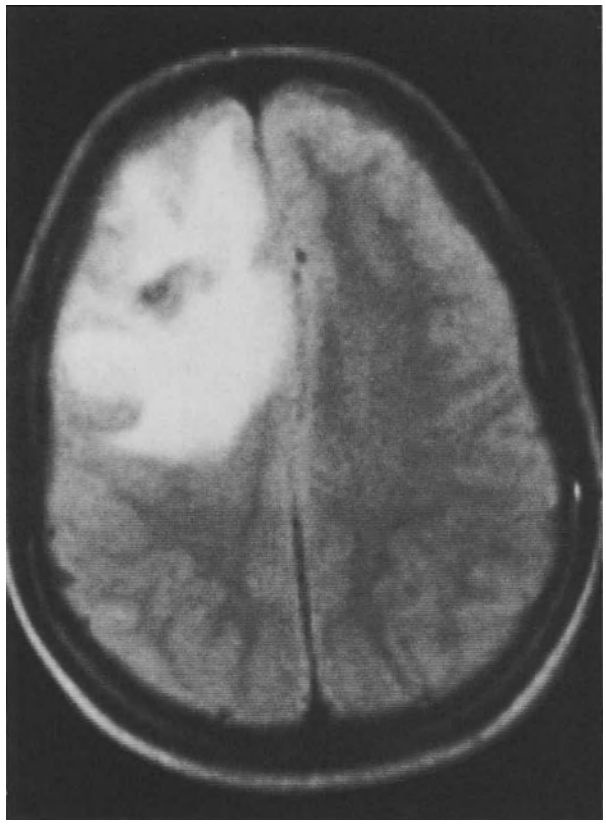


Fig. 2.23 a–d. CT appearance of a giant tuberculoma, observed in a mentally ill, not HIV-infected patient. Unenhanced CT (**a, c**) shows considerable midline shift *(white triangles)*, extensive perifocal edema *(white asterisk)*, and the tuberculoma as a mass with a density similar to that of normal brain tissue *(white arrow)*. The tuberculoma itself is very intensively contrast enhancing (**b, d**)



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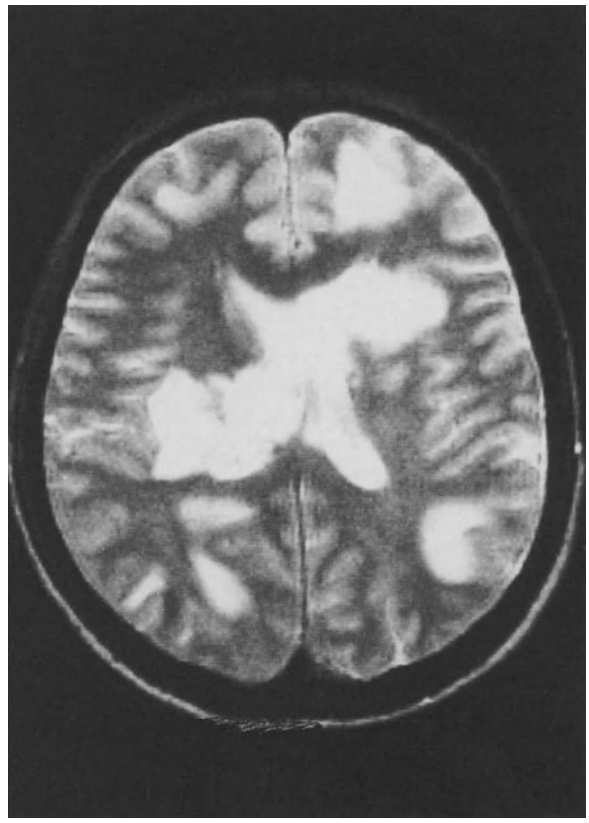

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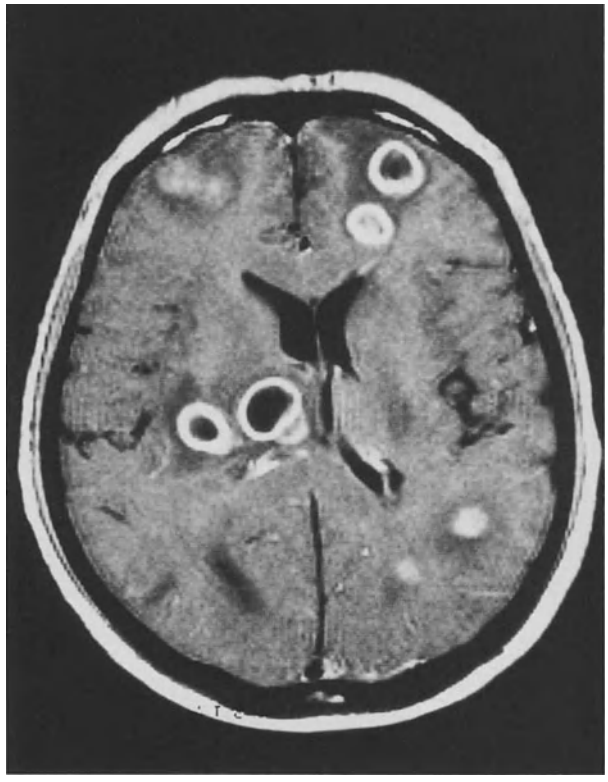

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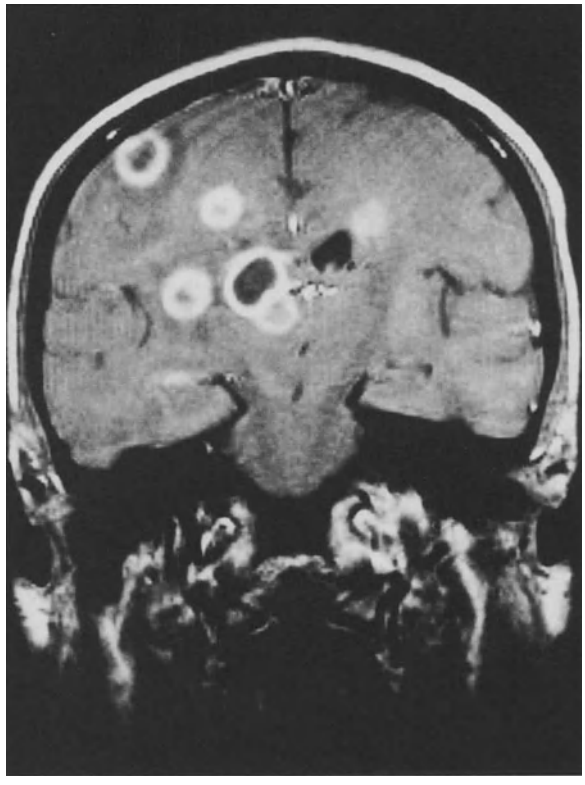

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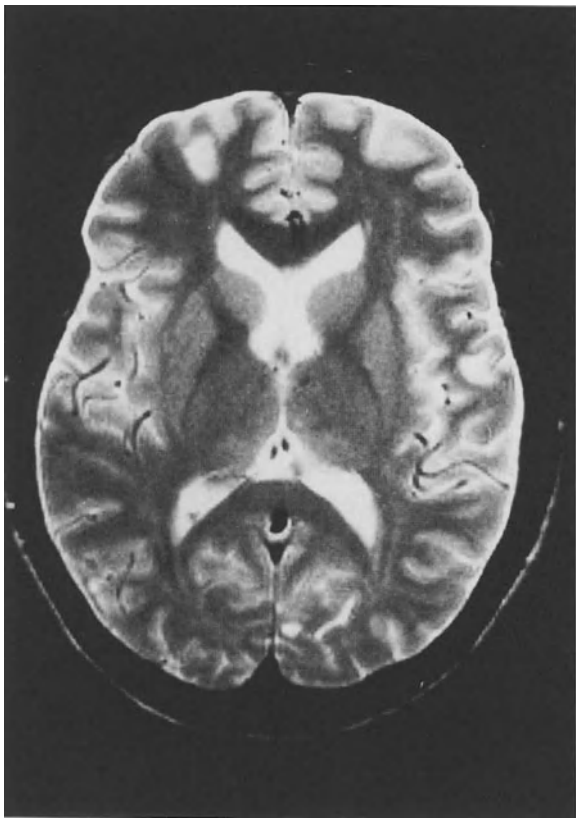

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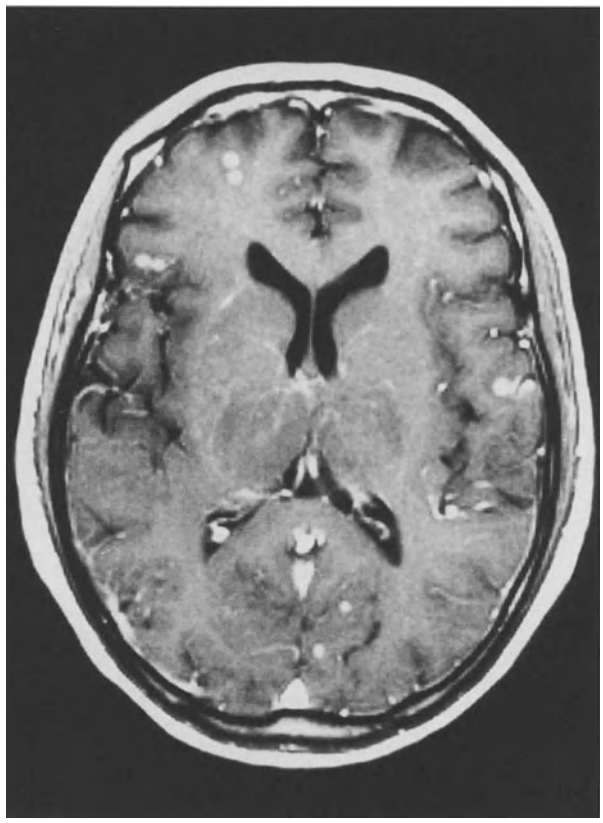
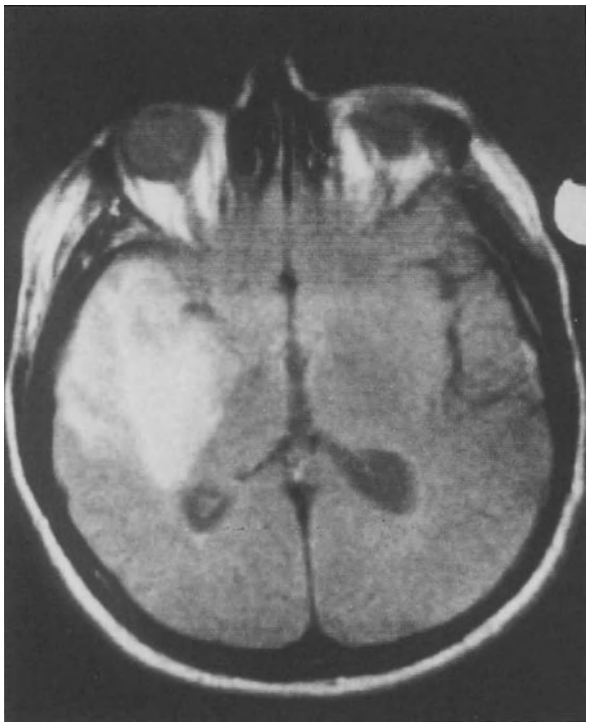


f

◀ **Fig. 2.24a–f.** MRI appearance of cerebral tuberculomas, observed in a non-HIV-infected patient. **a** The solitary tuberculoma of a patient presenting with chronic headache and remittent fever. On this T2-WI, the lesion itself shows low to brain-equivalent signal intensity, surrounded by extensive perifocal edema. The edema can also be less extensive (**b**), and the lesions can show abscesslike ring-enhancement (**c,d**). On heavily T2-WI, cortical tuberculomas can hardly be distinguished from sulci (**e**). In these cases, Gd-DTPA enhanced T1-WI show the lesions more clearly (**f**)

Guerrero et al. 1988; Hicks et al. 1987; Johns et al. 1987; Schultz et al. 1987; Zaidman 1986; Zambrano et al. 1987). Especially, ischemia caused by syphilitic vascular occlusion may occur (Bredesen and Messing 1983; Berger et al. 1984; Labauge et al. 1991; Lang et al. 1989; Matlow and Rachlis 1990; Tien et al. 1992). Tuite et al. (1993) presented MR images of a HIV-infected patient with meningovascular neurosyphilis. T2-WI showed ischemic parenchymal lesions whereas T1-WI revealed enhancing basilar meninges after Gd-DTPA application. Tien et al. (1992) observed a patient with a dura-based mass that was isointense with gray matter on T1-W1, hyperintense on T2-W1, and intensely contrast enhancing. At biopsy the mass turned out to be a syphilitic gumma. After penicillin treatment mass and perifocal edema resolved. Two similar cases were presented by Berger et al. (1992). Recently it was discussed whether the concurrence of HIV and *Treponema* infection results in an increased frequency and virulent forms of neurosyphilis. The concept of quarternary neurosyphilis with accumulation of treponemes, obvious immunological anergy towards these organisms, and necrotizing encephalitis has become especially topical (Morgello and Laufer 1989).

Many articles on the MRI diagnosis of bacterial infections have been published (Just et al. 1987; Schroth et al. 1987; Sze 1988). It can be noted in general that MRI detects inflammatory lesions with an extremely high sensitivity. For the initiation of effective antibiotic therapy, however, an etiological diagnosis is required, generally provided by other diagnostic methods such as CSF analysis and stereotactic biopsy. Berger (1991) reported on five HIV seropositive patients with neurosyphilis. Two of them had neurological symptoms. In



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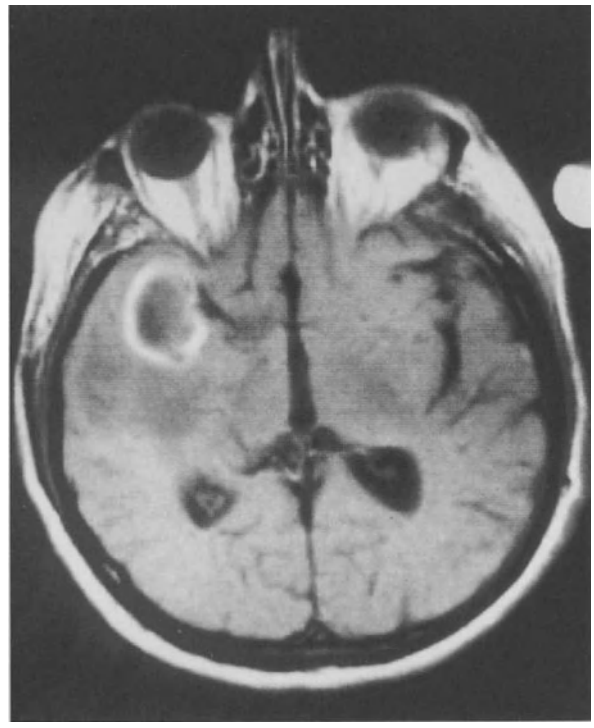

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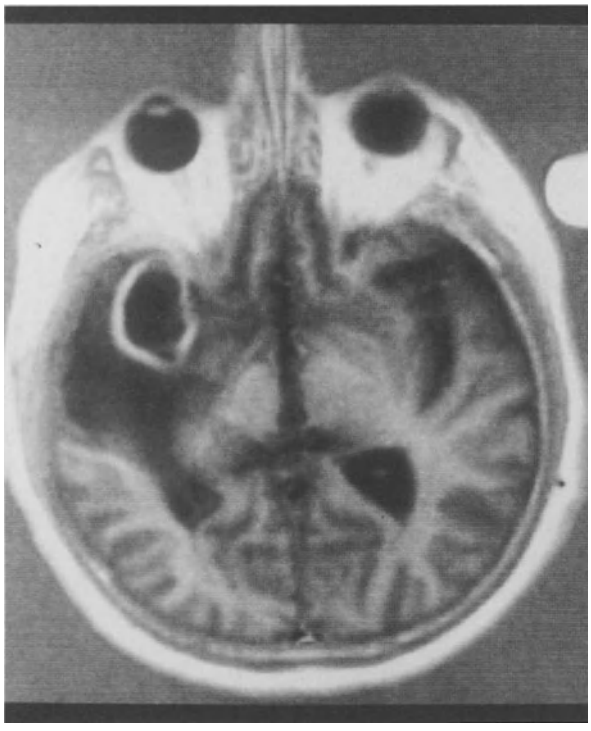


c

Fig. 2.25 a–c. MRI appearance of a bacterial brain abscess, diagnosed following mastoiditis in a non-HIV-infected patient. **a** T2-WI shows an almost homogeneously hyperintense lesion that involves the temporal lobe and is extending adjacent to the thalamus. Gd-DTPA enhanced spin echo (**b**) and inversion recovery image (**c**) allows differentiation of the thin-walled, contrast-enhancing abscess membrane, the hypointense necrotic center, and the also hypointense perifocal edema

all patients the MRI images were normal. Wang et al. (1986) examined an AIDS patient suffering from Whipple-like disease with cerebral involvement in whom *Corynebacterium equi* was detected. In a similar case report by Jankovic (1986), where no causative agent was isolated, MRI showed two lesions in the frontal regions of both hemispheres. The advantages of contrast-enhanced MRI were emphasized by the authors. Figures 2.24–2.26 give examples of tuberculoma, brain abscess, and focal metastatic encephalitis.

Mycotic Infections of the CNS

Cryptococcosis

Meningoencephalitis caused by *Cryptococcus neoformans* is the most important generalized mycosis in AIDS. It is found in about 4 %–5 % of neuropatholog-

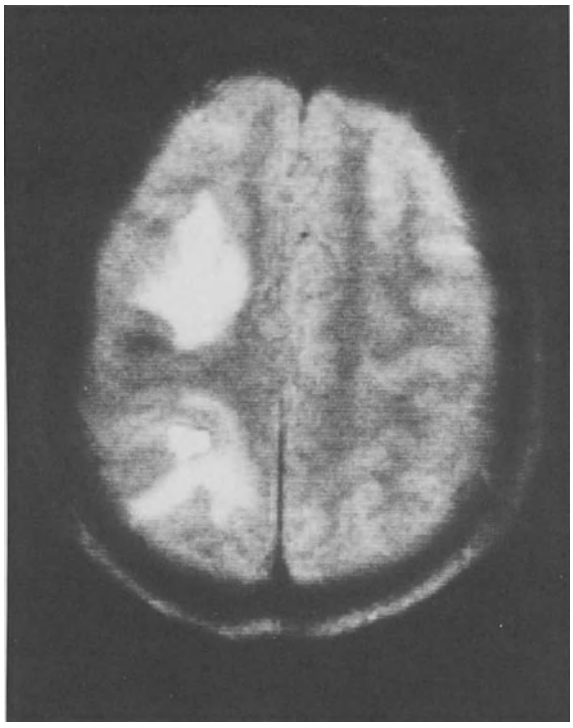


Fig. 2.26. MRI appearance of multiple brain abscesses of thromboembolic origin. This non-HIV-infected patient suffered from bacterial endocarditis. There is an atypical, targetlike pattern with a hyperintense center, nearly isointense rim, and hyperintense perifocal edema. Central hyperintensity on T1-WI (not shown) confirmed the hemorrhagic character of these lesions

ically examined cases. The morphological substrate is diffuse leptomeningitis, occasionally accompanied by granulomas, cerebral perivascular clusters, abscesses, and myelin damage (Lang et al. 1989; Mastroianni et al. 1990). It is a common experience that in cryptococcosis CT and MRI of the brain frequently yield normal findings (Catania et al. 1990; Cornell and Jacoby 1982; De Gans and Portegies 1989; Popovich et al. 1990; Sze et al. 1987; Whelan et al. 1983). Abnormal CT findings and an altered mental status at presentation are factors associated with poor prognosis (Clark et al. 1990).

In a case published by Catania et al. (1990) an episode of cryptococcal meningitis with normal CT finding was followed by clinical deterioration and the appearance of multiple lesions caused by fatal toxoplasmosis, as shown by CT. Tan et al. (1987) published data on 20 non-AIDS patients from Malaysia suffering from CNS cryptococcosis. In only 10 patients of this group did CT reveal abnormal findings such as hydrocephalus, gyral, focal or confluent contrast enhancement, or low density of white matter. Garcia et al. (1985) observed hypodense lesions without contrast enhancement. Their morphological substrate were pseudocysts of cryptococcal encephalitis. Tien et al. (1991) additionally described leptomeningeal and parenchymal calcifications. A larger series of CT findings in AIDS patients with cryptococcosis was published by Popovich et al. (1990). In 15 of 35 patients, CT was normal, representing uncomplicated cryptococcal meningitis. Cerebral atrophy due to HIV infection or age was seen in 12, and hydrocephalus resulting from chronic meningeal inflammation was present in 3 patients. One patient had cerebral edema as the only finding. Cryptococcal mass lesions were seen in four cases. The observed lesion patterns were ring-enhancing masses, nonenhancing "soap bubble" lesions or "gelatinous pseudocysts" of the basal ganglia or internal capsule and an intraventricular cryptococcoma. Cryptococcal meningitis was described as the cause of transient rostral basilar artery ischemia. In this case CT was normal, and cerebral angiography was not performed (Rafal and Friedman 1990).

Regarding abnormal MRI findings in intracranial cryptococcosis, four patterns can be distinguished (Balakrishnan et al. 1990; De Girolami et al. 1990; Jarvik et al. 1988a; Tien et al. 1991, Uterga et al. 1992; Wehn et al. 1989):

- Cryptococcomas appearing as parenchymal mass lesions, sometimes with contrast enhancement and perifocal edema, without a propensity to perivascular distribution.
- Dilated Virchow-Robin spaces seen as tiny, clearly delineated foci in the basal ganglia and midbrain. These are hyperintense on T2-WI and and do not show mass effect, perifocal edema, or contrast enhancement ("soap bubble" lesions). At autopsy Virchow-Robin spaces dilated in this way are filled with fungi and show surrounding perivascular inflammatory cell infiltrates.
- Multiple miliary parenchymal lesions and leptomeningeal nodules.

Any combination of the three above patterns may occur. Diffuse cisternal leptomeningeal enhancement, which can frequently be demonstrated by MRI in bacterial or tuberculous meningitis, is obviously not a typical finding in cryptococcal meningitis (Tien et al. 1991). The differential diagnosis of dilated Virchow-Robin spaces may include lacunar infarcts, which on CT are usually more hypodense. Lymphoma and toxoplasmosis frequently affect the basal ganglia. However, they are generally contrast enhancing.

In their thorough study, Mathews et al. (1992) evaluated the effectiveness of cranial CT and MRI in detecting autopsy findings of AIDS-related CNS cryptococcosis. Punctate lesions, located primarily in the basal ganglia and midbrain and with hyperintensity on T2-WI were the most frequent finding. At autopsy, cryptococcomas and, less frequently dilated perivascular spaces, were present in these areas. Compared to the autopsy findings, MRI demonstrated more lesions than CT. Both imaging modalities failed to detect the majority of cryptococcomas (especially the cortical ones) as well as meningeal disease. In this study contrast enhancement of cryptococcomas and cryptococcal meningitis was rare, probably due to only limited inflammatory reaction of the host organisms.

Other Mycoses of the CNS

While esophageal opportunistic infection by *Candida albicans* is one of the major manifestations of AIDS, intracranial candidiasis is obviously rare (De La Paz and Enzman 1988; Harris et al. 1985; Lemann et al. 1985; Levy et al. 1983, 1986b, Pitlik et al. 1983). Basically, multiple microabscesses, cerebral granulomata or meningeal infections can occur (Enzmann 1984). Kelly and Brant-Zawadzki (1983) described multiple cystic lesions each surrounded by a thick, contrast-enhancing rim. In the case reported by McGeachie and Nelson (1989), multiple small- and medium-sized abscesses were present in the white matter and the gray-white matter junction. Focal hemorrhage has been reported as a further phenomenon of *Candida* abscesses.

Aspergillus fumigatus or *A. flavus* is another possible agent that causes intracranial infections in AIDS patients (Berger et al. 1984; Kelly and Brant-Zawadzki 1983; Minamoto et al. 1992). The development of aspergillosis is related mainly to neutropenia or damage to lung parenchyma (Decker and Parenti 1991; Woods and Goldsmith 1990). CNS involvement occurs in about 50% of cases with invasive aspergillosis. It appears to be more frequent in AIDS patients than in other immunocompromised patients (Singh et al. 1991). Multiple hemorrhagic necroses scattered all over the CNS have been observed (Lang et al. 1989). The involvement of cerebral vessels can cause infarctions (McGeachie and Nelson 1989; Vinters and Anders 1990). *Aspergillus* endocarditis and myocarditis are a possible source for mycotic thromboemboli to the brain (Cox et al. 1990).

Coccidioidomycosis with peritonitis, interstitial lung infiltrates, and meningeal involvement has been observed as a manifestation of AIDS (Abrams et al. 1984; Byrne and Dietrich 1989; Jarvik et al. 1986b; Kovacs et al. 1984; Roberts 1984; Salberg and Venkatachalam 1986). In an AIDS patient with meningeal infection by *Coccidioides immitis,* CT showed only atrophy (Levy et al. 1986b). Cerebellar abscesses and brain stem lesions (Bronnimann et al. 1987; Jarvik 1988) and dilated Virchow-Robin spaces seen on MRI scans (Tien et al. 1991) were reported as the correlate of coccidioidomycosis.

Histoplasma capsulatum infection of an immunocompromised host can cause progressive disseminated histoplasmosis. CNS manifestation is the exception, but it can be the cause of meningitis or granulomatous encephalitis (Bonner et al. 1984; Davis et al. 1978; Johnson et al. 1986; Taylor et al. 1984; Wheat et al. 1985).

Mucormycosis of the CNS is also rare in AIDS patients. After a fulminant course the disease is rapidly fatal. Multiple, large, necrotic, hemorrhagic lesions of the subcortical gray matter and of the white matter have been observed (Blatt et al. 1991; Cuadrado et al. 1988; Micozzi and Wetli 1985; Wetli et al. 1984).

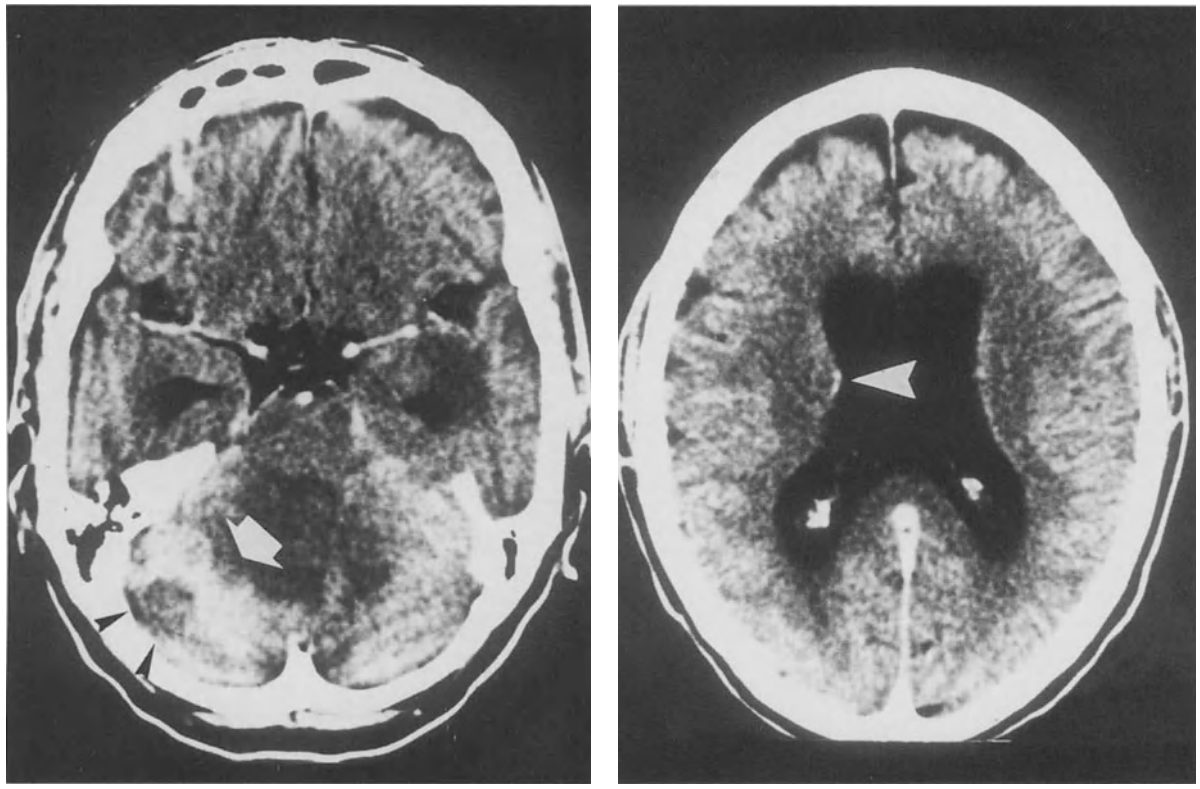
A unique case of a *Pseudoallescheria boydii* endocarditis with cerebral involvement was reported by Raffanti et al. (1990).

A comprehensive overview on mycoses in AIDS patients can be found in Bossche et al. (1990).

■ Cerebral Neoplastic Diseases in AIDS

Primary CNS Lymphoma

Malignant, primary cerebral lymphoma is a disease of immunocompromised patients – as opposed to the spontaneous lymphoma which is seen in only 0.3%–2% of cases located in the CNS and/or the meninges. In general, primary cerebral lymphoma is observed in recipients of organ transplants and in patients with congenital immunodeficiencies (e.g., Wiskott-Aldrich syndrome) or autoimmune disorders. An increasing incidence of this tumor both in risk groups and in the general population has been noticed (Jellinger and Paulus 1992). Primary cerebral lymphoma accounts for approximately 1.5% of all intracranial tumors. In 2%–5% of AIDS patients with neurological symptoms primary cerebral lymphoma is observed (Cordoliani et al. 1992; Doerr et al. 1987). As the development of the tumor probably requires a longer time than other AIDS manifestations, primary

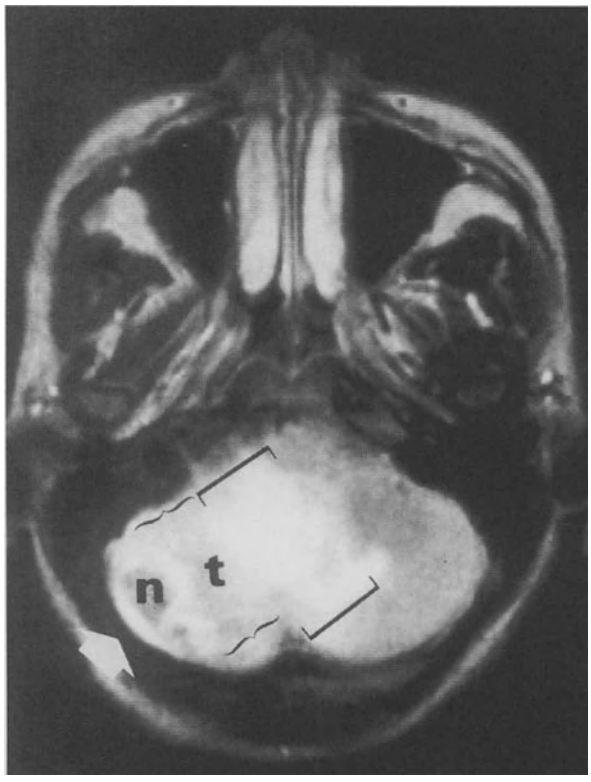


a b

Fig. 2.27 a, b. CT appearance of an AIDS-associated primary CNS lymphoma. In the right cerebellar hemisphere, an intensively contrast-enhancing mass is visible (*white arrow,* **a**). Note the nonenhancing compartment adjacent to the skull *(white arrowhead).* At the level of the cella media the enlargement of the ventricles due to obstructed CSF circulation is obvious. In the wall of the right lateral ventricle a small contrast-enhancing tumor nodule can be seen (*white arrowhead,* **b**)

CNS lymphoma is usually not the inital manifestation of the underlying disease (Fauci et al. 1984). Gill et al. (1985) published case reports of six AIDS patients with primary cerebral lymphomas. The most frequent tumor localization was in the frontoparietal region. In two patients the cerebellum and pons were involved. Four patients had lymphomas in multiple locations. The survival time was usually less than 2 months; a 28-month survival after diagnosis is very rare. Whole-brain radiation therapy significantly improves the prognosis of patients with AIDS-associated primary CNS lymphoma. In the series of Baumgartner et al. (1990) the survival time after the appearance of symptoms was between 8 and 127 days (mean 42 days) in 17 untreated patients. In the 29 patients who had received 40 Gy whole-brain radiation the survival time was with in the range of 33–380 days (mean 134 days). The patients who had completed the radiation therapy protocol died of opportunistic infections rather than tumor progression. Goldstein et al. (1991 a) treated 17 AIDS patients with primary CNS lymphoma by whole-brain radiation and reported a mean survival time of 72 days.

In CT the tumors are hypo-, iso-, or hyperdense, show mass effect and perifocal edema, and are intensively contrast enhancing (Fig. 2.27). A homogeneously enhancing nodular lymphoma was described by Bursztyn et al. (1984). Lee et al. (1986) studied 15 patients suffering from primary cerebral lymphoma with and without AIDS and compared CT findings and their neuropathological correlate. Regarding the CT findings they distinguished major morphological types with some overlapping. In non-AIDS patients the solitary or multiple lesions are generally below 5 cm in diameter, well demarcated, on unenhanced scans hyper- to isodense, and intensively and homogeneously contrast enhancing. The perifocal edema is of moderate degree. The most frequent structures involved by the tumor are basal ganglia, corpus callosum, periventricular white matter, and cerebellar vermis (Doerr et al. 1987; Laviopierre and



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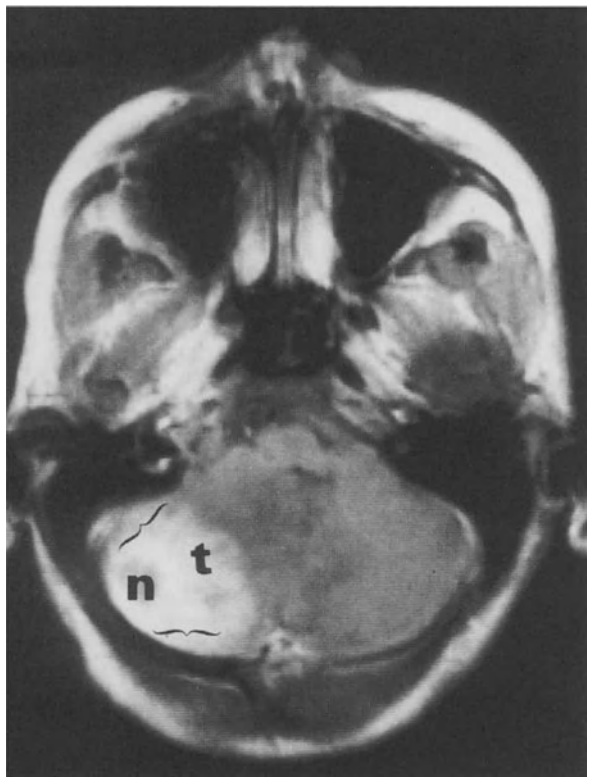

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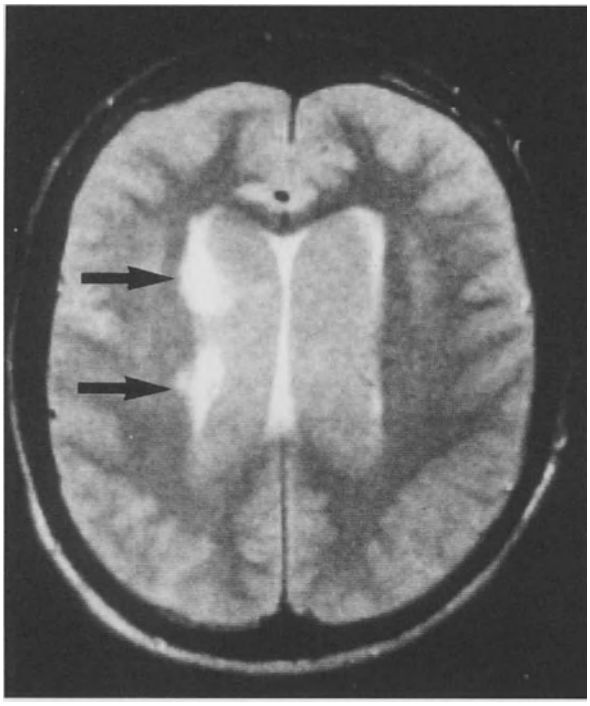

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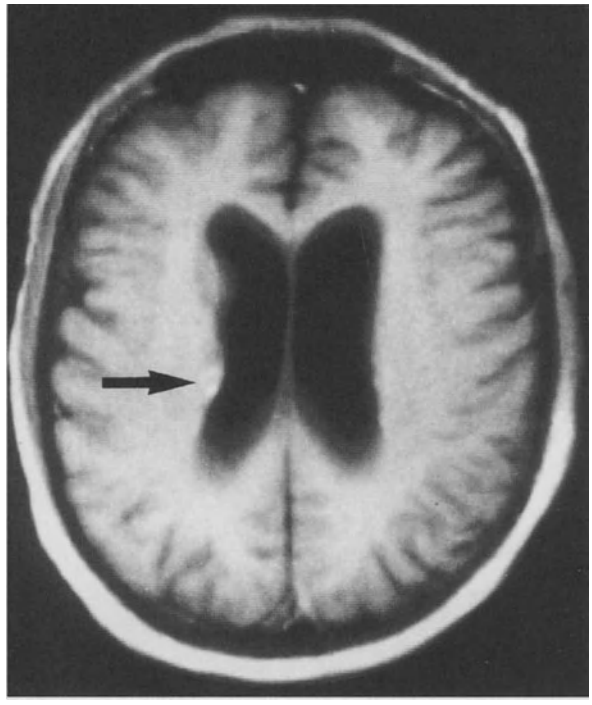


d

◀ **Fig. 2.28 a–d.** MRI appearance of an AIDS-associated primary CNS lymphoma; same patient as in Fig. 2.27. **a** T2-WI reveals involvement of the whole right cerebellar hemisphere. The lesion is inhomogeneously hyperintense and extends beyond the midline. Three different parts of the lesion can be delineated: adjacent to the skull a necrotic compartment with relatively low signal intensity *(n)*, followed by midgrade hyperintense tumor tissue *(t)* and surrounded by strikingly hyperintense edema. **b** After intravenous administration of Gd-DTPA an intensive increase in signal intensity of the tumor tissue *(t)* occurs. The peripheral necrotic area *(n)* is less intensively contrast enhancing; the edema appears as an area of low signal intensity. **c** The T2-WI at the cella media level shows two hyperintense foci in the wall of the lateral ventricle *(arrows)*. **d** The more occipitally located focus proved to be contrast enhancing *(arrow)*. The autopsy confirmed hemorrhagic and necrotic tumor tissue in the cerebellum and a lymphomatous tumor nodule in the ventricular wall

Lawler 1989; Peretti-Viton et al. 1991). Neuropathological examination shows dense cellular tissue without necroses.

The primary cerebral lymphomas in AIDS patients tend to be larger, are surrounded by more pronounced edema, are frequently hypodense on unenhanced scans, show ring or rim enhancement, and are located mainly in the fronto-parietal and subependymal areas. Ring enhancement in these tumors is the correlate of profound necrosis (Orron et al. 1989). Exclusive involvement of the white matter may be a characteristic feature (Kupfer et al. 1990). The differential diagnosis must consider brain abscess, glioblastoma, and toxoplasmosis. In both groups "gyral" contrast enhancement due to ischemic effects on the cortex or to meningeal tumor spread are observed. Lymphoma appearing as hyperdense, non-enhancing tumor is a rare finding (Anson et al. 1992).

Similar criteria for the CT diagnosis of this tumor have been described by many authors (Kelly and Brant-Zawadzki 1983; Arbaiza et al. 1992; Levy et al. 1985; Paolino et al. 1990; So et al. 1986; Watanabe et al. 1992). Goldstein et al. (1991 b) emphasized the wide variety of possible different CT appearances. Sze et al. (1987) pointed out that in cases with diffuse micronodular tumor spread, CT does not show the full extension of tumor involvement. In brain tumors in general, thallium (Tl 201) scintigraphy shows high uptake of the lesion on early and delayed scans. This makes it possible to distinguish lymphoma from inflammatory lesions (Vanarthos et al. 1992).

In AIDS patients with biopsy-confirmed primary CNS lymphoma who have undergone radiotherapy, CT follow-up examinations are required to determine the morphological therapy response. Posttreatment regression of the tumor is a frequent finding (Goldstein et al. 1991 a). A complete resolution can be expected in about 15 % of sufficiently irradiated patients (Baumgartner et al. 1990; Slade 1987). In a child that had undergone brain irradiation for primary CNS lymphoma therapy, fibrinoid necrosis and leukoencephalopathy occurred (Goldstein et al. 1990).

Liu et al. (1987) evaluated the MRI findings of 18 patients with confirmed cerebral lymphomas. Five of these were AIDS patients. The most frequent localization of the tumor was in the paraventricular parenchyma. Two lymphomas were located epidurally. In T2-WI 11 parenchymal lymphomas were iso- to hypointense to the brain tissue. Thus they could be clearly differentiated from the hyperintense perifocal edema (Fig. 2.28). On unenhanced T1-WI, the tumors appeared isointense to the adjacent white matter. They were detectable primarily due to their mass effect. Hemorrhagic areas were seen in two tumors. In one case, the involvement of brain areas of the contralateral hemisphere was detectable only after the application of Gd-DTPA. In the tumors in the epidural space the dura itself could be delineated as a rim with low signal intensity between tumor and brain tissue.

So et al. (1986) performed MRI examinations in 3 of their 20 AIDS patients with primary cerebral lymphomas. MRI allowed the detection of additional lesions and improved the planning and result of the subsequent biopsy. In terms of specificity the MRI findings were of limited help. Even the T2 shortening of the center, leading to a low signal intensity of the central parts of the foci surrounded by high signal intensity edema ("target sign"), does not allow the distinction between toxoplasmosis and lymphoma (Kupfer et al. 1990). Based on the findings in four AIDS and six non-AIDS patients, Schwaighofer et al. (1989) described two different MRI patterns of primary CNS lymphoma. In both groups the tumors were slightly hypointense on T1-WI, slightly hyperintense on Pd- and T2-WI, surrounded by mild edema and causing mild to moderate mass effect. In the AIDS patients, the tumors tended to be smaller in size (below 2 cm in diameter), were mostly multiple, and showed a predeliction for the temporal lobe and basal ganglia. In the non-AIDS patients, solitary and large tumors of the deep parietal lobe predominated. The mass effect was less pronounced than one might expect from the size of the lesions. In three cases, there was even no mass effect at al. Less than half of the tumors were homogeneous. Atypical MRI findings were marked mass effect, extensive edema, and gyral-like appearance. After radiotherapy, in two patients a decrease in tumor size but no change of signal intensity of the lesions was noted.

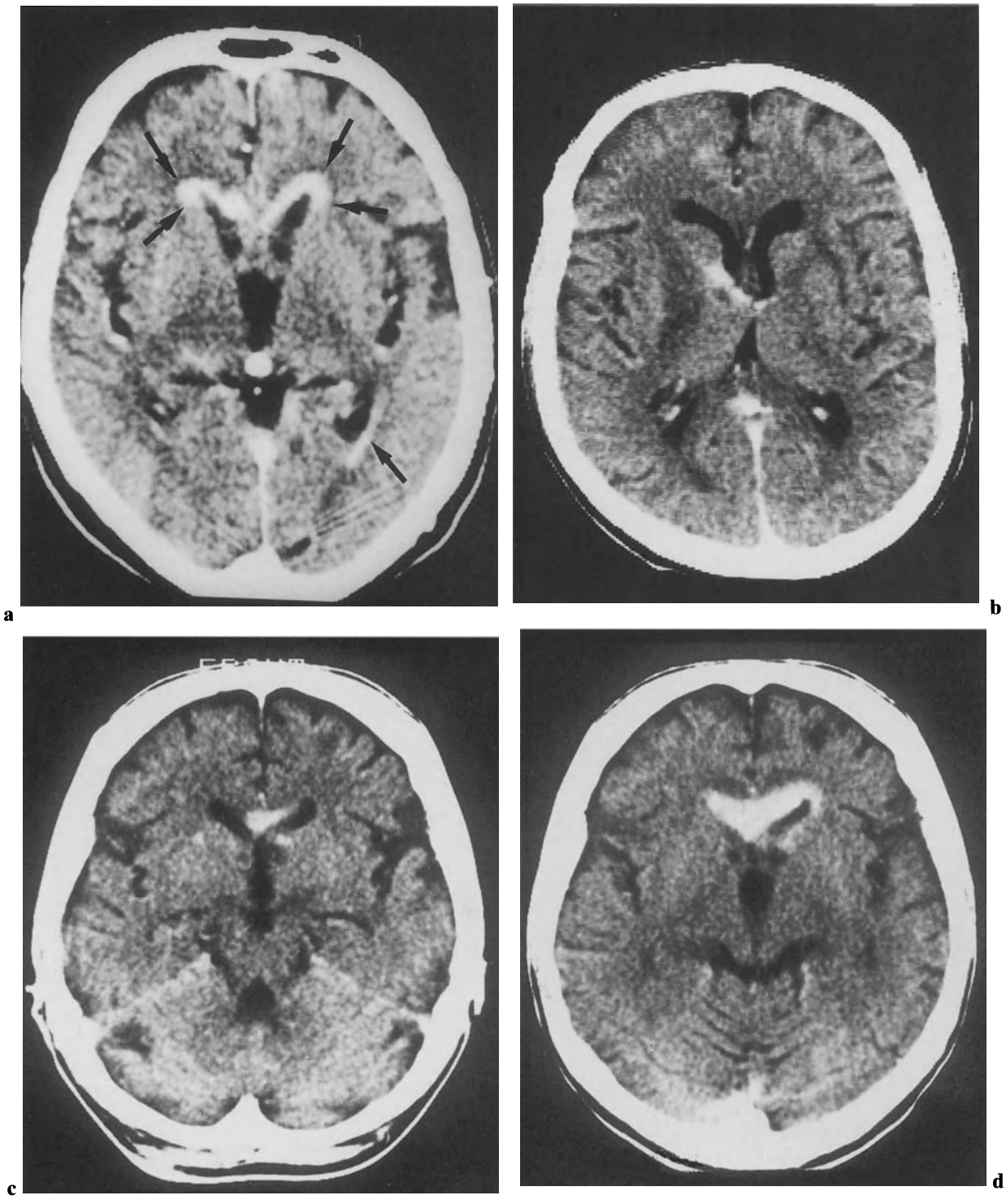


Fig. 2.29 a–d. CT appearance of periventricular, systemic lymphomas. **a** Demonstration of this very characteristic pattern of tumor spread. The image was obtained from a 52-year-old patient presenting with dementia and seizures, followed by coma. CSF analysis revealed lymphocytic pleocytosis. Contrast-enhanced CT showed very well the enhancing tumor tissue as subependymal rims bilaterally *(arrows)*. **b** A similar, more discrete finding. **c** Initial CT study. **d** Follow-up examination performed 4 weeks later. An extensive growth of the tumor can be seen

Cordoliani et al. (1992) analysed the MR features of biopsy-proved cerebral lymphomas in 17 patients with AIDS. In 10 of these cases the primary cerebral lymphoma was unifocal. The tumors were most frequently located in the paraventricular white matter (8/17); lymphomas at the gray matter-white matter junction (5/17), surrounding the ventricles (2/17) and originating from the basal ganglia (2/17) were less frequent. There was an obvious tendency to large lesions, with 14 tumors of 3 cm or more in diameter. On T1-WI, 11 lesions were hypointense, 2 were isointense and 3 were hyperintense to gray matter. A focus of increased signal intensity on T1-WI, corresponding to a hemorrhagic zone, was observed in 2 lesions only. On T2-WI 2 tumors were hypointense, 1 was isointense, 13 were heterogeneous with hypointense (4/17) or hyperintense (4/17) foci. The contrast enhancement was heterogeneous with peripheral predominance in 15, homogeneous and global in 2 patients. In 9 lesions the mass effect was less than expected from the tumor size, reflecting the infiltrating character of the lesions.

Ciricillo and Rosenblum (1990) reported that in their series 71 % of solitary lesions detected on MRI images were lymphomas. They advised not to treat such patients on a trial basis for toxoplasmosis but to perform early biopsy.

Neoplastic angioendotheliomatosis of the CNS as a variant of a malignant lymphoma was observed in an HIV-infected child with PDL and intracranial cryptococcosis (Dozic et al. 1990).

Very rarely the spinal cord is the original site of a primary CNS lymphoma. Thickening of the medulla, increased signal intensity on T2-WI, and contrast enhancement are the MRI findings (Itami et al. 1986; Klein et al. 1990).

Further aspects of MRI in CNS lymphomas are discussed in the literature (De La Paz et al. 1986; Jarvik et al. 1988 a).

CNS Involvement in Systemic Lymphoma

In about 20 %–40 % of AIDS-associated systemic non-Hodgkin's lymphomas CNS involvement is present (Ioachim et al. 1985; Ziegler et al. 1984). In patients with cerebral manifestation, contrast-enhancing lesions are demonstrated by CT and/or MRI (Fig. 2.29). The diagnosis of leptomeningeal spread, which is the most important pattern, can be confirmed by CSF analysis. It does not imply a worse prognosis (Levine 1991). The exact localization and determination of the extension of the meningeal involvement, however, is seldom successful by means of CT or MRI (Levy et al. 1985; Pagani et al. 1981; Palacios et al. 1982; Sze et al. 1987). There have been anecdotal reports on cases with intracranial non-Hodgkin's lymphoma appearing as nonenhancing cerebral lesions on CT (Brun et al. 1986). In our experience this can be interpreted as the development of perifocal edema, adjacent to leptomeningeal lymphoma.

Hodgkin's Disease

The probability of developing Hodgkin's lymphoma is not increased in HIV-infected patients (Kaplan 1988). The natural history and the response to therapeutic procedures, however, are influenced by the underlying immunodeficiency. Subtypes of a mixed cellularity are more frequent than nodular sclerotic variants. The median survival of these patients is less than 1 year, compared to 12 years in non-HIV-infected patients with Hodgkin's disease (Kaplan 1991). From a neuroradiological viewpoint it must be considered that these patients are at a very high risk of developing intracranial opportunistic infections. Hair et al. (1991) described the unusual case of a cerebral manifestation of Hodgkin's disease.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LG) is a multisystem disease in which pulmonary symptoms usually predominate. Generally it is rapidly progressive and has a fatal outcome because of respiratory failure or sepsis. CNS symptoms indicate an unfavorable prognosis. There are a few reports on therapeutic successes by the use of steroids, intrathecal methotrexate, or radiotherapy. Neuropathological examinations reveal localized or widespread foci of cerebral parenchymal softening, cavitation, and necrosis. They contain mixed inflammatory infiltrates of lymphocytes and histiocytes, and rarely granulomas. The infiltrates are angiocentric. The affected vessels show luminal thrombosis and fibrin deposits in the vessel wall. Infarction and coagulative necrosis result from these changes. The pathogenesis of LG is not definitely understood. It is classified among the T-cell lymphomas (Kadin and Said 1988) but has also been considered as a reactive or preneoplastic process (Hood et al. 1982). The complex relations between LG, HIV-type giant cells, and lymphoma (Mizusawa et al. 1987) and the role of EBV

infection in the pathogenesis of AIDS-associated lymphoma (Ciobanu and Wiernik 1986; Hochberg et al. 1983; Rosenberg et al. 1986) are not yet clear.

Anders et al. (1989) reported on clinical, CT, and neuropatholgical findings in three LG cases. Diagnostic imaging was performed in two of these cases, yielding normal findings in one and multiple intracranial mass lesions in the other. At autopsy gross neuropathological examinations revealed multiple necrotic foci in the deep frontal and periventricular white matter, in the thalamus and deep gray matter, and in the basis pontis.

The concept of LG has not gained general acceptance, and some authors discuss whether there is a true difference between what is called LG and lymphoma in the immunocompromised host (Colby 1989).

Intracranial Tumors and Metastases

The risk of HIV-infected person aquiring a carcinoma is at least slightly increased (Höffken et al. 1988; Monfardini et al. 1989; Müller-Hermelink and Borisch 1988). Cutaneous Kaposi's sarcoma is the second most frequent clinical manifestation of AIDS and the most frequent extracerebral tumor in this group (Jaffe et al. 1983). The incidence is estimated from 12% to 30% (Helm et al. 1988; Enzinger and Weiss 1988; Ziegler and Dorfmann 1988) of all AIDS patients. Metastatic spread of the tumor to visceral organs is seen with a high frequency. Intracranial manifestation is rare (Gorin et al. 1985; Hymes et al. 1981). Levy et al. (1985) reported on two patients suffering from cerebral Kaposi's sarcoma metastases. The CT findings of the two patients of Levy et al. (1985) had been published by Kelly and Brant-Zawadzki in 1983. In one patient a homogeneously contrast-enhancing lesion of the frontal lobe without mass effect was seen. At the neuropathological examination, the lesions of both patients proved to be hemorrhagic. Bernstein (1992) described a patient with AIDS and metastatic adenocarcinoma to the brain whose CT showed multiple lesions in the hemispheres with rim enhancement and moderate mass effect and perifocal edema. To our knowledge, no MRI findings or data concerning intracranial metastases in AIDS patients have been published. With respect to MRI of intracranial metastases in non-AIDS patients, we refer to the literature (Claussen et al. 1985; Healy et al. 1987; Kortman and Bradley 1988; Russel et al. 1987).

Further reports on extraordinary cases include the observation of an eosinophilic granuloma of the orbital apex and cavernous sinus in an HIV-infected patient. Radiotherapy led to clinical improvement (Gross et al. 1989). In a retrospective study evaluating the clinical data of intravenous drug addicts in Italy, three cases of glioblastoma and one of medulloblastoma were found (Monfardini et al. 1989). Whether the natural course, response to therapy, or appearance of the tumors on CT or MRI differed, however, from that in non-HIV-infected patients was not reported in this article. Ho et al. (1991) examined an astrocytoma of a HIV-infected patient that was severely infected by CMV. They pointed out that these tumor cells are susceptible to the CMV infection, and that the hyperplasia of the endothelium and the disrupted blood-brain barrier even facilitate the entry of CMV into the tumor.

■ Vascular Manifestations

Cerebrovascular diseases are frequently seen in unselected patient groups. Thus, it is difficult to confirm a pathogenetic relation when an AIDS patient presents with a cerebrovascular disease. Generally such disturbances are far less frequent than opportunistic infections and neoplasms. As in the non-AIDS population, acute and chronic, hemorrhagic and ischemic lesions can be distinguished. The incidence of vascular complications in AIDS patients has been estimated between 7% and 19% (Anders et al. 1986; Levy et al. 1988; Snider et al. 1983). Berger et al. (1990) evaluated autopsy data and found evidence of recent cerebrovascular disease in 8% of adult patients with AIDS. The autopsies of 111 patients without HIV infection in the age range of 20–50 years, however, revealed recent cerebrovascular disease in 23%.

Aneurysms of major cerebral vessels have been documented in 2 HIV-infected children on antiretroviral treatment protocol (Husson et al. 1992). Lazar et al. (1992) presented a case of cerebral arteritis in an AIDS patient with a history of amphetamine abuse who was on antiretroviral therapy. CT and MRI revealed multiple foci of contrast enhancement at the periphery of the hemispheres, together with ischemic and hemorrhagic parenchymal lesions. Angiography and autopsy revealed arteritis with aneurysmal dilatation and stenoses of leptomeningeal vessels. We neither expected nor observed systematic differences in the CT and MRI findings of cerebrovascular lesions between non-AIDS and AIDS patients. Thus diagnostic imaging of intracranial hemorrhage and cerebral infarction can be guided by the experience gathered in the non-AIDS population.

Hemorrhagic Lesions

Intracranial hemorrhage associated with metastases of Kaposi's sarcoma and cerebral lymphoma has been described (Elkin et al. 1985; Levy et al. 1985). Thrombocytopenia, as an autoimmune phenomenon or as a side effect of medication, frequently occurs in HIV infection (Walsh et al. 1985). There are some casuistic reports on subarachnoid hemorrhage in thrombocytopenic AIDS patients (Bursztyn et al. 1984; Elkin et al. 1985; Silvestrini et al. 1990; Snider et al. 1983), on hemorrhage due to mycotic aneurysm (De Gans and Portegies 1989), and on subdural hematoma (Maleßa et al. 1988). However, it must be noted that the clinical relevance of these findings is frequently limited by the poor general condition of the patients. Generally, HIV-infected hemophiliacs are at an increased risk of suffering from an intracranial hemorrhage in the course of their disease (De Behnke and Angelos 1990; Esiri et al. 1989; Takayama et al. 1990). We observed one hemophilic patient with a CMV encephalitis and hemorrhagic lesions and one intravenous drug-addicted patient who incurred a hemorrhagic parenchymal contusion following a generalized seizure. In one female patient with severe AIDS-related thrombocytopenia we observed a fatal intracranial mass hemorrhage during the terminal stage (Figs. 2.30, 2.31). During the acute phase of hemorrhage, CT showed hyperdense lesions in these patients, as is well known from nonimmunocompromised patients. A similar case of fatal parenchymal hemorrhage due to immune thrombocytopenia was found with a child (Park et al. 1990).

CT shows the acute cerebral hematoma as a sharply demarcated, hyperdense area, surrounded by a more or less thin hypodense rim. The X-ray absorption of the hematoma is determined by the blood components. Plasma absorbs with 24 HU, hemoglobin increases the absorption with 0.2 HU per 1 g Hb/I. In anemia, hematoms can therefore show an atypical low density. Shrinkage of the clot during the subacute phase can result in an increase in density. Degradation of hemoglobin and resorption of the clot lead to decreased density up to isodense values. During this phase contrast enhancement of the surrounding tissue, due mainly to neovascularization and scar formation, can give most important diagnostic clues.

CT is a highly effective diagnostic method for confirming a subarachnoid hemorrhage. Thus lumbar puncture is not needed in most of these cases. The key finding is hyperdense liquid in the basal cisterns, over the convexities, and in the interhemispheric fissure. Due to degradation of blood and CSF circulation, the visibility of subarachnoid blood collection is limited to the fourth to sixth days after hemorrhage. Subdural hematomas frequently show a biconcave configuration. Initial densities are between 55 and 85 HU. Occasionally, different layers with increased density in the lower and decreased density in the upper parts are visible. The density of subdural hematomas shows a variable time course. They are hyperdense during the first 7–10 days, isodense during the following weeks, and after clearance become hypodense to the brain tissue. After the administration of contrast material either direct enhancement of a pseudocapsule or indirect demarcation due to increased density of the normal brain can occur. Numerous factors such as age and localization of hemorrhage, magnetic field strength, and applied pulse sequences influence the MRI ap-

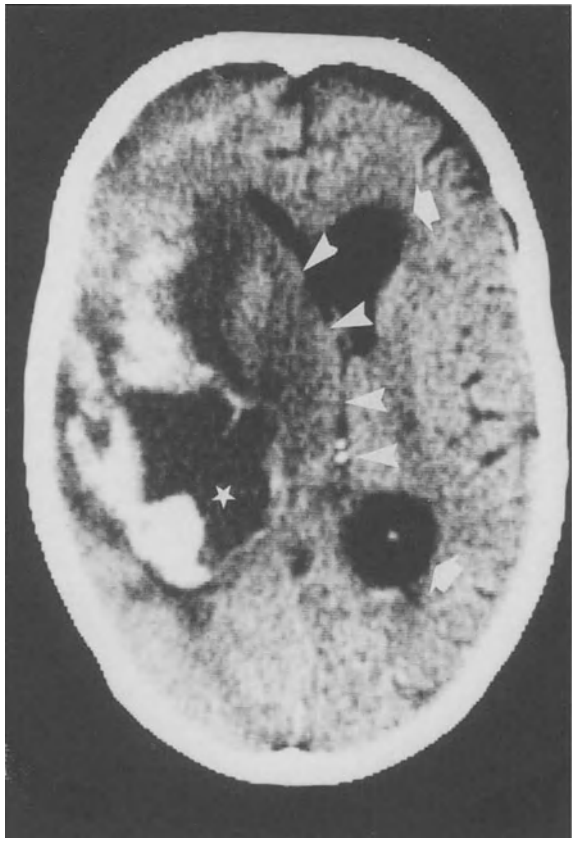
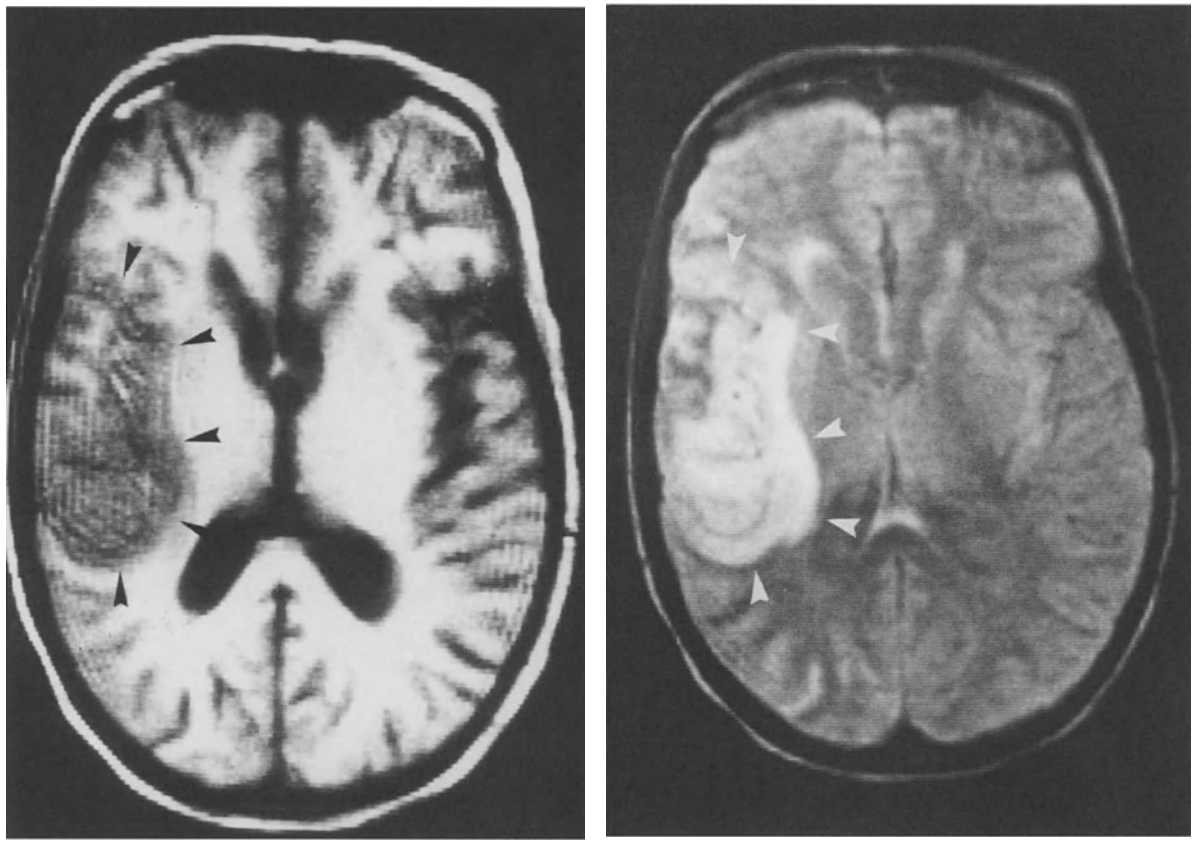


Fig. 2.30. CT appearance of a subacute, massive intracranial hemorrhage that occurred during the terminal stage of an AIDS patient with pancytopenia. The examination was performed 6 days after the worsening of the patient's condition. The hemorrhage is depicted as an inhomogeneous, hyperdense area, surrounding a hypodense mass *(asterisk)*. There is considerable midline shift *(arrowheads)* and enlargement of the contralateral ventricle *(arrows)* due to disturbed CSF circulation. At autopsy, the hypodense mass proved to be a collection of a semiliquid, plasmalike substance



a **b**

Fig. 2.31 a, b. MRI appearance of an acute intracranial hemorrhage; same case as in Fig. 2.30 – however, the MRI examination was performed 4 days earlier, 2 days after the worsening of the patient's condition. **a** T1-WI shows a large, oval lesion *(black arrowheads)* adjacent to the region of the right basal ganglia, involving basal ganglia, white matter, and cortex. **b** At the T2-WI the lesion appears hyperintense. Taking the development of the lesion *(white arrowheads)* into account (note the difference to Fig. 2.30), a slowly progressing or a recurrent hemorrhage must be presumed

pearance of extravasated blood. The major factor is the content of hemoglobin and its degradation products in the clot. In its functionally intact intravascular state, hemoglobin is able to bind oxygen in a reversible fashion, forming oxyhemoglobin from deoxyhemoglobin. A prerequisite for this mechanism is the presence of reduced Fe^{2+} in the hemmolecule. Fe is sustained in this reduced form by energy-dependent metabolic processes. When these mechanisms are disturbed (e. g., in extravasated blood), oxidation to Fe^{3+} results in the formation of methemoglobin. Further oxidative degradation leads to hemichromes. The paramagnetic methemoglobin in particular causes a shortening of the T1 relaxation time.

The MRI appearance of parenchymal hemorrhage has been described with respect to various categories (Bradley 1988). These are: (a) age of hemorrhage and clot (i. e., hyperacute <24 h, acute 1st–3rd days, subacute 3rd–14th days, chronic >14 days), (b) structure of the lesion (inner and outer core, rim, adjacent brain tissue), (c) image contrasts (T1-WI, T2-WI, type of pulse sequence), and (d) magnetic field strength. On T1-WI inner and outer compartments of the hematoma are initially isointense to the brain tissue. Formation of methemoglobin leads to a shortening of T1 relaxation time and thus to an increase in signal intensity. The formation of methemoglobin progresses from the outer to the inner parts. Increased signal intensity on T1-WI is therefore first observed in the outer core (in the subacute phase), followed by an increase in signal intensity in the inner core (in the chronic phase). On T2-WI hyperacute hemorrhages are generally isointense to the brain tissue. Intact erythrocytes in the clot contain an increasing amount of deoxyhemoglobin; thus, especially when a higher field strength is used, the center of a clot appears hypointense. The subsequent lysis of erythrocytes and methemoglobin formation causes a lengthening of the T2 relaxation time, seen as high sig-

nal intensity on T2-WI during the subacute and chronic stages. A rim of low signal intensity surrounding the hematoma can be seen on higher magnetic field strength during the subacute and chronic phase. This is caused by hemosiderin-containing macrophages, which lead to a local shortening of the T2 relaxation time. The adjacent brain tissue is hypointense on T1-WI and hyperintense on T2-WI during the hyperacute to the subacute stage. This results from the formation of perifocal edema.

For special aspects of the use of high or low magnetic field strength and gradient-echo sequences we refer to the literature (Gomori et al. 1985; Sipponen et al. 1985; Edelman et al. 1986).

Epidural and Subdural Hematoma, Subarachnoid Hemorrhage

Generally, CT is the most sensitive method during the first 24 h after the onset of intracranial hemorrhage. Regarding the time course of signal intensity on MRI images, epidural and subdural hematomas follow basically the same schedule. In the hyperacute phase subdural hematomas are partially coagulated and contain oxy- as well as deoxyhemoglobin. At the time they appear slightly hyperintense to the brain tissue on T1- and T2-WI. In the acute phase the signal itensity decreases. Deoxyhemoglobin in intact red blood cells shortens the T2 relaxation time. Subdural hematomas in the acute phase appear isointense on T1- and hyperintense on T2-WI. The subacute subdural hematoma is isodense on CT (Fig. 2.32). Its red blood cells are lysed. Deoxyhemoglobin is oxidated to methemoglobin. The resulting decrease in T1 and increase in T2 relaxation time is the cause of the hyperintensity of the hematoma on T1- and T2-WI (Fig. 2.33). During the chronic stage, when the hematoma has become hypodense on CT, further degradation products of hemoglobin determine its MRI appearance. Hemichromes are not paramagnetic. Their T1 relaxation time is longer than that of methemoglobin. Subdural hematomas in the chronic stage therefore have a reduced signal intensity as compared with the subacute stage. However, they are still hyperintense to CSF and brain tissue.

The signal intensity of subarachnoid blood is determined by the protons of the CSF and the state of the extravasated hemoglobin. Recently extravasated blood in the subarachnoid space shows only a slightly higher signal intensity than the adjacent brain tissue on T1-WI. Subsequently the signal intensity increases,

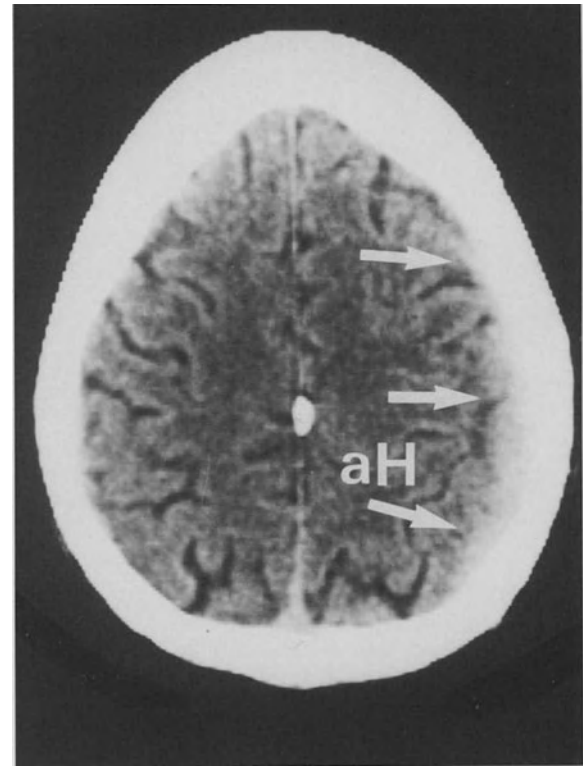
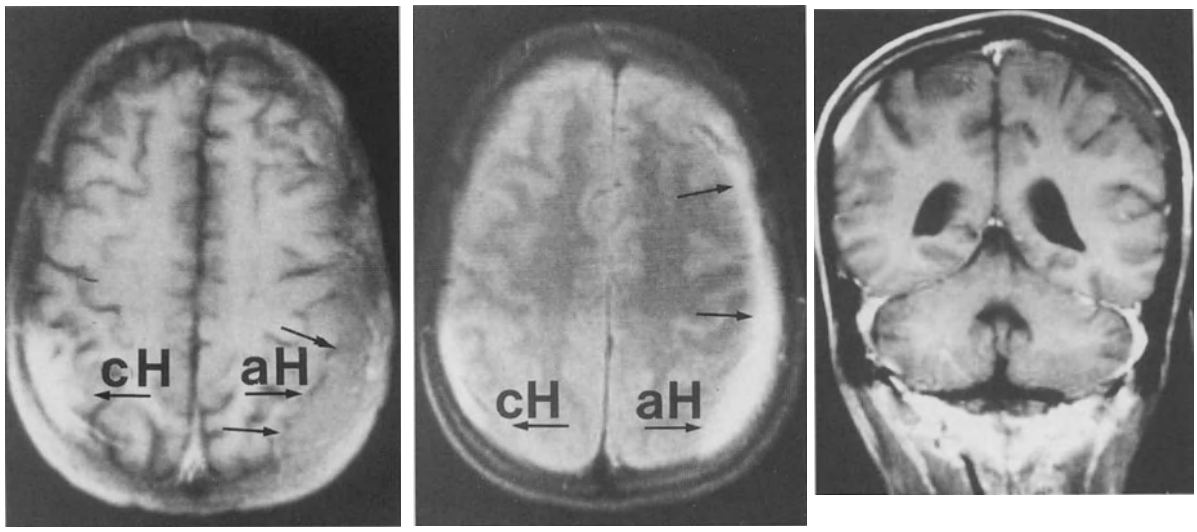


Fig. 2.32. CT appearance of a spontaneous subdural hematoma in an AIDS patient suffering from Burkitt's lymphoma. Over the left hemisphere, a concave, hyperdense rim can be seen between the cortical surface and the inner surface of the skull. This corresponds to a subacute hemorrhagic effusion in the subdural space *(white arrows)*

and after 1 week the subarachnoid blood appears hyperintense on T1-WI (Bradley and Schmidt 1985).

Ischemic Lesions

Ischemic cerebral infarction is a relatively rare complication of AIDS. The retrospective analysis of clinical and pathological data of over 1000 AIDS patients by Engstrom et al. (1988) suggested cerebral ischemia or infarction in 28 patients. In the autopsy study published by Berger et al. (1990) ischemic brain disease was more common than cerebral hemorrhage in AIDS patients. Associated cardiac disease was among the major risk factors. Most of the cerebral infarctions found by neuropathological examination had been clinically silent (Mizusawa et al. 1988). Infections that may result in vasculitis are caused by *Treponema pallidum,* CMV, *Mycobacterium tuberculosis* (Villoria et al. 1992), *Cryptococcus neoformans,* VZV, *Aspergillus*



a–c

Fig. 2.33 a–c. MRI appearance of a spontaneous subdural hematoma; same case as in Fig. 2.32. **a** T2-WI reveals hyperintense rims over both hemispheres. **b, c** T1-WI show a hyperintense effusion over the right hemisphere (chronic hematoma, *cH*) and a isointense hematoma over the left hemisphere (acute hematoma, *aH*)

fumigatus, Mucor mucor, and *Toxoplasma gondii* (Carneiro et al. 1991; Engstrom et al. 1989). Even HIV has been discussed as a causative agent for alterations in the leptomeningeal and cerebral vessels (Park et al. 1990; Scaravilli et al. 1989). Lang et al. (1989) reported on one case of fatal basilar artery occlusion due to syphilitic arteritis. In the case reported by Morgello and Laufer (1989) cerebral angiography revealed moyamoya disease. At autopsy quaternary neurosyphilis with meningovascular changes and necrotizing foci was found. Berthoty et al. (1988) investigated formalin-fixed brains of patients with AIDS encephalopathy. In this postmortem study they observed infarctions of basal ganglia, brain stem, and cerebellum, caused by an infection of local endothelium by CMV (see also Grafe et al. 1990).

Among the possible noninfectious causes of ischemic brain infarctions in AIDS patients are circulating lupus anticoagulant factors (Bloom et al. 1986; Cohen et al. 1986; Fisher and McGhee 1986; Kelly et al. 1984), anticardiolipin antibodies (Keeling et al. 1990), the development of hyperviscosity syndrome (Martin et al. 1989), and lymphomatoid granulomatosis (Anders et al. 1989). Further available data concerning ischemic brain lesions in AIDS patients are related mainly to infarctions of thromboembolic or vasculitis origin (Anders et al. 1986; Atalaia et al. 1992; Bursztyn et al. 1984; Cho et al. 1987; De Gans and Portegies 1989; Garcia et al. 1983; Joshi et al. 1987; Kugler et al. 1991; Labange et al. 1991; Levy et al. 1985; Moskowitz et al. 1984b; Scaravilli et al 1989; Schwartz et al. 1986; Snider et al. 1983; Sze et al. 1987; Vinters et al. 1988).

CT imaging in cerebral infarctions has been extensively investigated in the past (Valk 1980). In most cases, 24–48 h after the stroke CT is negative. At that time a hypodense lesion is visible on CT in only 10% of cases. Between the third and seventh days such a lesion is detectable in about 70% of all cases. A mass effect may be present; however, it is generally not representative of the spatial extension of the lesion. The sites of predilection are in accordance with the territories of vascular supply and their border zones. An increase in density after intravenous administration of contrast material at that time is in most cases detectable only after quantitative evaluation. From the second week after onset of the stroke, and subsequently for 1–3 months, focal contrast enhancement due to blood-brain barrier disruption, luxury perfusion, and neovascularization is observed. In this phase, the infarct can be isodense (so-called "fogging effect"), so that only indirect signs such as mass effect or contrast enhancement allow a detection by CT (Becker et al. 1979). The end-stage is characterized mainly by scar formation and substance loss. Then, the lesion is isodense to CSF, not contrast-enhancing, and smaller than the formerly infarcted area. Traction effects to surrounding structures may result. Aneurysmal arteriopathy associated with HIV antigen in the arterial wall is a possible origin of thrombi and subse-

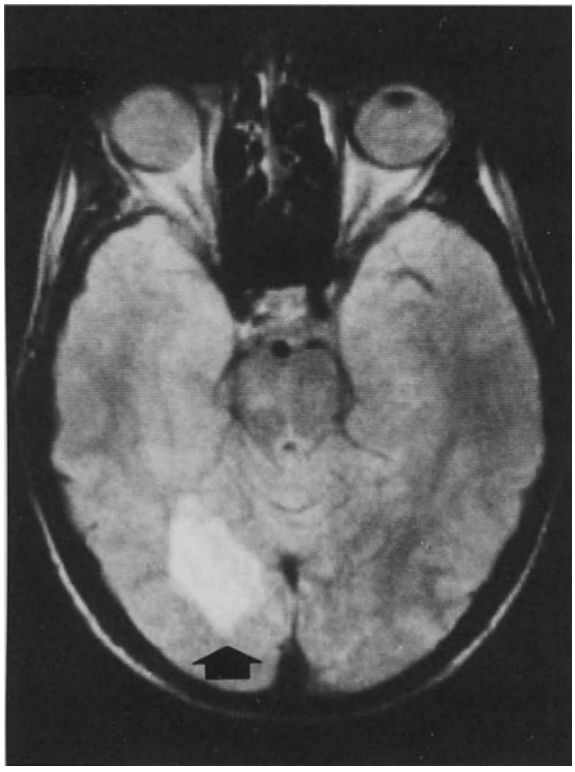


Fig. 2.34. MRI appearance of an ischemic brain infarct, observed in an AIDS patient with previous cerebral toxoplasmosis. T2-WI shows a confluent, hyperintense lesion in the right occipital lobe that can be attributed to the territory of the posterior cerebral artery. An ischemic infart was confirmed at autopsy

quent infarctions. In the case reported by Kure et al. (1989b) both cerebral angiogram and contrast-enhanced CT demonstrated tortuosity and dilatation of the arteries of the circle of Willis. Yankner et al. (1986) published the imaging findings of an AIDS patient with focal neurological deficits caused by granulomatous angiitis. The CT scan showed multiple nonenhancing parenchymal lesions; the cerebral angiography revealed multisegmental vessel narrowing.

Generally MRI can be regarded as more sensitive than CT for early detection of cerebral ischemic lesions (Brant-Zawadzki 1988; Steinbrich et al. 1986; Fig. 2.34). In the subacute phase, Gd-DTPA enhanced MRI depicts more clearly than any other method the disruption of the blood-brain barrier (Imakita et al. 1987; Henkes et al. 1989).

There are also reports concerning the MRI of ischemic lesions in HIV-infected patients. In the pediatric case of Raphael et al. (1989), T2-WI was better than CT at revealing lesions of the thalamus and parieto-occipital region, which at autopsy proved to be HIV-induced vasculitic infarctions. Tien et al. (1992) reported on neurosyphilis in HIV carriers as a cause of ischemic lesions of the basal ganglia and cortex. The subcortical gray matter was hyperintense on T2-WI, post-Gd-DTPA T1-WI showed patchy enhancement. The affected cortical regions showed gyriform enhancement.

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Chapter 3

Neuropathology of AIDS

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■ Introduction and Overview of Cases

Between 1986 and 1991, around 1000 HIV patients were treated at the Auguste-Viktoria Krankenhaus (AVK) in Berlin. Among the 395 AIDS patients who died at the Hospital during this period, 180 autopsies (46 %) were carried out. From 1986 to 1990 the annual number of autopsies rose continually. Table 3.1 presents the distribution of opportunistic infectious complications typical of AIDS that we found in these 180 autopsies.

Occurring in 14 cases (8 %), invasive aspergillosis was twice as frequent as cryptococcosis, a mycotic complication typical of AIDS; however, aspergillosis is a mycosis not exclusively dependent on AIDS and occurs in AIDS patients as a result of additional dispositional factors. The same is true of *Candida* mycosis in its disseminated course or as deep organ mycosis. By contrast, pure oropharyngeal or esophageal mucosa involvement through *Candida albicans* can occur very frequently in AIDS patients, but as a result of prophylactic and local therapeutic measures it was found hardly at all in our autopsy material. The first cases of an invasive aspergillosis were diagnosed at the beginning of 1988. Each of these acute *Aspergillus* infections signaled a terminal stage in AIDS, with multiple complications in the lungs and substantial impact on therapy. To a large extent, the frequency of cytomegalic disease (Cytomegalovirus, CMV infection) and the atypical mycobacterial infection (*Mycobacterium avium* intracellulare) remained constant over the study period from 1986 to 1991. Only in the case of toxoplasmosis did we observe an increase when comparing the first and second half of the autopsy material (12 cases from 1987–1988, compared with 31 cases from 1990–1991). Among the 56 cases of toxoplasmosis, 8 (15 %; 4 % of all 180 AIDS autopsies) showed an extracerebral manifestation. *Pneumocystis carinii* pneumonia remained almost constant in terms of frequency in our autopsy material; however, there was a change in the clinical picture, with chronic or chronically recurrent pulmonary changes with interstitial fibrosis, emphysema, or cavernous-cystic pulmonary changes becoming prominent. In connection with this, at the end of 1988 we saw the first cases with a spontaneous pneumothorax and with a disseminated pneumocystis infection. Among the 54 cases of *P. carinii* pneumonia there were 8 (15 %; 4 % of all 180 AIDS autopsies) with extrapulmonary and sometimes disseminated *P. carinii* infection.

The neoplastic complications in the 180 AIDS autopsies are presented in Table 3.2. Of the cases of Ka-

Table 3.1. Opportunistic infectious complications in 180 AIDS autopsies

	n	%
Cytomegalovirus infection	90	50
Toxoplasmosis of the CNS	56	31
Pneumocystis carinii pneumonia	54	30
Mycobacterium avium intracellulare	26	14
Invasive *Aspergillus* infection	14	8
Mycobacterium tuberculosis	9	5
Progressive multifocal leukoencephalopathy	8	4
Cryptococcal infection	7	4
Candida infection (pulmonary or disseminated)	4	2

Table 3.2. Neoplastic complications (n=180)

	n	%
Double infection	56	31
Triple infection	25	14
Fourfold infection	5	3
Total	86	48

Table 3.3. Multiple opportunistic infections (n=180)

	n	%
Double affection	59	33
Triple affection	40	22
Fourfold affection	10	6
Fivefold affection	2	1
Total	111	62

Table 3.4. Multiple complications (opportunistic infections and neoplasias; n=180)

	n	%
Double affection	59	33
Triple affection	40	22
Fourfold affection	10	6
Fivefold affection	2	1
Total	111	62

Table 3.5. Autopsies of AIDS patients in whom one single opportunistic infectious complication was the cause of death (n=180)

	n	%
Toxoplasmosis	14	7.8
Cryptococcal infection	5	2.8
Pneumocystis carinii pneumonia	4	2.2
Progressive multifocal leukoencephalopathy	4	2.2
Tuberculosis	3	1.7
Total	30	16.7

Table 3.6. Autopsies of AIDS patients in whom the direct cause of death was a neoplastic complication (n=180)

	n	%
Kaposi's sarcoma	5	2.7
Malignant lymphoma	6	3.3
Total	11	6.0

posi's sarcoma 56 % showed tumor infiltrates outside the integument, sometimes with a disseminated spread. Of the 25 cases of malignant lymphomas, 44 % had a lymphoma manifestation exclusively in the CNS (11 cases; 6 % of all 180 autopsy cases). In the patients who died in the terminal stages of AIDS, the opportunistic infections and neoplastic complications were frequently combined, with multiple complications up to five simultaneous affections in the same patient. As Table 3.3 shows, in 86 patients (48 %) out of the 180 autopsy cases there were two or more simultaneous opportunistic infectious complications. In 111 (62 %) of the cases we detected between two and five simultaneous affections in the same patient (Table 3.4). On the other hand, in some individual autopsy cases (four) we detected no clear opportunistic infectious or neoplastic AIDS complications. In four more cases it was a direct CNS alteration caused by HIV, without any additional opportunistic infectious complications or neoplasia that was evidently responsible for the fatal outcome. Otherwise, in most cases the cause of death was protracted circulatory insufficiency or pulmonary changes with multiple opportunistic infections, sometimes associated with cachexia (the so-called wasting syndrome) and sometimes complicated by simultaneous neoplastic infiltrates or influenced by side effects of therapy. In several cases only one individual opportunistic infection was responsible for the fatal outcome (Table 3.5). Table 3.6 presents the cases in which neoplastic processes were the only detectable AIDS complication resulting in death. In four cases a malignant lymphoma of the CNS alone was responsible for the death due to pressure in the brain. Another interesting finding was a combination of CNS lymphoma and toxoplasmosis of the CNS, which we detected in five cases.

In some individual cases, AIDS complications which had been detected clinically could not be detected in the autopsy, or at most only in minimal residues. This applied to some AIDS patients in whom *P. carinii* pneumonia was practically no longer detectable, and where quite different complications had been the cause of death. Of particular interest were two patients with a histologically detected, highly malignant non-Hodgkin's lymphoma in local manifestation. Following lymphoma therapy, we detected no residue of these neoplastic changes in the patients, who had also died of other complications.

■ Methods

The neuropathological findings in AIDS autopsies reveal a very broad spectrum; in addition to the findings already described in classical neuropathology, there are special AIDS-associated changes, the interpretation of which is often uncertain, and which overlap with tissue lesions through opportunistic pathogens. The morphological exploration also repeatedly produces new and unexpected findings, so that all available methods must be used to clarify the etiology and pathogenesis.

The fundamental prerequisite for optimum treatment of the CNS is the early and proper collection of material. The whole brain and spinal cord should be available for the study. The collection and fixation of tissue samples for the various studies must take place during the autopsy and require the presence of the neuropathologist in the autopsy room and close cooperation between the pathologist and the neuropathologist. The later sending of parts of the CNS or only individual tissue samples for neuropathological investigations is problematic and inexpedient; in accordance with observations in the literature (Sotrel 1989), these should not serve as the basis of publications.

The exact macroscopic description and any photographic documentation can take place before the fixation. The storage of tissue samples of the CNS for the conventional histology, the embedding in methacrylate, electron microscopy, immunohistochemistry, microbiology, and whole-brain slide technique is time consuming and cannot as a rule be carried out by the pathologist, who must guarantee the compilation of findings in the remaining organs while adhering to all the measures governing safety and protection against infections. Our experience has shown that this requires the presence of two physicians (pathologist and neuropathologist). The exact opening of the body cavities, proper collection of spinal cord, and optimum hygienic care of the AIDS autopsy corpse (for protection against infections) require in addition the cooperation of an experienced and reliable autopsy assistant or dissector.

For the large majority of findings to be compiled, the embedding of the tissue material in paraffin is ade-

quate. However, the recommendations made for gentle treatment of tissue, which are, for example, also relevant for lymphoma diagnosis, should be heeded (Lennert and Feller 1990). Since the examined tissue samples of the CNS are exclusively autopsy material which – depending on the time that has passed between death and tissue storage – can also exhibit autolytic changes to varying degrees. Embedding these in glycol methacrylate is often useful (Carson 1990). This medium provides an excellent support for every tissue and allows 1- to 2-μm sections to be cut. It is especially useful for vulnerable tissues, such as bone marrow and lymph nodes, and allows the use of numerous staining methods, such as hematoxylin-eosin, period acid–Schiff (PAS), Giemsa, Gomori's method of silver staining, naphthol-AS-D chloracetate esterase, and lectin histochemical methods (mistletoe lectin I; Artigas et al. 1991 c, 1992; Franz et al. 1991). The cytological picture of autolytic tissue is also usually far better conserved than after embedding it in paraffin.

The locations of tissue samplings of the brain and cerebellum for microscopic examination are as follows (terminology from Nieuwenhuys et al. 1988):

- Gyrus rectus + white matter (left)
- Radiatio corporis callosi (left)
- Gyrus frontalis superior + white matter (left)
- Centrum semiovale (frontal white matter) (left)
- Gyrus temporalis superior + planum temporale + gyri temporales transversi (Heschl)
- White matter temporal (left)
- Cuneus + area striata + stria gennari + gyrus occipitotemporalis medialis + white matter (left)
- Radiatio optica + white matter occipital (left)
- Caput nuclei caudati + capsula interna, crus anterior + putamen (left)
- Caput nuclei caudati + capsula interna, crus anterius + putamen (right)
- Thalamus (left)
- Thalamus (right)
- Substantia nigra + nucleus ruber + nucleus subthalamicus (left)
- Substantia nigra + nucleus ruber + nucleus subthalamicus (right)
- Corpus callosum + gyrus cinguli (left)
- Capsula interna, crus posterius (left)
- Capsula interna, crus posterius (right)
- Hemispherium cerebelli (gray matter cerebelli; right)
- Corpus medullare cerebelli (cerebellar white matter; right)
- Nucleus dentatus (right)
- Pons
- Medulla oblongata
- Plexus choroideus
- Spinal cord (cervical)
- Hypophysis
- Plus additional samples from macroscopically visible lesions

For the spinal cord, samples should be taken from two to four transversal sections and from one to three longitudinal sections, through the posterior tracts, at every level (cervical, thoracic and lumbal).

The staining methods and antibodies for immunohistochemical reactions used in this study are presented in Table 3.7. Especially suitable for the representation of HIV antigens in the histological preparation are the antibodies against p24 (Artigas et al. 1989 a) and gp41. Use with paraffin-embedded material is possible; the use of shock-frozen material with frozen sections is, however, much more sensitive, and more positive cells are registered. Our experience shows that tissue material fixed for a short time in formalin is more suitable than tissue which is older and has been fixed for longer (Lutz 1993).

The Epstein-Barr virus (EBV) is a herpesvirus infecting more than 90% of the human population worldwide.* EBV is the etiologic agent of infectious mononucleosis. It is best known for its association with certain malignancies, for example, Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma (Herbst et al. 1990). In vitro, peripheral blood lymphocytes from infected individuals give rise to spontaneous lymphoblastoid cell lines. In these a characteristic set of EBV latent genes is expressed. Two small nuclear RNAs (EBER-1 and -2) with unknown function are transcribed at high copy numbers. Due to their abundance in viral latency, the EBERs are a highly sensitive marker for EBV infection. Moreover, six nuclear proteins (EBNAs) and two membrane proteins (latent membrane protein and terminal protein) are expressed. While little is known about the functions of most of these proteins, the oncogenic potential of the latent membrane protein is well established (Herbst et al. 1991). The latent membrane protein of EBV was detected with a mixture of four monoclonal antibodies, CS 1–4, using the

* The section on EBV detection was written by Gerald Niedobitek and Hermann Herbst, Institute of Pathology, Klinikum Steglitz, Free University of Berlin and Institute of Pathology, Univ. of Birmingham, UK.

Table 3.7. Immunohistochemical staining methods and antibodies

Conventional histological methods	
Hematoxylin-eosin (H&E)	
Periodic acid–Schiff stain (PAS)	
Gomori's reticulin stain	
Van Gieson's stain	
Weil's myelin stain	
Bodian's method (nerve fiber stain)	
Giemsa stain (modification by Lennert)	
Grocott's methenamine silver nitrate fungus stain technique	
Gridley's fungus stain	
Brown-Hopps' modification of the Gram stain	
Ziehl-Neelsen's acid-fast stain	
Auramine O-rhodamine B fluorescent method for tubercle bacilli	
Immunohistochemical methods	
Pathogen antigens	
HIV	
Anti-p17	(British Biotech)
Anti-p24	(Du Pont; DAKO)
Anti-gp41	(Du Pont)
Anti-gp120/160	(Biogenesis)
Anti-gp160	(Biogenesis)
Anti-reverse transcriptase	(British Biotech)
Cytomegalovirus (monoclonal)	(DAKO-CMV, CCH2)
Herpes simplex virus types 1, 2	(DAKO)
Pneumocystis carinii	(DAKO, 3F6)
Toxoplasmosis	(Dr. Deschlein, Berlin, Biogenesis)
Polyomaviruses (polyvalent rabbit antiserum)	(D. L. Walker, Univ. of Wisconsin, USA)
EBV latent membrane proteins CS 1–4	(Drs. L. S. Young and M. Rowe, Birmingham, UK)
Cell markers	
Leukocyte common antigen (2B11+PD7/26)	(DAKO-LCA)
T cell CD45RO	(DAKO, UCHL 1)
B cell CD20	(DAKO, L 26)
Anti-CD4(?)	(DAKO, OPD4)
Macrophage CD68	(DAKO, KP-1)
Ki-1 Antigen CD30	(DAKO, Ber-H2)
HLA-DR	(DAKO, CR3/43)
Epithelial membrane antigen	(DAKO-EMA, E29)
Kappa (light chains)	(DAKO RaO-21-F3)
Lambda (light chains)	(DAKO, N10/2)
IgA rabbit	(DAKO)
IgG rabbit	(DAKO)
IgM rabbit	(DAKO)
Lysozyme (muramidase), rabbit	(DAKO)
Alpha-1-antichymotrypsin	(DAKO)
Mistletoe lectin I (ML I)	(Prof. Dr. Franz, Berlin)
Specific polyclonal rabbit antibody against ML I	(Prof. Dr. Franz, Dr. U. Pfüller, Berlin)
Anti-AZT (azidothymidine, zidovudine)	(Sigma)
Anti-aciclovir	(Sigma)
Glial fibrillary acidic protein	(DAKO, GF2)
Neurofilament protein	(DAKO-NF, 2F11)
Synaptophysin	(DAKO-Sy38)
Tumor necrosis factor α	(T. Meager, NIBSC, Potters Bar, UK)

APAAP technique (Rowe et al. 1987; Herbst et al. 1991; Niedobitek et al. 1991); these were kindly provided by Drs. L. S. Young an M. Rowe (Birmingham, UK). In situ hybridization applies molecular biological principles to tissue sections, thus allowing the demonstration of specific nucleic acid sequences at the single cell level. In situ hybridization for the demonstration of the EBERs was performed according to established protocols (Niedobitek and Herbst 1991). ^{35}S-labeled RNA probes were generated from two plasmids, pBSJJJ1 and pBSJJJ2, harboring EBER-1 and EBER-2 specific inserts, respectively. Transcripts with a sequence complementary to the EBERs (antisense) served as probes, and transcripts with identical sequence (sense) were used as negative controls. To increase the sensitivity, antisense probes from both plasmids were mixed. In brief, paraffin sections were dewaxed, rehydrated, and then exposed to 0.2 *N* HCl, 0.125 mg/ml pronase, and 0.1 *M* triethanolamine pH 8.0/0.25 % (v/v) acetic anhydrid. Sections were dehydrated and hybridized to 2–4×10^5 dpm of labeled probe per slide (in 50 % formamide, 0.3 *M* NaCl 0.03 *M* sodium citrate pH 7.6, 10 % dextran sulfate, 0.5 mg/ml yeast tRNA, 0.1 *M* dithiothreitol) at 50 °C overnight. After washing in 50 % formamide/1×SSC at 52 °C, an RNase digestion (20 µg/ml) was performed to remove non-specifically bound single-stranded RNA probe. The slides were then dehydrated and dipped in Ilford G5 emulsion, exposed for 2–10 days, developed, and counterstained with hematoxylin-eosin.

■ HIV Encephalitis and HIV Leukoencephalopathy

Introduction

Soon after the recognition of AIDS in 1981 it was observed that many patients presented with a varied spectrum of neurological complications. Initially, patients with neurological abnormalities were considered to be affected by opportunistic infections or lymphoma of the CNS. A short time later there appeared the first reports that described in some patients an unusual encephalopathy which had not been noted in other immunosuppressed persons (Horowitz et al. 1982; Gopinathan et al. 1983; Snider et al. 1983a). Mental dysfunction occurs commonly in the setting of fully developed AIDS, but in some cases an inexplica-

ble encephalopathy appears in the course of the disease. This may also be the presenting sign of HIV infection (Mirra et al. 1986b; Petito et al. 1986; Navia et al. 1986b; Navia and Price 1987), and it may appear as the sole manifestation of AIDS (Navia and Price 1987; Kleihues et al. 1991).

Detailed clinicopathological studies (Navia et al. 1986a, b) confirmed that the encephalopathy had a different origin than the neurological abnormalities caused by opportunistic infections and lymphoma observed in AIDS patients (Snider et al. 1983a; Nielsen et al. 1984; Levy et al. 1985a). This condition has been termed clinically as AIDS encephalopathy (Sharer et al. 1985, 1986a; Koenig et al. 1986) and AIDS dementia (Johnson et al. 1988), and currently it is widely known as AIDS dementia complex (ADC; Navia et al. 1986a; Price and Brew 1988; Price et al. 1988a, 1991). However, this term is clinically not fully correct and leads to misinterpretations, and it has therefore been criticized by European authors (Gutierrez-Molina 1989; Möller et al. 1991).

The presence of HIV in the CNS was not recognized until 1985 when Shaw et al., using Southern blot and in situ hybridization techniques, demonstrated the presence of HIV in the brain (Table 3.8). Since then the presence of HIV in brain tissue has been largely demonstrated by direct isolation (Gartner et al. 1986b; Ho et al. 1985; Koenig et al. 1986; Levy et al. 1985b), Southern blot analysis (Shaw et al. 1985), in situ hybridization (Koenig et al. 1986) Stoler et al. 1986; Vazeux et al. 1987; Wiley et al. 1986a) immunohistochemistry (Gabuzda et al. 1986; Gyorkey et al. 1987; Pumarola-Sune et al. 1987; Vazeux et al. 1987; Wiley et al. 1986a) and electron microscopy (Epstein et al. 1985; Gyorkey et al. 1987; Koenig et al. 1986; Meyenhofer et al. 1987; Sharer et al. 1986; Gutierrez-Molina 1989).

The main aim of neuropathological work in the study of AIDS was to find a morphological correlate for the HIV-related encephalopathy, known as ADC, and simultaneously to look for specific HIV-related changes in the CNS. Snider et al. (1983a) and Moskowitz et al. (1984c) described the presence of small and giant multinucleated cells (MNCs) in AIDS brains. In 1985 Sharer et al. first emphasized the importance of MNCs in brains with encephalopathy because similar cells had been reported in lymph nodes in AIDS patients (Brynes et al. 1983; V. V. Joshi et al. 1984; J. R. Anderson 1988). Thereafter, neuropathologists observed remarkable and morphologically new changes in the CNS of some AIDS patients. These were characterized by perivascular infiltration of macrophages and MNCs in the subcortical structures.

Table 3.8. Chronology of principal features in the study of the CNS in AIDS

	Year
Recognition of AIDS	1981
Description of the first peculiar neurological abnormalities in AIDS patients	1982–1983
Description of MNCs in the brain of AIDS patients	1983–1984
First report of the presence of HIV in the brain	1985
Description of vacuolar myelopathy	1985
First detailed clinicopathological studies in ADC	1986
MNCs as histological hallmark of HIV infection of the CNS	1985–1987
Description of HIV myelitis	1991
Neuropathological consensus in the nomenclature of neurological AIDS: HIVE	1991

Table 3.9. Diagnostic criteria for HIV encephalitis

First step: H&E, PAS
Perivascular infiltration of macrophages: as predominant finding can be overlooked in H&E, better recognition in PAS.
Multinucleated cells: obligatory for the diagnosis, but in exceptional cases without MNCs the diagnosis must be confirmed by evidence of HIV antigen (p24/gp41).
Ten examined blocks as minimum; essential regions for examination: centrum semiovale, temporal lobe, corpus callosum, cerebellar white matter, capsula interna and pons.[a]

Second step: myelin stain
Small patchy demyelination: perivascular and correlated with the cell infiltrates

Third step: immunohistochemical methods
Macrophage markers (CD 68: KP1, EBM 11; PG-M1; Lectins:RCA-1, ML I): demonstrate an extensive infiltration of macrophages and microglial cells with formation of perivascular glial nodules, also some MNCs[a]
HIV antibodies (p24/gp41) evidence of HIV antigen in macrophages and MNCs to a variable extent; Definitive probe.[a]
The tissue should not be overfixed, spinal cord < 2–3 weeks in 10% formalin, brain < 6–10 weeks in 10% formalin

[a] Cases with the morphological changes of HIVE visible only in one region we consider to be initial HIVE.

This condition received different names: multifocal giant cell encephalitis (Budka 1986, 1989; Budka et al. 1987; Lang et al. 1989), subacute encephalitis with MNCs (Petito et al. 1986), subacute AIDS encephalitis (Kure et al. 1990a, b), MNC encephalitis (Price et al. 1988), and giant cell encephalitis (Michaels et al. 1988a). Recently, European and American neuropathologists, in a consensus about the nomencla-

ture of HIV-associated diseases of the nervous system, decided to name this condition HIV encephalitis (HIVE; Budka et al. 1991). HIVE has emerged as a basic aspect of the biology of HIV, and it is now known that primary infection of the nervous system by HIV may involve brain, meninges, and spinal cord.

The diagnostic criteria for HIVE are presented in Table 3.9.

The AIDS Virus: HIV

HIV is a ribonucleic acid (RNA) virus of the Retroviridae family and a member of the Lentivirinae subfamily (Chiu et al. 1985). Lentiviruses are so named because of the typically slow progression from infection to overt disease (Latin: *lentus* = slow). HIV-1 and HIV-2 produce immune dysfunction by elimination of CD4 cells. Since excellent papers on HIV are available, we refer the reader to these articles and books (Barnett and Levy 1991; Barré-Sinoussi et al. 1983; Gallo et al. 1984; Levy et al. 1984; Gelderblom et al. 1985, 1989, 1990; Leestma 1991; Meyenhofer et al. 1987; Sidhu 1990).

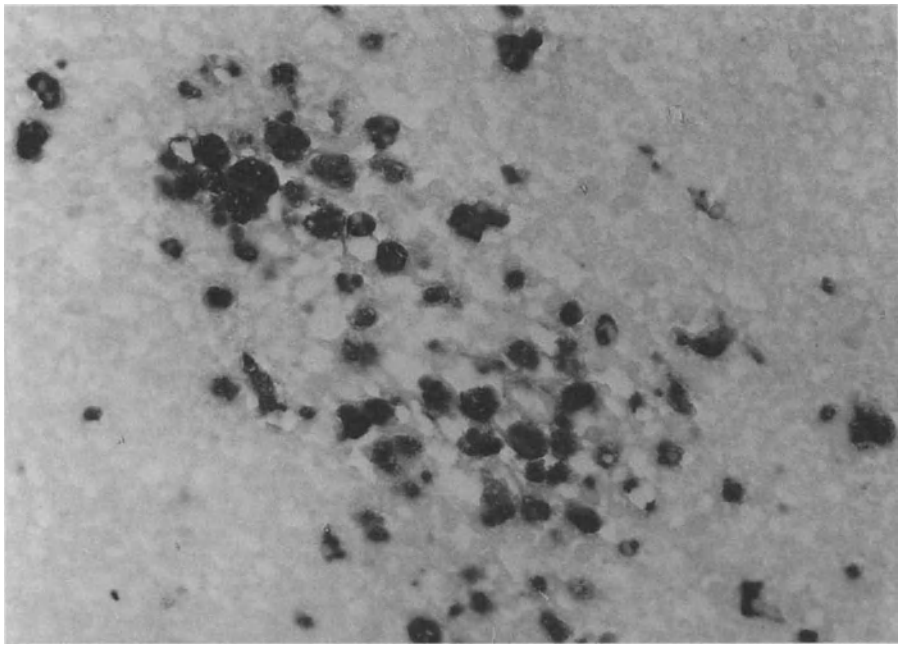
Pathogenesis and Entry of HIV into CNS

HIV is not the only virus that produces immunosuppression (e.g., CMV). However, the immunosuppression in AIDS is more severe because HIV selectively infects and destroys two important cells in the immune system: the helper T-cell and the monocyte. The infection of a stem cell of the bone marrow is questionable (Rübsamen-Waigmann 1990). Loss of helper T-cells results in a decrease in CD4 cells and an inversion of the CD4:CD8 cell ratio. The loss of helper lymphocytes cripples the immune response to HIV and to many other opportunistic infections. The infection of monocytes, as the pivotal cell in the immune response to any infectious agent, is as important as the loss of helper T-cells. With regard to virus replication, recent studies point out the importance of the activated germinal centers of the lymphatic tissue, the interaction between memory-helper T-cells, centroblasts and follicular dendritic cells, and tumor necrosis factor-alpha production in the activated B-cells of the germinal center (Stein et al. 1991). In addition to the memory-helper T-cells and macrophages, the same studies show the follicular dendritic cells in the lymphatic tissue to represent a large HIV reservoir.

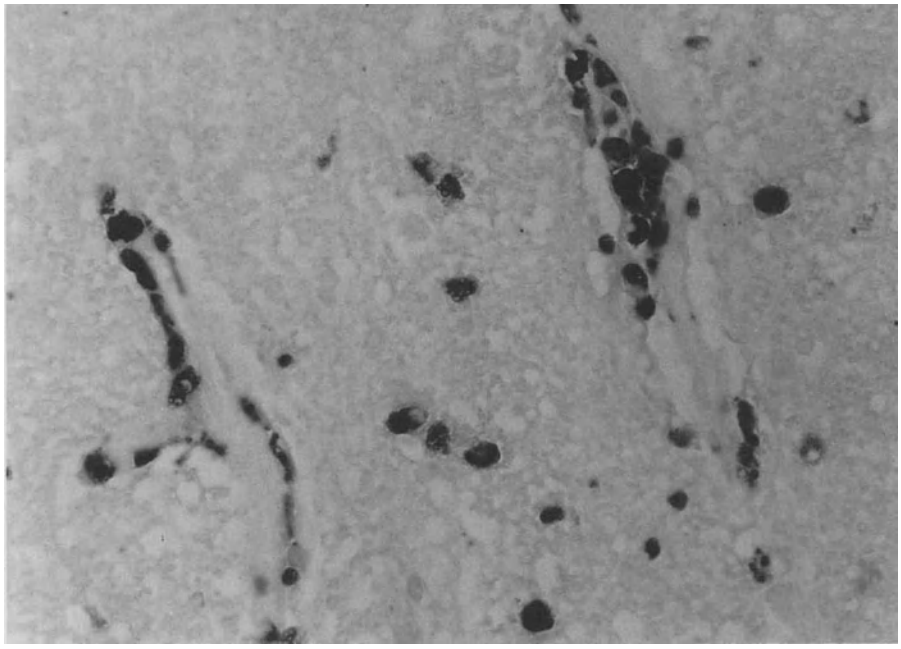
HIV appears early in the course of infection in the cerebrospinal fluid, and an acute or chronic meningitis may occur in the pre-AIDS stages (Johnson et al. 1988; Michaels et al. 1988b; Price et al. 1991). This aseptic meningitis may accompany the early seroconversion-related illness, but it is more common later in the course of HIV infection (Brew et al. 1988). The relationship between meningitis and later progression to parenchymal infections is unclear (Achim et al. 1991). The localization of encephalitic changes due to HIV does not correlate with its spread in the meninges (Budka 1991a).

The most likely candidates for the transport of HIV into the brain are cells belonging to the monocyte/macrophage system. The route of entry of HIV-infected cells is not completely clear. Furthermore, it is not possible to distinguish whether macrophages are infected peripherally and migrate to the CNS, or, less probably, whether they are infected after settling in brain tissue (Vinters and Anders 1990). The latently HIV-infected circulating monocytes are possibly transported across the capillary endothelium in the cerebral tissue (Trojan horse mechanism) (Achim et al. 1991). Another mechanism of viral entry could be through the endothelial cell itself (Tyler and Fields 1989). Wiley et al. (1986a) and Ward et al. (1987) demonstrated HIV infection of endothelial cells; however, these findings were not confirmed by other investigations (Kure et al. 1990a). HIV might also enter the brain transported by infected activated T-lymphocytes, which are known to be the only leukocytes that under physiological conditions cross the brain-blood barrier to patrol the CNS (Meyermann et al. 1987). In numerous preparations of our study material we detected scattered lymphocytes in the perivascular space that immunohistochemically expressed the T-cell marker (CD45RO, UCHL1).

HIV has the ability to cause neurological disease. It enters the CNS, but it does not replicate within the neural or glial cells (astrocytes and oligodendrocytes) of the CNS. Accordingly, HIV shows the characteristics of neuroinvasiveness and neurovirulence, but it lacks the property of CNS cell tropism (Wiley and Budka 1991). Indirect mechanisms of tissue damage appear likely and are probably caused by the release of toxic agents from infected macrophages (tumor necrosis factor, Fig. 3.1; oxidative radicals, proteases, and neurotoxins, e.g., quinolinic acid). Excessive production of these substances is capable of profound destruction of any tissue, and especially the CNS because of its high content of lipids and oxidizable substrates (Halliwell and Gutteridge 1984, 1989; Konat and Wiggings 1985; Nathan 1987; Selmaj and



a



b

Fig. 3.1. a Severe HIV encephalitis. Numerous macrophages in the white matter of the brain showing cytoplasmic positivity to TNF-α. **b** Macrophages and pericytes around two small blood vessels with positive reaction to TNF-α in the cytoplasm. (Monoclonal antibody to TNF-α, biotin streptavidinperoxidase method, ×40, Immunohistochemical study performed by Prof. D. Männel M. D. and A. Kist, Regensburg/Heidelberg, FRG)

Raine 1988). Immunocytochemical studies have shown in our material that active macrophages, represented by large, vacuolized phagocytic cells, as well as MNCs, produce lysozyme, alpha-1-antichymotrypsin, lactoferrin, peroxidase, and tumor necrosis factor. Lysozyme can be demonstrated in variable amounts in a fine-granular or coarse-granular form within the cytoplasm of macrophages and MNCs (giant cells) and occasionally in flat pericytes located around capillaries and small blood vessels; sometimes intravascular leukocytes react positively.

Recent studies using transgenic mice suggest that the Long Terminal Repeats of two CNS-derived HIV strains are detectable within the neurons of particular regions of the brain. The authors conclude that the expression of LTRs in CNS neurons may represent neuroadapted strains of HIV-1 (Corboy et al. 1992).

Pathology

The neurological abnormalities that constitute the HIV-related encephalopathy known as ADC have not been noted in other immunosuppressed patients (Snider et al. 1983 a). The pattern of clinical and neuropsychological abnormalities in ADC conforms to what has been termed subcortical dementia (Cummings and Benson 1984), reflecting an extensive pathological involvement of hemispheric white matter and deep gray structures as well as a relative sparing of the neocortex (Sotrel 1989). In fact, the distinctive morphological changes that appear in AIDS patients are found principally in the subcortical structures (Navia et al. 1986 b; Petito et al. 1986; Budka 1986; Sharer et al. 1986 a; Rhodes 1987; Kato et al. 1987 b).

The frequency of HIV encephalitis varied greatly among the early reported autopsy series of AIDS patients (R. M. Levy et al. 1985; Petito et al. 1986; de la Monte et al. 1987; Budka et al. 1987; Lang et al. 1989). Today, the incidence of HIV encephalopathy seems to be relatively constant, oscillating slightly around 30 % (28 %–34 %). This figure corresponds to that in our series (Gray et al. 1988; Sotrel 1989; Budka 1991 b).

Macroscopic Findings

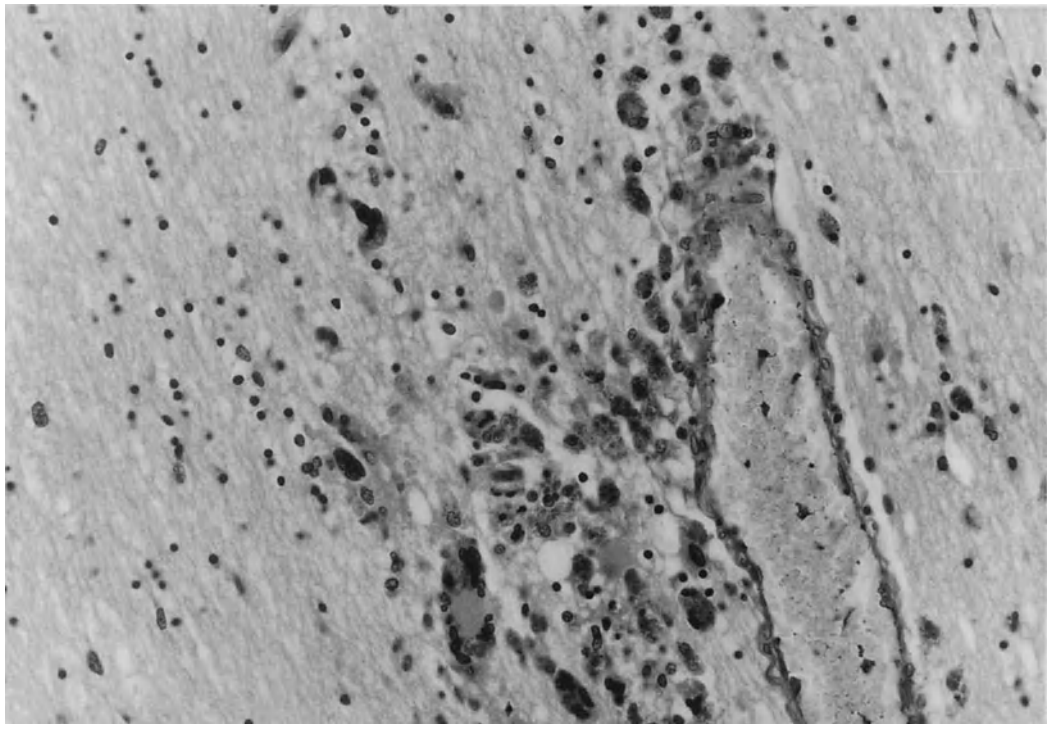
The macroscopic study of the brain does not as a rule produce any notable findings (Anderson 1988; De Girolami and Smith 1992). The pia mater is mostly clear, although it is also described as thickened and opaque (Sotrel 1989; Smith et al. 1990). Speaking very generally, there are indications in some cases of a loss of tissue. There may be a reduction in the weight of the brain (Sotrel 1989). Nonetheless, it has been established that in most cases there is no correlation between brain findings, particularly brain weight, and clinical signs of dementia (Navia et al. 1986 b). Likewise, there is as a rule no recognizable connection between brain weight and the degree of severity of the histological changes. In most cases, the diagnostic evaluation of brain weight is dubious, as a result of the more or less pronounced cerebral edema which occurs in the terminal phase of the illness and can conceal a loss of tissue (Cho and Sharer 1990).

In our study material we measured brain weight in 175 autopsies. The mean brain weight (arithmetic mean) was 1.431 g, and the median was 1.420 g; the range was 1.129–1.730 g. A similarly wide range of brain weights from 1.240 to 1.700 g (mean 1.400 g) in cases of HIVE was reported by Burns et al. 1991. Nevertheless, with ventricular dilatation and widening of the sylvian fissures and the cortical sulci the macroscopic findings may show the typical hallmarks of brain atrophy (Anderson 1988; Burns et al. 1991; De Girolami and Smith 1992). A narrowing of the brain cortex, however, is not evident. In some cases, notable findings are made in the cerebral white matter, especially in the centrum semiovale. Depending on the degree and extent of demyelinization, the cerebral white matter shows a softer consistency and a gray discoloration, sometimes also the aspect of a finely granular cut surface. These findings point to progressive diffuse leukoencephalopathy (see below). In individual cases that run a very serious course, this can also end up as fulminant necrotizing leukoencephalopathy (Vinters and Anders 1990). Focal changes are generally not evident. Only by way of exception does the subcortical white matter reveal small circumscribed demyelinization foci with a diameter of 2–3 mm, which look very similar to the foci in progressive multifocal leukoencephalopathy (Petito et al. 1986; Sotrel 1989; one case in our series).

Microscopic Findings

The histopathological findings in HIVE are highly characteristic, and the correct diagnosis can generally be made rapidly and reliably. Similar findings in connection with AIDS are not known in any other condition caused by opportunistic agents or other injuries.

The microscopic picture is characterized by multiple disseminated foci composed of macrophages, mi-



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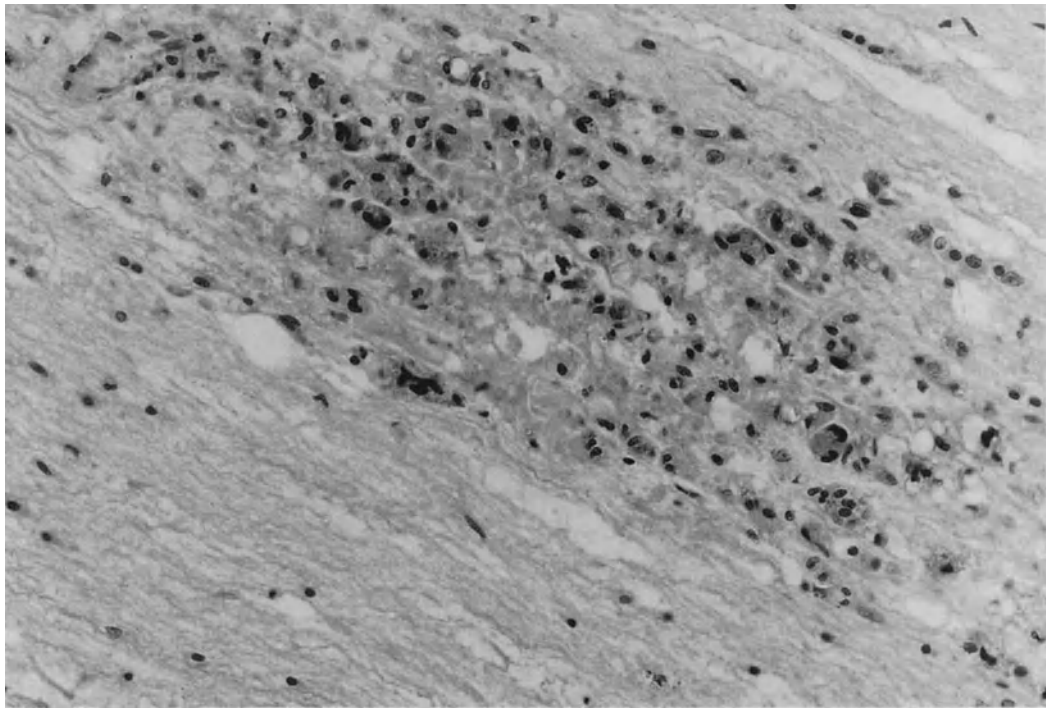


b

Fig. 3.2 a, b. HIV encephalitis. **a** Circumscribed perivascular cell infiltration in the white matter composed of macrophages, microglia cells, and a few MNCs. H&E, ×20. **b** Circumscribed cell infiltration in the white matter composed of macrophages, microglia cells, and a few MNCs with central necrosis. H&E, ×20

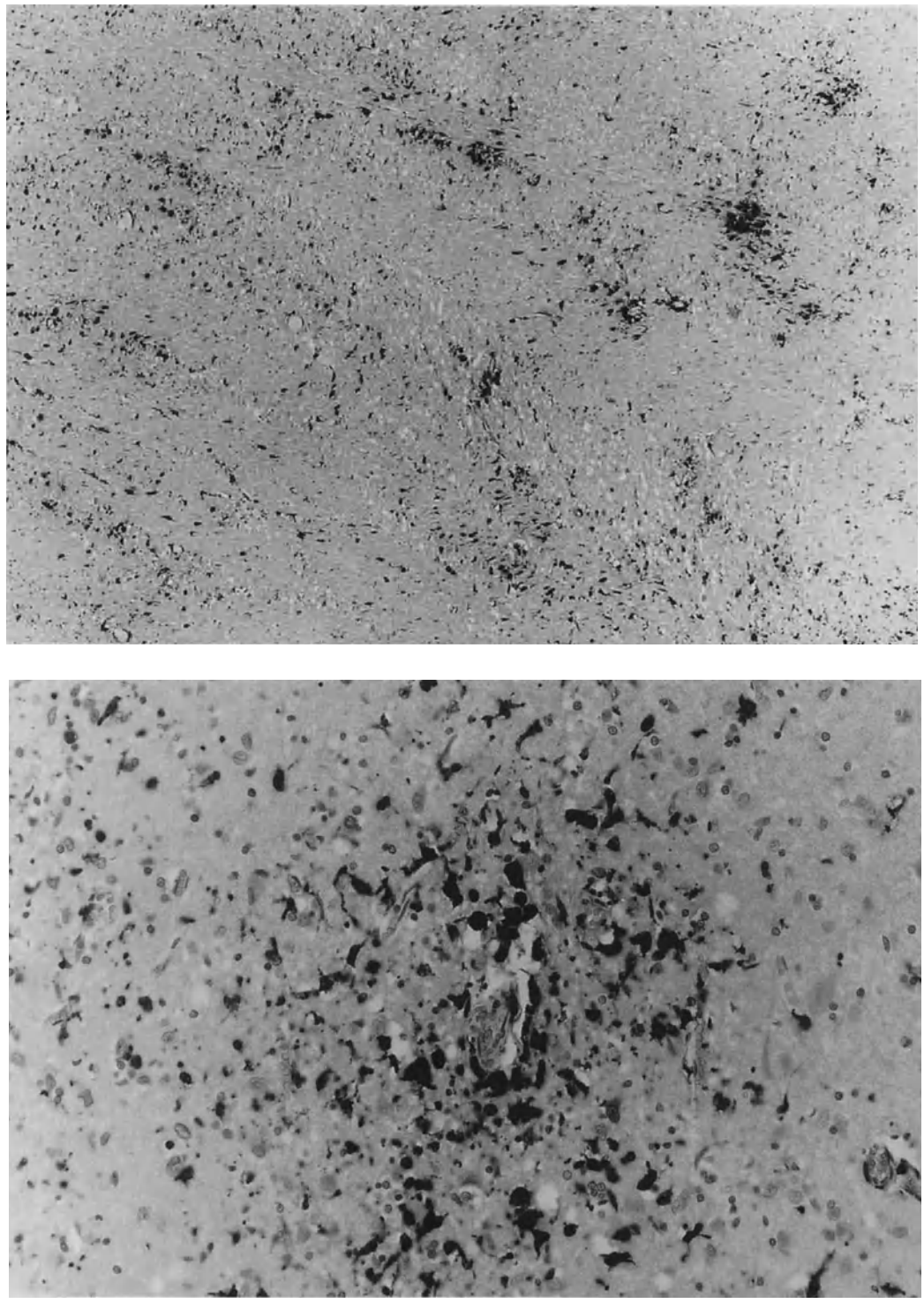


Fig. 3.3a,b. HIV encephalitis. **a** Conspicuous and extensive diffuse cell infiltration and nodular cell concentration (so-called glia nodules of the mixed type) in the white matter. KP-1 (CD68) antibody; APAAP, ×4. **b** Higher magnification of a perivascularly arranged and typically loosely structured nodule. KP-1 (CD68) antibody; APAAP, ×20

croglia cells, and MNCs (Fig. 3.2 a; Sharer et al. 1985; Gray et al. 1988; Johnson et al. 1988; Michaels et al. 1988 a, b; Budka et al. 1987; Budka 1989; De Girolami et al. 1990; De Girolami and Smith 1992; Yoshioka et al. 1992). In HIVE, perivascular infiltrates of lymphocytes, characteristically present in almost all forms of viral encephalitis, are lacking. Using immunocytochemical techniques, few T-lymphocytes are observed (Weidenheim et al. 1993), while B-lymphocytes are absent. The white matter, basal ganglia, and brain stem are preferentially involved. It is noteworthy that similar infiltrates are only rarely detected in the cerebral cortex (Ciardi et al. 1990; Cho and Sharer 1990). When present, they are found in the deep layers of the cortex (Gutierrez-Molina 1989).

The characteristic infiltrates of HIVE appear to be most concentrated perivascularly. Closer examination using immunocytochemical stains (CD68 markers such as EBM/11 and KP-1 or with the lectins RCA-1 and ML I) reveals that the histologically discrete lesions are part of a larger, more diffuse infiltrate of macrophages and activation of microglia extending into the adjacent neuropil (Fig. 3.3 a, b). The number and size of macrophages collections vary widely from case to case. In exceptional cases, small central necroses may develop within the foci (Fig. 3.2 b; Budka 1991 b). The phenotype of the cellular infiltrates is primarily that of monocyte/macrophages which express CD68 and MHC class II antigens. Most of these cells also react with the antibody OPD4 (DAKO). In some cases the infiltrating cells form relatively dense collections, giving the appearance of glial nodules often concentrically disposed around a blood vessel (Fig. 3.3 b). By contrast to the classic glial nodules, which are smaller and composed of tightly packed cells arranged around a single focus, glial nodules in HIVE are ill-defined and consist of widely separated microglia cells intermingled with macrophages and occasionally MNCs.

The macrophages, which are often very large, plasma-rich, and vacuolated, show high metabolic activity and, in the immunohistochemical preparations, numerous enzyme systems (e. g., lysozyme). We have no clear details of the significance of these systems for the tissue lesions that we have described, but they do demonstrate the biological activity of the cells.

Multinucleated Cells

The presence of MNCs has been regarded as a hallmark of HIVE (Epstein et al. 1985; J. A. Levy et al. 1985; Sharer et al. 1985, 1986 a; Budka 1986; Dickson 1986; Gartner et al. 1986 a; Navia et al. 1986 b; Stoler et al. 1986; Wiley et al. 1986 a; de la Monte et al. 1987; Kato et al. 1987 b; Meyenhofer et al. 1987; Pumarola-Sune 1987; Vazeux et al. 1987; Ward et al. 1987). MNCs appear within the perivascular and parenchymal infiltrates of macrophages. They can also be seen isolated in the neuropil. MNCs present different forms. Most frequently observed are medium-sized, rounded cells with foamy cytoplasm and two or more nuclei. They range from 15 to 25 μm in diameter (Kato et al. 1987 b). Less frequently there appear larger MNCs, from 20 to 40 μm in diameter. The cells show eosinophilic granular cytoplasm more densely stained in the center than at the periphery and numerous fine PAS-positive granules, occasionally vacuoles or lucent areas. The MNCs often contain sudanophilic, diastase-resistant, PAS-positive, and alcianophilic materials (Budka 1986). Up to 20 nuclei may be found in a cell section forming circles or semicircles at the periphery. Less frequently, the nuclei are located at the center of the cell or scattered haphazardly. Usually the size of MNCs increases with the number of nuclei. Some MNCs consist of aggregates of nuclei with cytoplasm that is scarcely demonstrable, if at all (Michaels et al. 1988 a). MNCs stain well with all macrophage markers (Dickson 1986; Koenig et al. 1986; Budka 1986; Gray et al. 1987; Vazeux et al. 1987), and they show strong positivity with the lectins RCA-1 (Michaels et al. 1988 a) and ML-I (Artigas et al. 1991 c).

The formation of MNCs may result from HIV-induced fusion of mononuclear cells, which is a known cytopathic effect seen in infected lymphocytes and macrophages in vitro, and it depends on the CD4 receptor (Popovic et al. 1984; Hoxie et al. 1985; Gartner et al. 1986 a; Lifson et al. 1986). The high level of HIV replication in infected CD4 cells, as manifested by the budding of viral particles from the plasma membrane, may result in cell fusion with neighboring uninfected CD4 cells (Fauci 1988). In this context, we refer to recent results in the literature, according to which a mixture of HIV variants of varying virulence is generally transmitted in infection with HIV; some strains are characterized by the ability to form cell syncytia (Miedema et al. 1990).

In only a few exceptional cases of HIVE do the cellular infiltrates not reveal MNCs on a scrutinizing search; in such cases the diagnosis should be confirmed by immunohistochemistry using antibodies against HIV antigens, for example, p24 and gp41. This was seen in only one case in a series of 160 (Budka 1991 b) and in two cases in our series. In routine stains, however, HIVE can be diagnosed only in the presence of MNCs. MNCs in general may appear in cryptococ-

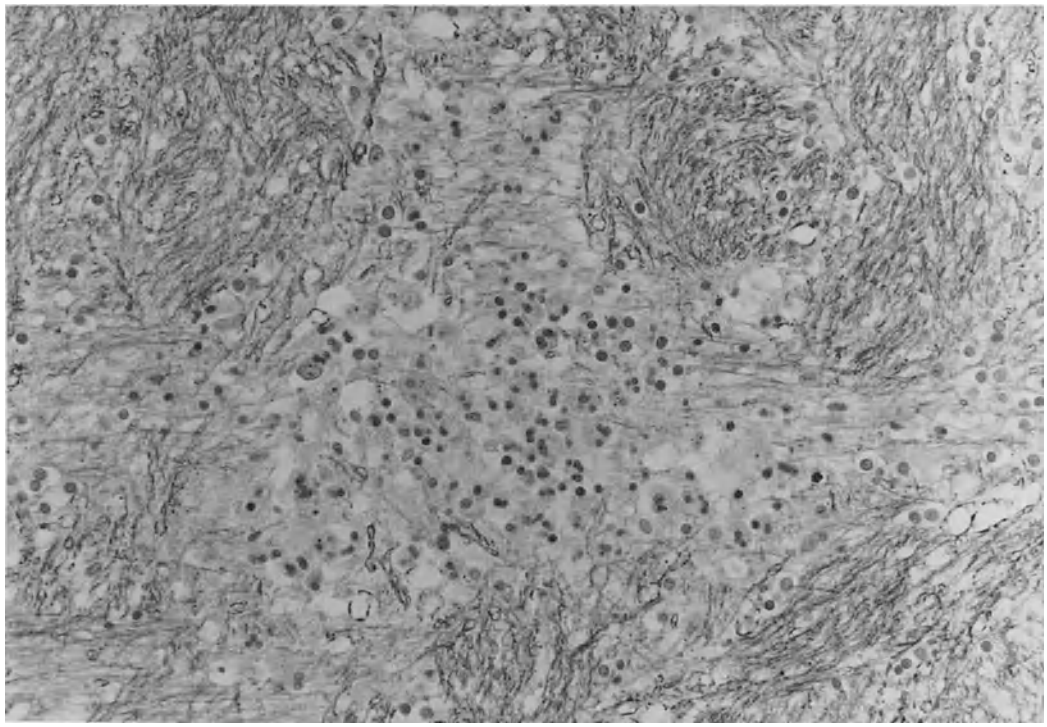


Fig. 3.4. HIV encephalitis. Small patch of myelin loss in the white matter with infiltration of numerous macrophages. Myelin stain after Heidenhain, × 20

cosis, CMV encephalitis, and malignant lymphoma and accompanying macrophages in the inflammatory rim of toxoplasmic lesions. However, typical MNCs indicating HIVE are easy to recognize in the context of the morphological changes characterized by perivascular and parenchymal infiltrates of macrophages.

The background neuropil in HIVE may remain unaltered, or it may show a variable degree of sponginess in areas of cell infiltration. In other cases it shows marked focal rarefaction, with loss of myelin (Fig. 3.4).

Neurons

Morphologically, neurons in HIVE usually remain intact even when they come into close contact with the cytoplasm and processes of infected cells. However, occasionally we observed macrophages and multinucleated cells in close contact with neurons of the basal ganglia (Artigas et al. 1989 d). These neurons showed severe signs of degeneration and cell death (Fig. 3.5). They never reacted positively for p24 and gp41, whereas macrophages did. In vitro studies reported in the recent literature have shown that HIV-infected monocytes destroy neural cells after cell-to-cell adhesion (Tardieu et al. 1992). This cytopathic effect is in accordance with our histopathological findings.

Using stereological techniques recent investigations have shown a significantly lower numerical density of neurons in the frontal cortex of patients with HIV infection (Everall et al. 1991) and especially in the fronto-orbital cortex (area 11) of AIDS brains (Weis et al., 1993).

Glial Cells

In HIVE, despite a constant astrocytosis, changes of glial cells, astrocytes, and oligodendroglial cells, are scarce and unspecific. HIVE is always accompanied by a prominent hyperplasia of hypertrophic astrocytes in the white matter. Sometimes the astrocytosis seems to follow anatomically, some white matter tracts contrasting with a very scarce astrocytic proliferation in neighboring tracts. Astrocytosis is the most common response of the nervous tissue to any kind of injury. It is very frequently present in AIDS brains without HIVE and is constantly found in cases with

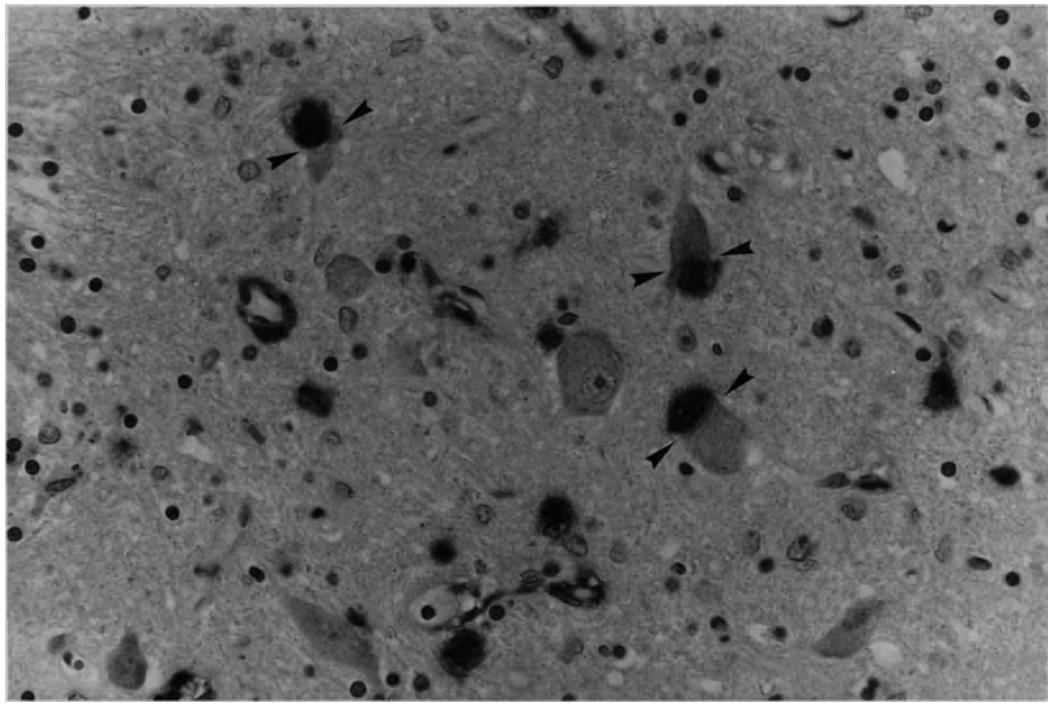


Fig. 3.5. Macrophages *(stained black, arrowheads)* showing cell-to-cell adhesion with neurons in the thalamus. Neurons show degeneration of the cytoplasm and loss of nuclei. (CD68 marker KP-1, APAAP, ×40)

HIVE. Quantitative studies have shown a significant increase in the number of astrocytes in the frontal white matter and in the pons in brains of AIDS patients without HIVE, as compared with brains of HIV-negative persons (Schwenk et al. 1987 a).

Some authors have reported that oligodendroglial cells often increase focally in number, and that their nuclei double in size (de la Monte 1987) while others have described a decreased number of oligodendroglial cells in areas with severe demyelinization (Sotrel 1989). Still others, however, deny any changes in the oligodendroglia (Smith et al. 1990). In our material we have noted no remarkable changes in the size or shape of oligodendroglial cells.

Comparison with Animal Models

The comparison of HIVE with CNS infection in animal models of immunosuppression and visna may be helpful for understanding the pathogenesis and clinicopathological correlation of HIV infection of the CNS. Animal models of immunosuppression disease with viruses genetically closely related to HIV, as well as other animal diseases produced by lentiviruses, may provide insight into the pathogenesis and causes of neuropathological features. In simian and feline models of immunosuppression the morphological findings in CNS infection are strikingly similar to those seen in HIVE (Ringler et al. 1988; Sharer et al. 1988). An excellent review of the neurobiology of simian and feline immunodeficiency virus infection compared to HIV infection is given by Lackner et al. (1991). Two other viruses, visna and caprine arthritis-encephalitis virus, also belong to the lentiviruses and are capable of producing slow progressive and persistent infections of the nervous system in sheep and goats (Fauci 1988).

HIV Leukoencephalopathy

The diagnostic criteria for HIV leukoencephalopathy are presented in Table 3.10. In some cases of HIVE there are conspicuous changes in the white matter of the cerebral hemispheres involving the centrum semiovale, with a pallor of the myelin stain visible in the whole brain mount, although without affecting the

subcortical U fibers (Fig. 3.7–3.9). There is a similar loss of myelin in the white matter of the cerebellum and to a lesser extent in the corpus callosum, the internal capsules, and the long tracts of the brain stem. These findings are known in the American literature under the broad concept of myelin pallor (Navia et al. 1986b; Price et al. 1988a), whereas in the European literature they were first described as progressive diffuse leukoencephalopathy (Kleihues et al. 1985).

In contrast to the changes in the white matter, the findings in the cerebral cortex are generally slight; macroscopically, the cerebral cortex is not noticeably changed or reduced (De Girolami et al. 1992). An accurate diagnosis of HIV leukoencephalopathy can be made only using large brain slices embedded in paraffin or celloidin. A coronal whole mount through cerebral hemispheres shows the typical finding (Figs. 3.7–3.9).

Demyelination is, however, seldom as extensive as illustrated by Kleihues et al. (1985). Instead, there is usually a rather discreet but recognizable demyelination in the centrum semiovale, corresponding to the representation by Smith et al. (1990). In less severe cases the process is reduced to focal perivascular loss of myelin (De Girolami et al. 1992). There are also transitional forms between focal lesions and diffuse processes. Occasionally one finds asymmetrical demyelination (Fig. 3.8). In our study material of HIVE with distinct microscopic findings we found 12 cases of HIV leukoencephalopathy. With higher magnification the demyelination foci visible in the whole brain mount also show rarefaction of the neuropil, often a grainy disintegration of the myelin sheaths, and vacuolation with round-oval cavities of varying size and larger irregular ones apparently created through confluence. These sometimes contain axons or axon remnants and axonal spheroids (Fig. 3.6b,c). In severe cases there is a clear loss of axons in the centrum semiovale and in the long fiber tracts (De Girolami et al. 1992). The number of oligodendroglia cells is more or less heavily reduced; the still recognizable cells show regressive changes with nuclear pyknosis and karyorrhexis; sometimes there are anuclear remnants of cells (Fig. 3.6a). In every case we found infiltration with macrophages and giant MNCs, although in areas with severe damage there was often also an overall impression of cell deficiency.

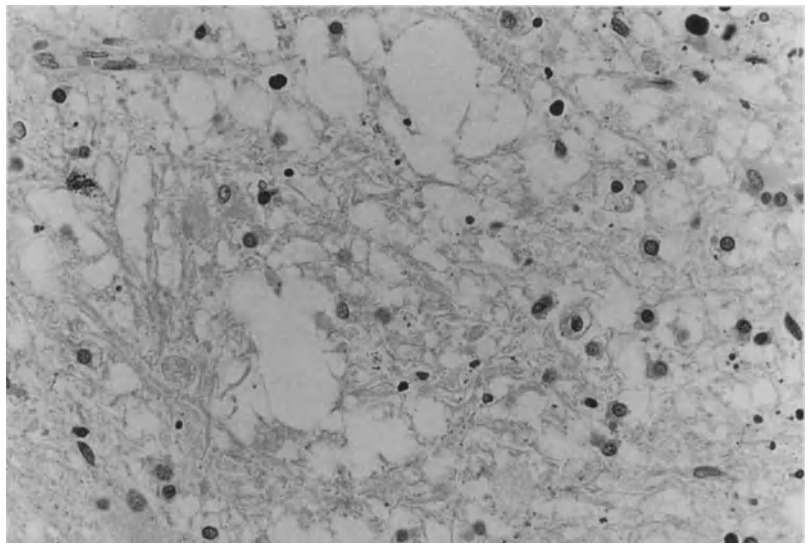
The actual extent of cell infiltration is recognizable only in immunohistochemical preparations with macrophage markers (KP-1, EBM11, PG-M1, ML I, RCA-1) (Fig. 3.10b). The glial fibrillary acid protein preparations usually show a distinct astrocytosis, especially at the rim of the demyelination foci and subcortically, while the number of astrocytes decreases toward the center of the lesions. The blood vessels (capillaries, venules, small arteries) in the demyelination foci often have thickened walls and are sometimes dilated, and the lumen occasionally contains aggregations of fibrin and platelets. Often there are hypertrophied endothelial cells with enlarged and pleomorphic nuclei (Fig. 3.10a; Smith et al. 1990; De Girolami et al. 1992). In larger blood vessels these kinds of endothelial changes are less noticeable.

Table 3.10. Diagnostic criteria for HIV leukoencephalopathy

Whole mount sections of the brain
Diffuse demyelination of the white matter, especially of the centrum semiovale and of the capsula interna. In many cases additional changes of spongiform leukoencephalopathy and vacuolar leukoencephalopathy accentuate the morphological picture. In exceptional cases a severe destruction of the brain tissue in the centrum semiovale may appear.
The changes of HIV encephalitis are an obligatory precondition for the diagnosis of HIV leukoencephalopathy.

In *immunohistochemical preparations* HIV core and envelope proteins are present in the cytoplasm and processes of microglial cells, macrophages, MNCs, and pericytes (Epstein et al. 1985; Gabuzda et al. 1986; Gartner et al. 1986b; Koenig et al. 1986; Sharer et al. 1986a; Stoler et al. 1986; Wiley et al. 1986a; Kato et al. 1987b; Pumarola-Sune et al. 1987; Vazeux et al. 1987; Michaels et al. 1988a; Artigas et al. 1989), that is to say in cells of the monocyte/macrophage system. We found that monoclonal antisera to the HIV-1 core protein p24 provided the most consistent results with our formalin-fixed, paraffin-embedded material (Artigas et al. 1989a). Other groups had good results with antisera to the transmembrane protein gp41 (Wiley et al. 1988a; Budka 1990; Smith et al. 1990). In our experience with p24, it appears as a fine-granular positivity at the surface of the cell membrane and cytoplasmic branches and less commonly in more dense aggregates in the center of the cytoplasm. Sometimes it appears as a semicircle accompanying the nuclei of MNCs.

Neurons, astrocytes, oligodendrocytes, endothelial cells, ependymal cells, and plexus choroideus cells do not stain for HIV-1. In seven cases with HIVE we performed immunocytochemical studies in frozen material with p17, p24, gp41, gp120, gp160, and reverse transcriptase. Optimal results were obtained with p24 and gp41 (Table 3.11; Fig. 3.11). In some cases staining with p17 and gp160 showed positive cells, while gp120 and reverse transcriptase were always negative.



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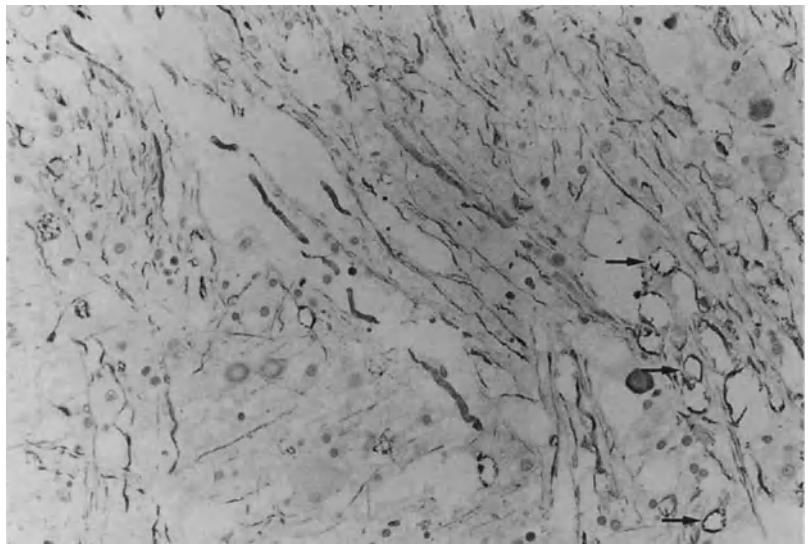

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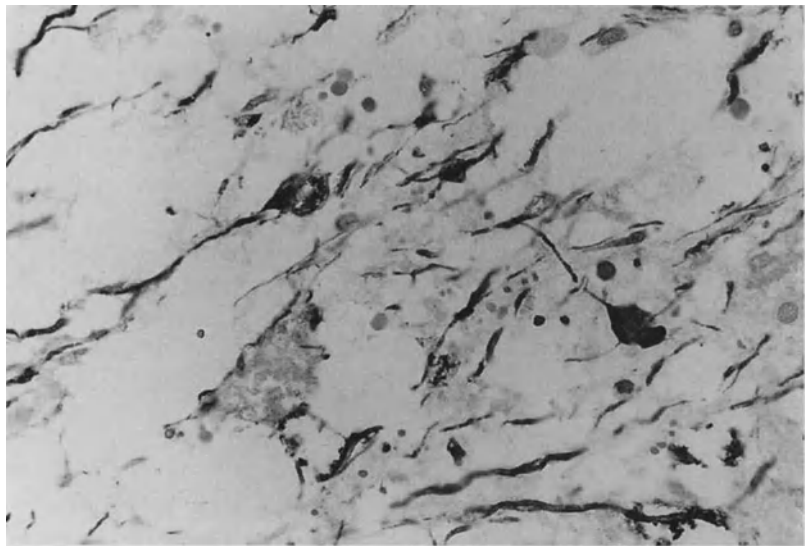
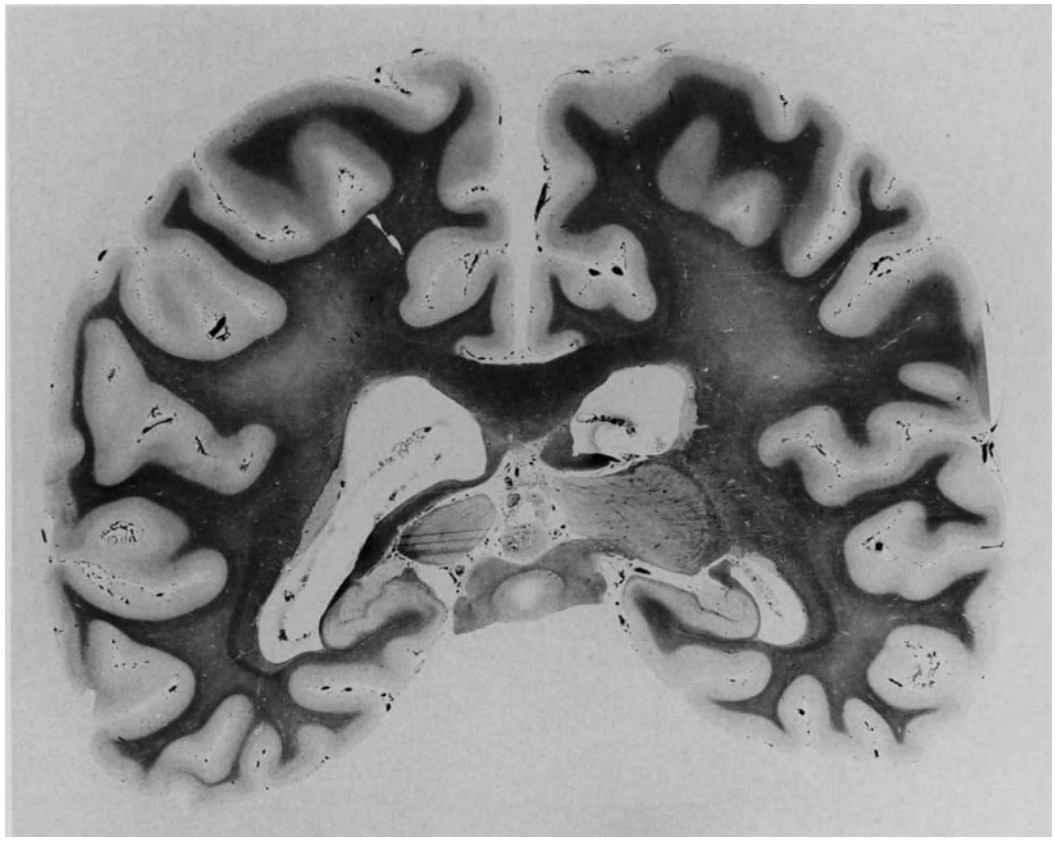


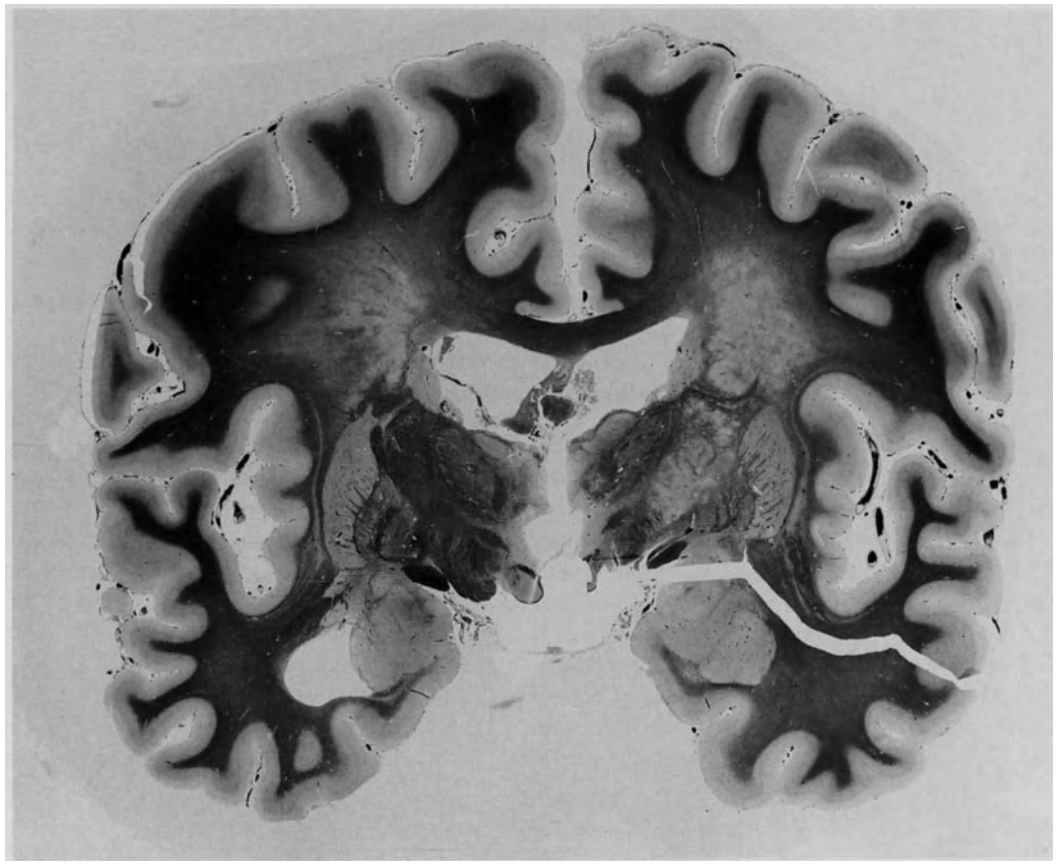
c

Fig. 3.6a–c. HIV leukoencephalopathy. **a** Severe white matter destruction with vacuolar changes, karyopyknosis, microcalcifications, some macrophages and reactive astrocytes. H&E, ×20. **b** Fragments of axons within vacuolar defects of thewhite matter; numerous axonal vacuoles (→) and axonal swellings. Neurofilament antibody; ×10. **c** Fragments of axons and spheroid axon swellings in an area of vacuolar degeneration of the white matter. Neurofilament antibody; ×20

Fig. 3.7. HIV leukoencephalopathy. Coronal whole mount at level of the splenium corporis callosi with large nearly symmetrically developed and ill-defined demyelination in the white matter of both hemispheres. Celloidin; myelin stain. (Celloidin slides performed in the Institute of Neuropathology, Free Univercity, Berlin) ▶

Fig. 3.8. HIV leukoencephalopathy. Coronal whole mount at level of the corpora mamillaria with sharply demarcated areas of complete demyelination and necrosis of the white matter within larger fields of ill-defined incomplete demyelination (centrum semiovale on both sides, capsula interna on the right). Celloidin; myelin stain ▶





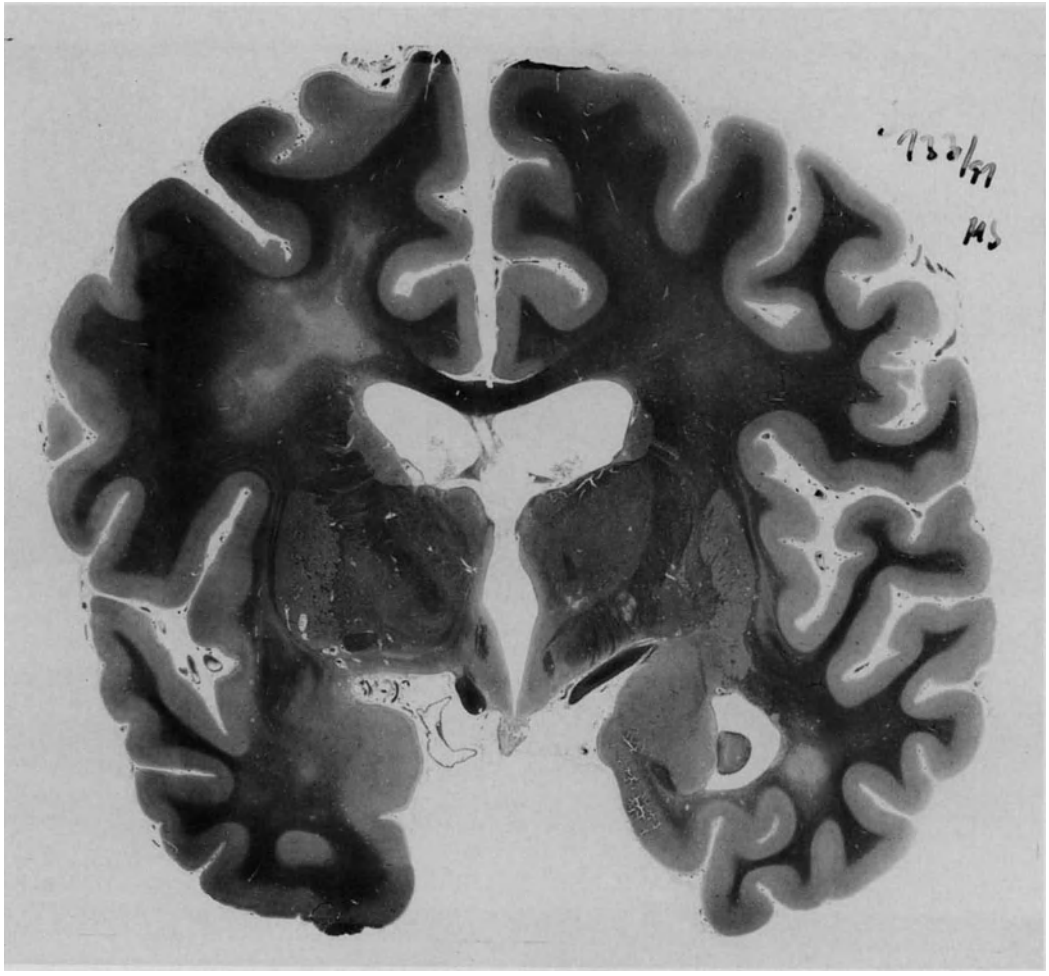
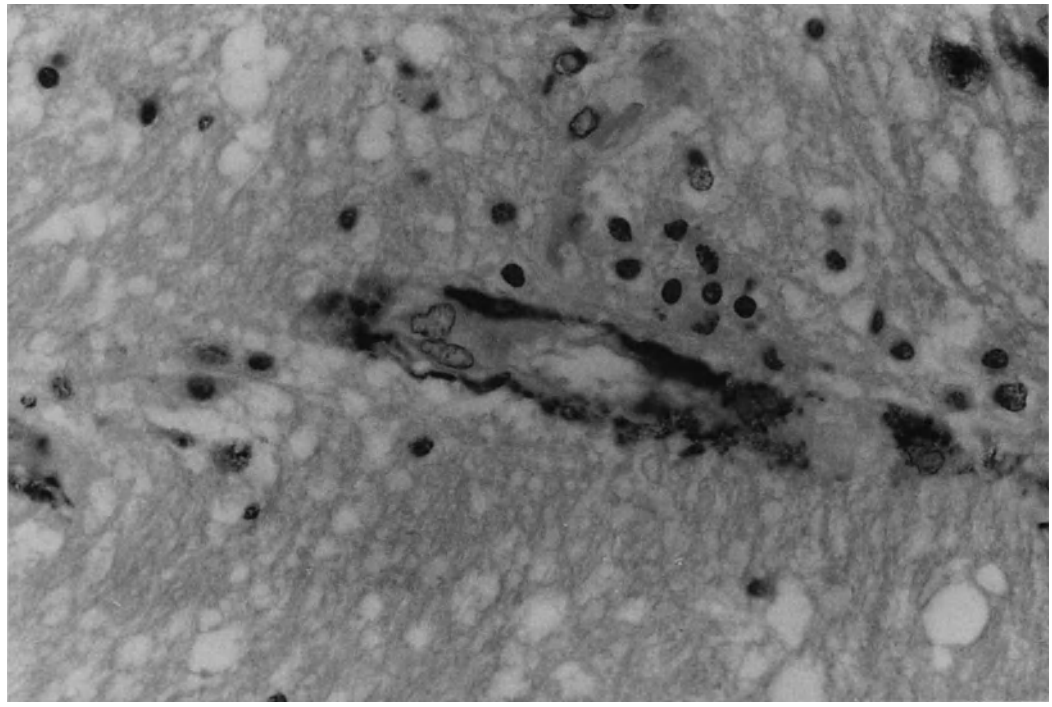


Fig. 3.9. HIV leukoencephalopathy. Coronal whole mount at level of the infundibulum with demyelination areas in the white matter of the centrum semiovale on both sides and an extensive branched focus of severe asymmetrical destruction (left side); additional smaller foci of destruction in the temporal white matter (right side) and minute foci in the internal capsule. Celloidin; myelin stain

In situ hybridization studies with HIV RNA-specific probes repeatedly demonstrated viral nucleic acid sequences in macrophages, microglial cells, and MNCs (Koenig et al. 1986; Stoler et al. 1986; Wiley et al. 1986a; Vazeux et al. 1987). Our colleague G. Gosztonyi (Institute of Neuropathology, Free University of Berlin) studied 17 cases of our material with and without HIVE with HIV-specific cDNA and cRNA probes; a relationship between the presence and distribution of HIV DNA and RNA sequences and HIV antigens was found (Artigas et al. 1990a; Gosztonyi and Artigas 1990). Further important immunohistochemical findings concern the distinct enzymatic activity of the cells of the monocyte/macrophage system, documented among other things by the representation of lysozyme and tumour necrosis factor; thus the flat pericytes adjacent to the vascular wall often show clear lysozyme activity (Fig. 3.12). The enzymes represented generally provide only exemplary proof of the strong metabolic activity of these cells, but they are not necessarily the decisive damaging agent.

The leptomeninges usually show only moderate infiltration with mononuclear cells and macrophages; giant MNCs, on the other hand, are not found as a rule.

The *pathogenesis* of HIV leukoencephalopathy has not yet been fully explained (Sotrel 1989; Vinters and Anders 1990; De Girolami et al. 1992). We are of the opinion that there is a direct connection between



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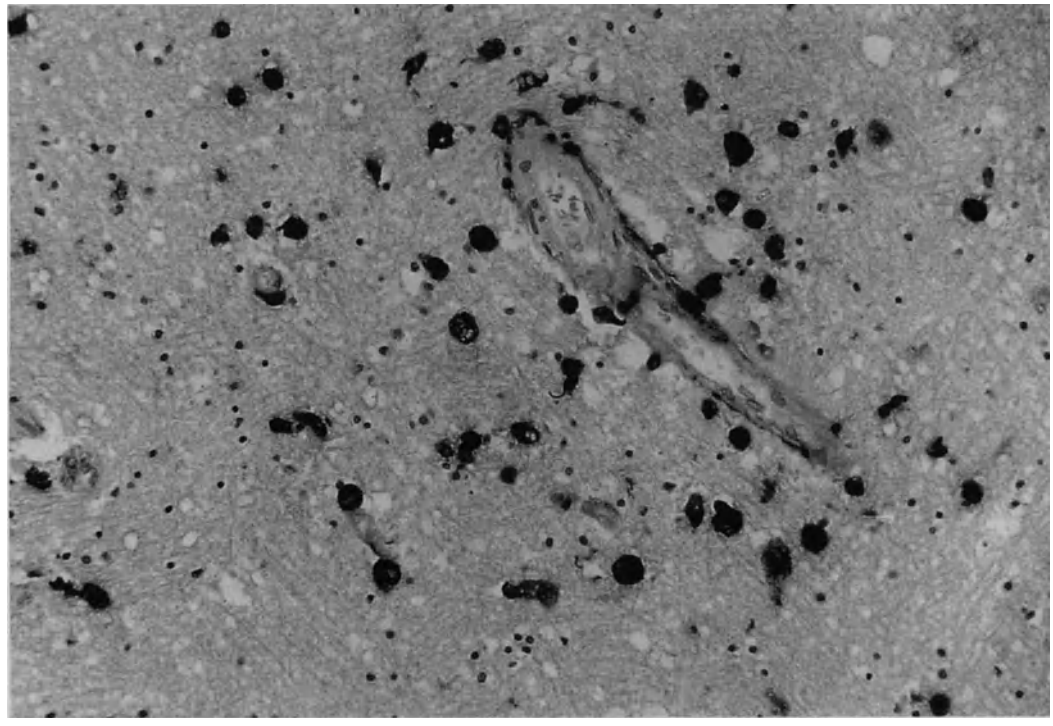


b

Fig. 3.10 a, b. HIV leukoencephalopathy. **a** Capillary blood vessel in the white matter with enlarged and polymorphic endothelial nuclei; flat and darkly stained pericytes (KP-1 positive); conspicuous spongiform changes in the neuropil. KP-1 (CD68) antibody; APAAP, ×40. **b** Numerous darkly stained macrophages in the surroundings of a venule and moderate spongiform changes. KP-1 (CD68) antibody; APAAP, ×20

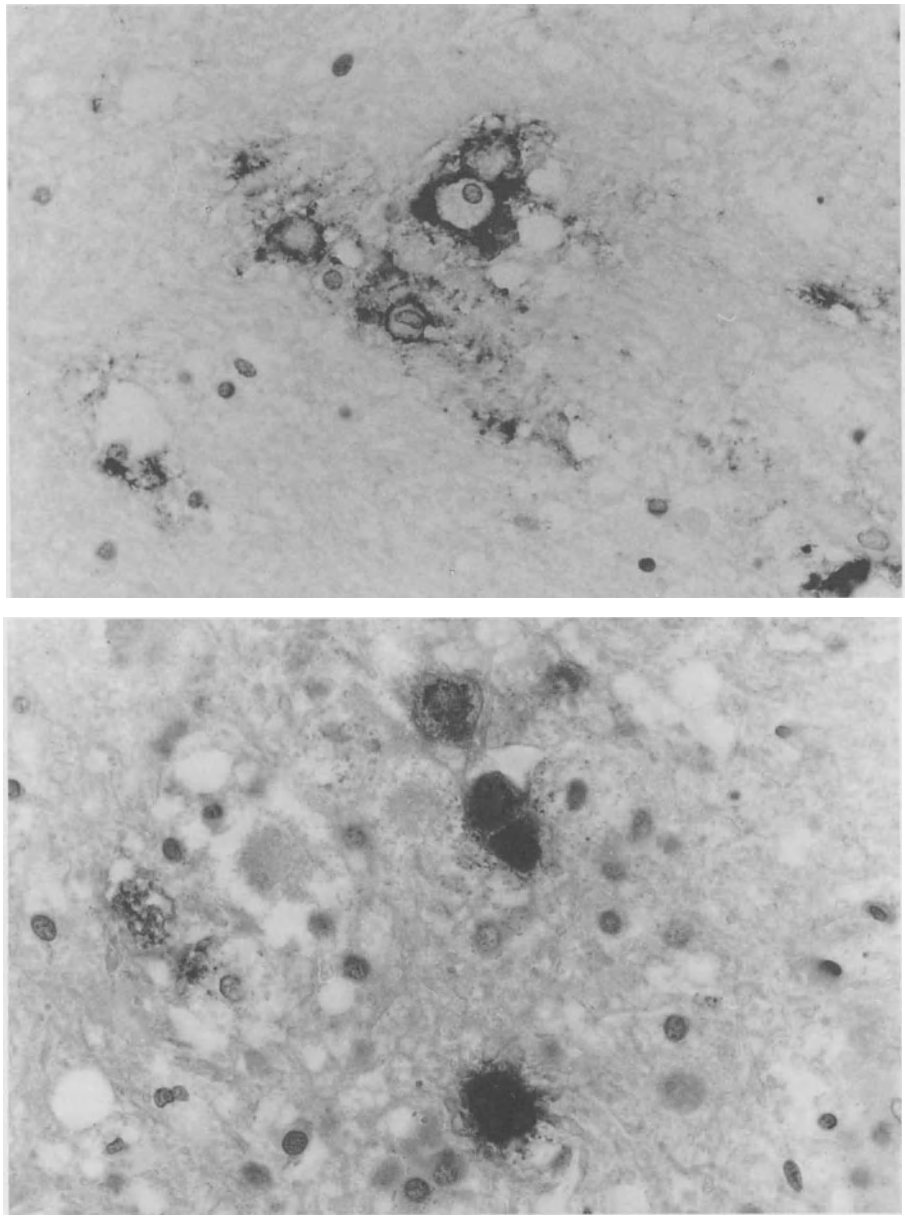


Fig. 3.11 a, b. HIV leukoencephalopathy. **a** Several macrophages in the white matter with HIV p24 marking of the cell surface. HIV p24 antibody; APAAP, ×40. **b** A few macrophages in the white matter with HIV gp41 marking. HIV gp41 antibody; APAAP, ×40

Table 3.11. Results of immunocytochemical studies with different HIV proteins in HIV encephalitis

HIV proteins	Paraffin-embedded material	Frozen tissue
p17	–	+
p24	+++	+++
gp41	++	+++
gp120	–	–
gp160	–	+
Reverse transcriptase	–	–

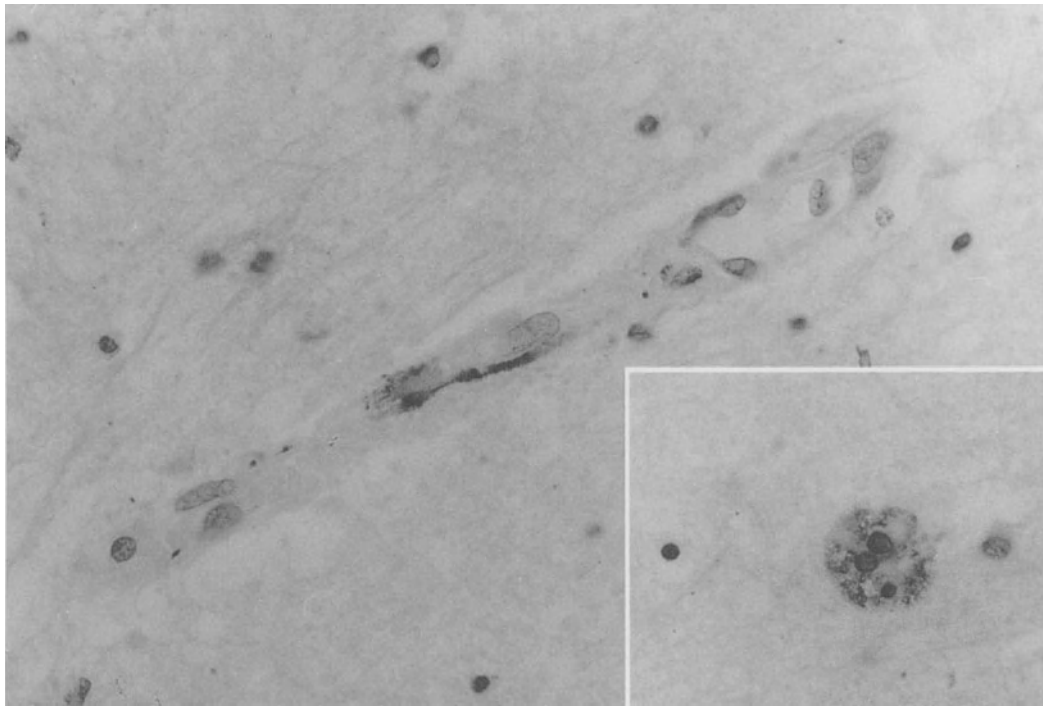


Fig. 3.12. HIV leukoencephalopathy. Capillary vessel in the white matter with enlarged endothelial nuclei and flat portion of cytoplasm of a pericyte reactive for lysozyme. *Inset,* large plasma-rich macrophage with granular lysozyme reactivity. Lysozyme antibody; ABC method, × 40

the changes described in the white matter and HIVE, and that leukoencephalopathy must be seen as an advanced form of HIVE. The occurrence of distinct demyelination in cases of HIVE with a prolonged course (Kleihues et al. 1985) can support this assumption. The pathogenetic significance of other opportunistic viral infections, clinically apparent or occult, in the sense of superimposed infections must also still be regarded as unclear; however, they are able to intensify or accelerate a demyelination (Kleihues et al. 1985). In principle, similar demyelinations can occur in the vicinity of lymphomas and toxoplasmosis foci. Here, as far as the cause of myelin sheath decomposition is concerned, it might be appropriate to consider the influences of an alteration in vascular permeability, with concomitant tissue edemas and possibly so-called edema necrosis (Staemmler 1958). However, for the extensive diffuse damage to the white matter, a direct influence of HIV on the myelin-producing oligodendrocytes must also be discussed (De Girolami and Smith 1992). Furthermore, the already mentioned toxic-enzymatic tissue damage caused by release reactions from HIV-infected monocytes is presumably important in this connection. It also seems reasonable to use comparative observation of other demyelination processes in human pathology for the discussion of the pathogenesis (De Girolami and Smith 1992), even if they are etiologically unclear.

The histomorphological findings that we have described, which as a whole form a characteristic pattern of damage despite all the uncertainties in the pathogenetic processes, are by no means completely new. Cellular infiltration with the activation of perivascular macrophages, the occurrence of giant MNCs, and the extensive white matter lesions have all been described in the older literature, namely, in connection with syndromes that have been assigned to the degenerative diffuse sclerosis complex (Hallervorden 1957). Especially in Krabbe's familial infantile diffuse cerebral sclerosis there are descriptions and illustrations of histological changes that are very similar to the findings described here (Krabbe 1913). In this connection, no special mention needs to be made of the problem of drawing pathogenetic conclusions from similar morphological findings.

Clinicopathological Correlation

Citing the early work of Navia et al. (1986a), it has often been reported that the clinicopathological correlation is poor in at least about one third of AIDS patients. Clinical diagnosis of the etiology of the encephalopathy in AIDS patients is not easy. It has been established, however, that patients with severe clinical manifestations present more severe morphological changes (Price et al. 1988a; de la Monte et al. 1987; Artigas et al. 1990b).

Clinicians in our center use the terms AIDS encephalopathy or HIV encephalopathy to refer to the classic neuropsychological changes in AIDS patients. However, these diagnoses are used as exclusion diagnoses. Only in cases with encephalopathy or dementia, in which clinical, laboratory, and radiological tests fail to show opportunistic lesions, the diagnosis of HIV encephalopathy is made.

Morphologically, in all cases with dementia or severe encephalopathy, clinically diagnosed, we found the picture of HIV leukoencephalopathy. In five cases with clinically diagnosed mild encephalopathy there were no signs of HIVE or HIV leukoencephalopathy in the neuropathological study. In two of these cases we found CMV encephalitis with severe vacuolar myelopathy, and in one case we found only spongiform encephalopathy and spongiform leukoencephalopathy. Cases with early histological changes of HIVE have never shown clinical signs of neuropsychological disorder. Of the 30 cases with HIVE only 17 showed signs of neuropsychological abnormalities. HIVE is a chronic process. Clinically, the encephalopathy has an insidious onset and a relatively slow, steady, or step-by-step, progressive course. Its mean duration is 5–9 months, although occasionally the clinical course is more fulminant, and death may ensue within 1 month (Navia et al. 1986a; Sotrel 1989; Price et al. 1991).

■ Opportunistic Viral Infections

Two main groups of viruses dwarf all others in their importance as opportunistic pathogens in the nervous system of AIDS patients: The herpesviruses, especially CMV but also varicella or herpes zoster (HZV) and herpes simplex virus (HSV), and papovaviruses. The latter produce a single well-defined syndrome – progressive multifocal leukoencephalopathy (PML) – whereas the former induce highly variable neuropathological changes, and different herpesviruses can be found in a single brain (Pepose et al. 1984).

Viruses of the Herpes Group

Various members of the herpesvirus family, individually or in combination, are the most common causative agents of encephalitis, ventriculitis, or myelitis in adults with AIDS. The family of human herpesviruses includes HSV types I and II (HSV I and II), varicella zoster virus (VZV), EBV, and CMV. These are all ubiquitous, intracellular viruses that can cause persistent, clinically inapparent infection of previously healthy individuals, but they may be reactivated in the form of an acute CNS disorder with or without decline in host immunoresistance. While HSV varieties latently infect neural cells, EBV and CMV usually reside in the cells of the hematopoietic system. Herpesviruses are among the largest DNA viruses, measuring 150–200 nm in diameter. Although ultrastructurally similar, they are antigenically distinctive from one another.

Herpes Simplex Virus. HSV encephalitis (Dix et al. 1985) and myelitis (Britton et al. 1985; Tucker et al. 1985) may occur in patients with AIDS. Histological diagnosis is usually confirmed by immunocytochemic studies. We have found no case of it in our series comprising 180 patients who died of AIDS. Burns et al. (1991) note the perplexingly low frequency of HSV encephalitis in the HIV-infected population, since it is a relatively common cause of sporadic viral encephalitis in the general population.

Varicella Zoster Virus. VZV encephalitis has been reported in a few cases of AIDS patients (Petito et al. 1986; Ryder et al. 1986; Morgello et al. 1988; Burns et al. 1991; Gray et al. 1992). The lesions may show edema, perivascular or leptomeningeal chronic inflammation, perivascular demyelination, fibrin thrombi in

vessels, necrosis, and hemorrhage (De Girolami et al. 1990). Sometimes, viral inclusions appear in glial cells, and rarely in endothelial cells. In rare instances there may appear a leukoencephalitis with multifocal demyelinating lesions resembling PML, with inclusions in glial cells and neurons surrounding the lesions (Gray et al. 1988; Sotrel 1989; De Girolami et al. 1990). We observed a case with a history of HZV affection of a cervical dermatoma (C7) and severe unilateral necrotizing retinitis not CMV related. Neuropathological examination disclosed complete destruction of the optical nerve, partial destruction of the optic chiasma, and an ipsilateral brain infarct with severe surrounding edema affecting the whole cerebral hemisphere. HZV ophthalmicus with delayed ipsilateral cerebral infarction (Bourdette et al. 1983) and cervical HZV with delayed ipsilateral pontine and occipital infarction are well-described entities in non-HIV-infected persons (Ross et al. 1991).

Cytomegalovirus Infection of the CNS

Introduction

As early as 1904, when Jesionek and Kiolemenoglou noted large, inclusion-bearing cells in the viscera of a fetus, there appeared the first evidence of CMV as a human pathogen. Goodpasture and Talbot (1921) noted the similarity between these enlarged cells, which they found in various organs of a 6-week-old infant, and the cells observed in varicella infections and in the salivary glands of guinea pigs. These authors proposed the term cytomegalia to emphasize the abnormal enlargement of the inclusion-bearing cells and the term cytomegalic inclusion disease to describe this condition. Subsequent authors reported cytomegalic disease and noted similarity to other disorders, such as HSV infections (von Glahn and Pappenheimer 1925). Thirty years later the viral etiology of this disease was confirmed (Rowe et al. 1956; Smith 1956; Weller et al. 1957). In the late 1960s CMV infections became recognized as a major complication in organ transplantations, with an incidence that approaches 100% (Bale 1984). Between 1962 and 1978, 31 cases of CMV encephalitis were reported. It occurred in immunocompromised patients after organ transplantation (Schneck 1965; Dorfman 1973; Schober and Herman 1973; Yanagisawa et al. 1975; Linneman et al. 1978) and in immunocompetent hosts (Perham et al. 1971; Chin et al. 1973; Philips et al. 1977; Duchowny et al. 1979).

CMV encephalitis and HIVE are the most common viral infections of the CNS in patients with AIDS (Morgello et al. 1987; Vinters et al. 1989; Wiley and Nelson 1988; Vinters and Anders 1990; Artigas 1990). The frequency of CMV encephalitis (20%–30% in the literature, 30% in our series) is similar in patients with AIDS and in non-AIDS immunocompromised persons (Bale 1984; Petito et al. 1986; Morgello et al. 1987; Vinters et al. 1989).

Pathogenesis

Human CMV is an enveloped virus with a diameter of 200 nm and a molecular weight of 150×10^6 DA. The virus particle or capsid encompasses double-stranded DNA. It is an icosahedron, a 20-sided body, 100 nm in diameter. This shape is common to all herpesviruses. Some studies suggest that the sites of latency of CMV are blood leukocytes: monocytes, T- and B-lymphocytes, and natural killer cells (Wu and Ho 1979; Ost and Einhorn 1984; Rice et al. 1984).

CMV infection occurs worldwide, and by late adulthood most human beings have been infected. It is estimated that 60%–80% of all healthy adults in the United States are infected with CMV (Bale 1984). Pregnant women and homosexual men have a higher prevalence of latent CMV infection. According to one study, 94% of all healthy homosexual men were CMV seropositive compared with 54% of healthy heterosexual men so tested (Drew et al. 1981).

CMV infection can occur by several routes. Congenital infection is the result of viremia during maternal infection. The effects of damage from CMV infection on the CNS of the fetus and infant are devastating. It may results in mental retardation, motor deficits, seizures, microcephaly, hydrocephalus, optic atrophy, chorioretinitis, and deafness (Bale 1984; Dix and Bredesen 1988; Bale and Jordan 1989). The virus can be recovered from tears, saliva, blood, urine, feces, cervical secretions, semen, and breast milk (Bale and Jordan 1989). Transmission of CMV after the neonatal period usually results from close personal contact with an infected individual. Although the major routes of transmission seem to be oral and respiratory (Hutto et al. 1985), sexual contact is also an important route of transmission (Bale and Jordan 1989). In healthy adults, primary CMV infection may be asymptomatic or may results in a mononucleosislike syndrome accompanied by viremia (Klemola 1973; Bale 1984; Bale and Jordan 1989).

CMV infects many cells in almost every organ with a particular tendency to infect endothelial cells of capillaries. As a general rule patients with CMV encephalitis have evidence of systemic infection (Morgello et al. 1987; Klatt and Shibata 1988; Vinters et al. 1989). We found in our AIDS autopsy material (n=180) 91 cases with systemic CMV infection (51 %). The sites most commonly involved were the lung, adrenal glands, and gastrointestinal tract, in roughly decreasing order of frequency (Morgello et al. 1987; Vinters et al. 1989; and our series).

Infected leukocytes may directly infect endothelial cells of the CNS, and there consequently follows the infection of astrocytes throughout the end-foot, and finally neurons and oligodendrocytes that have close contacts with the astrocytes also become infected. Thus the infection results either in the appearance of isolated cytomegalic cells, glial nodule encephalitis, or small focal parenchymal necroses. Vascular thrombosis, secondary to infection of endothelial cells, can also result in parenchymal necroses (Koeppen et al. 1981). Moreover, infected leukocytes, especially activated lymphocytes, may cross the intact blood-brain barrier (Weberle et al. 1986) and directly infect glial cells or neurons (Dix and Bredsen 1988). On the other hand, the presence of plexitis and subpial lesions and the propensity of CMV to seed ependymal and subependymal surfaces clearly indicate a second form of dissemination of the virus via CSF, very probably after a primary blood-borne infection of the plexus choroideus (Morgello et al. 1987).

It is important to remember that CMV infection can induce immunosuppression that may even be superimposed on that caused by HIV infection itself (Rinaldo et al. 1980; Carney and Hirsch 1981; Dix and Bredesen 1988). CMV viremia increases with progressive immunodeficiency in HIV-infected patients (Fiala et al. 1986). It is very likely that HIV and CMV, as immunosuppressive viruses, facilitate the spread of each other throughout the body, greatly increasing their bidirectional interactions as the disease advances.

Pathology

In our series (n=180) we found 39 cases with CMV infection of the CNS (22 %). The extent of neuropathological changes was highly variable, as is reported in the literature, ranging from nonnecrotizing lesions (e.g., scatered CMV inclusion-bearing cells, or glial nodule encephalitis), to necrotizing lesions (e.g., ventriculoencephalitis). In many cases there were more than one lesion in the same patient; the lesions included: glial nodule encephalitis (n=32), ventriculoencephalitis (n=16), focal parenchymal necroses (n=9), and necrotizing myelitis (n=7). The spectrum of CMV-related lesions may be explained according to the two ways in which the virus disseminates, via CSF and blood, and by its ability to infect all cell types of the CNS. The first group of lesions, indicating the dissemination of the virus via CSF, are characterized by infection of the cells of the plexus choroideus and ependyma and by ventriculoencephalitis. In the second form, the virus reaches the CNS through the blood vessels and results in glial nodule encephalitis and in parenchymal necroses of variable size.

Macroscopic Findings

The macroscopic changes in CMV infection of the CNS are infrequent and not very specific. However, CMV ventriculoencephalitis can sometimes be suspected on gross inspection of the ventricular system. There is moderate dilatation of the lateral ventricles and shaggy irregular material that replaces the ependymal surface and extends into periventricular matter. In advanced cases the periventricular white matter, splenium and truncus corporis callosi, and septum pellucidum show hemorrhagic necroses. Furthermore, the ependymal lining of the cerebral aqueduct may be absent, and the periaqueductal tissues are hemorrhagic (Vinters et al. 1989). In extreme cases, occlusion of the cerebral aqueduct with development of a noncommunicating hydrocephalus occurs (Vinters 1989).

The nucleus dentatus and neighboring white matter of the cerebellum are predilection sites of necrotizing CMV encephalitis (Fig. 3.13 a). We found such necroses in nine cases. This tendency is well illustrated by Vinters et al. (1989) in one case with identically and symmetrically located lesions in both cerebellar hemispheres. The necroses appear as poorly demarcated gelatinous lesions. More rare are necroses in the putamen, brain stem (Fig. 3.13 b) and deep white matter of the frontal lobe (centrum semiovale). Recenty, we observed multiple necroses in the cortex up to 3–4 mm in diameter in a case of CMV plexitis and severe ventriculitis (Fig. 3.14).

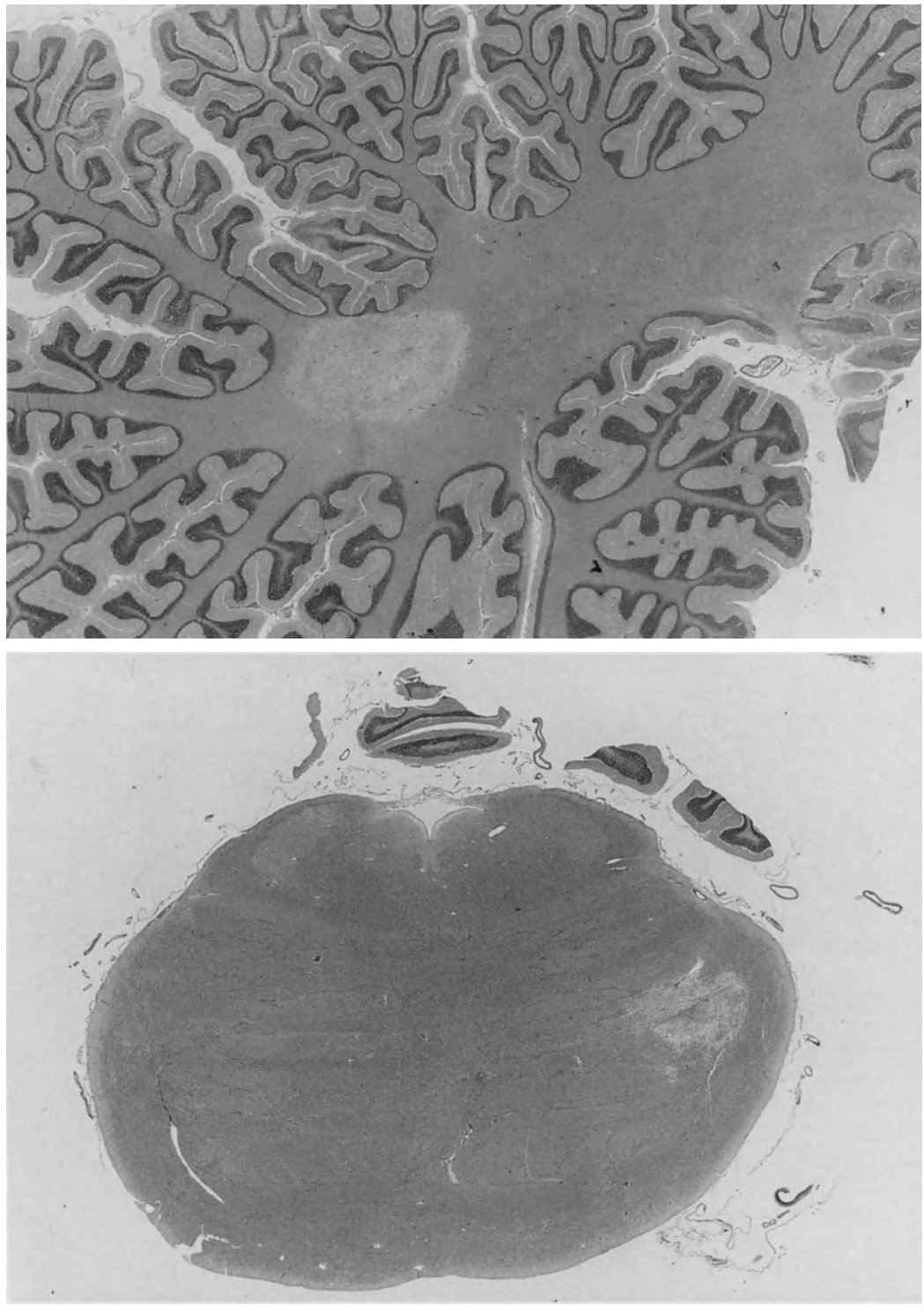


Fig. 3.13 a, b. CMV infection of the CNS. **a** Extensive necrosis in the white matter of the cerebellar hemispheres. H&E. **b** Extensive necrosis in the lateral section of the pons. H&E

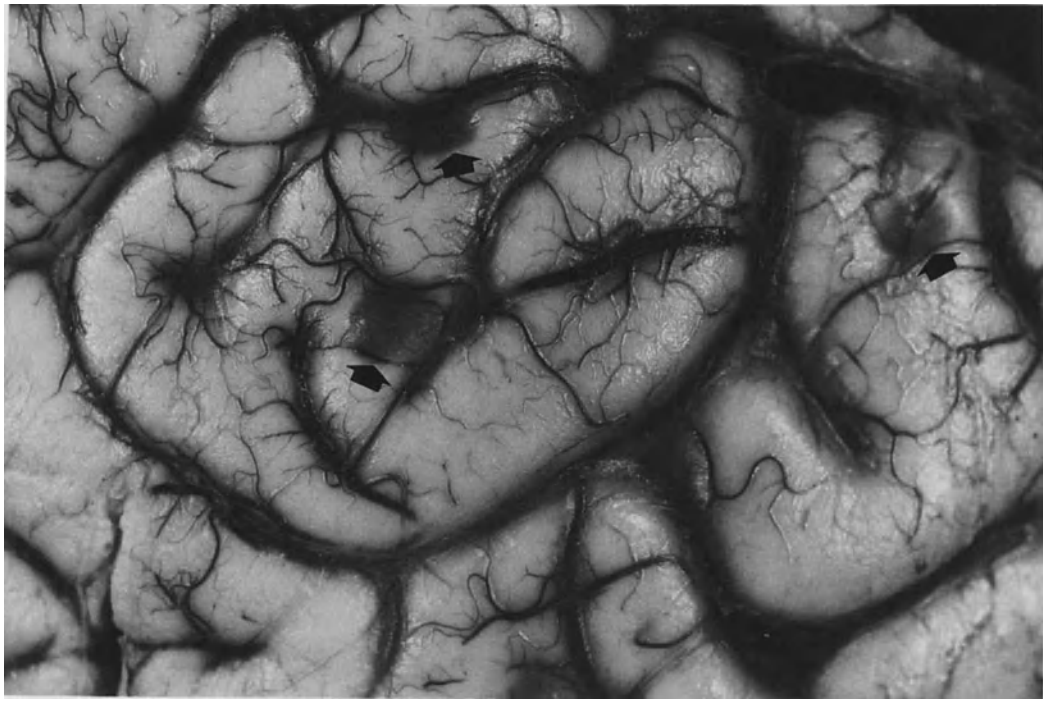


Fig. 3.14. Small cortical necroses *(arrows)* in the parietal lobe in a case of CMV infection (furthermore in the same case severe CMV ventriculitis)

Microscopic Findings

The histological diagnosis of CMV infection is supported by the identification of karyomegalic and cytomegalic cells. These are enlarged and show a large basophilic intranuclear inclusion (Cowdry type A) and multiple small cytoplasmic inclusions. The cytomegalic cells range in size from 25 to 40 μm, three to four times the size of adjacent uninfected cells. The intranuclear inclusion, approximately 10 μm in diameter, is separated from the nuclear membrane by a halo, the nucleus gaining an "owl's eye" appearance. Cytoplasmic inclusions consist of aggregates of viruses.

The most common lesions in CMV encephalitis are glial nodule encephalitis and ventriculoencephalitis. Other manifestations of CMV infection described in AIDS, in other immunosuppressed patients, and in immunocompetent persons include: focal parenchymal necrosis, plexitis, necrotizing myelitis, CNS vasculitis, and focal demyelination of the brain and spinal cord (Schneck 1965; Perham et al. 1971; Dorfman 1973; Schober and Herman 1973; Chin et al. 1973; Yanagisawa et al. 1975; Philips et al. 1977; Linneman et al. 1978; Duchowny et al. 1979; Koeppen et al. 1981; Hawley et al. 1983; Moskowitz et al. 1984b; Cohen and Corey 1985; Morgello et al. 1987; Vinters et al. 1989; Burns et al. 1991).

Glial Nodule Encephalitis. The most commonly described form of CNS pathology attributable to CMV in non-AIDS patients, has been glial nodule encephalitis (Schneck 1965; Vortel and Plachy 1968; Schober and Herman 1973; Dorfman 1973; Duchowny et al. 1979). CMV was the first pathogen to be linked to the glial nodules commonly observed in brains from AIDS patients (Nielsen et al. 1984).

We found glial nodules in 32 cases among a total of 39 cases with CMV infection of the CNS. Morgello et al. (1987) found glial nodules in all 30 cases with CMV infection of the brain. Glial nodules consist of loosely to densely cellular clumps containing multiple small nuclei of active microglial cells and a few astrocytes. The number of glial nodules varies greatly from case to case (Morgello et al. 1987; Vinters et al. 1989). They represent a general immunocellular reaction to an infected cell. However, only a few glial nodules contain CMV inclusion-bearing cells (Fig. 3.15; Nielsen et al. 1984; Morgello et al. 1987). This is not surprising since it is known that not all infected cells show karyomegaly or cytomegaly (Myerson et al. 1984; Wiley et al. 1986b; Schmidbauer et al. 1989).

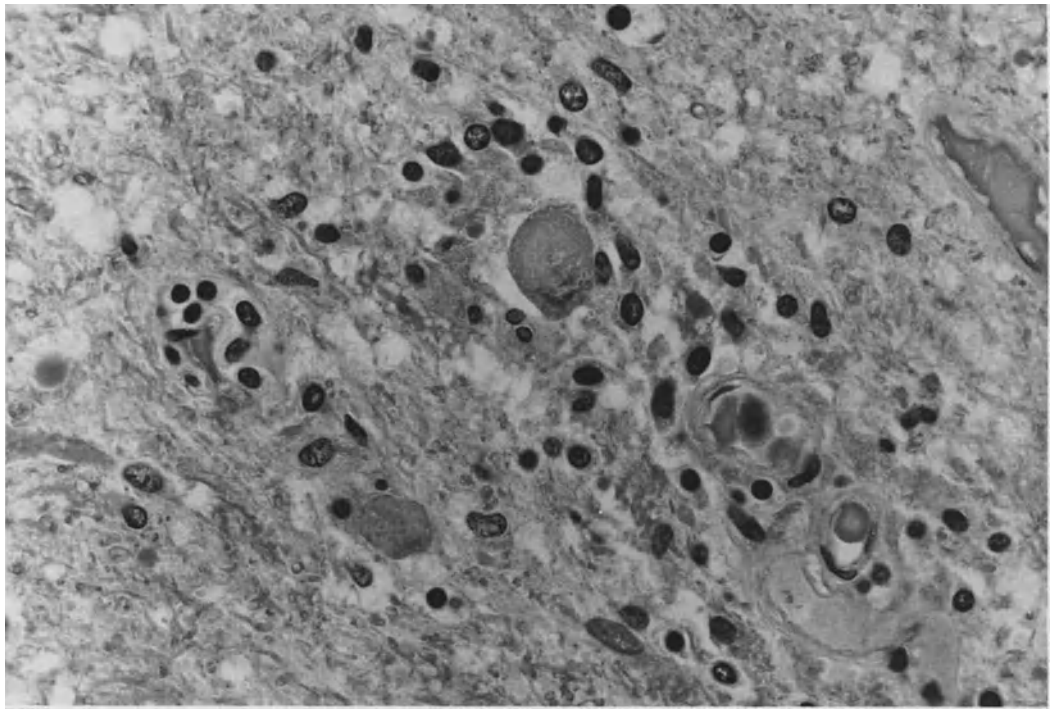
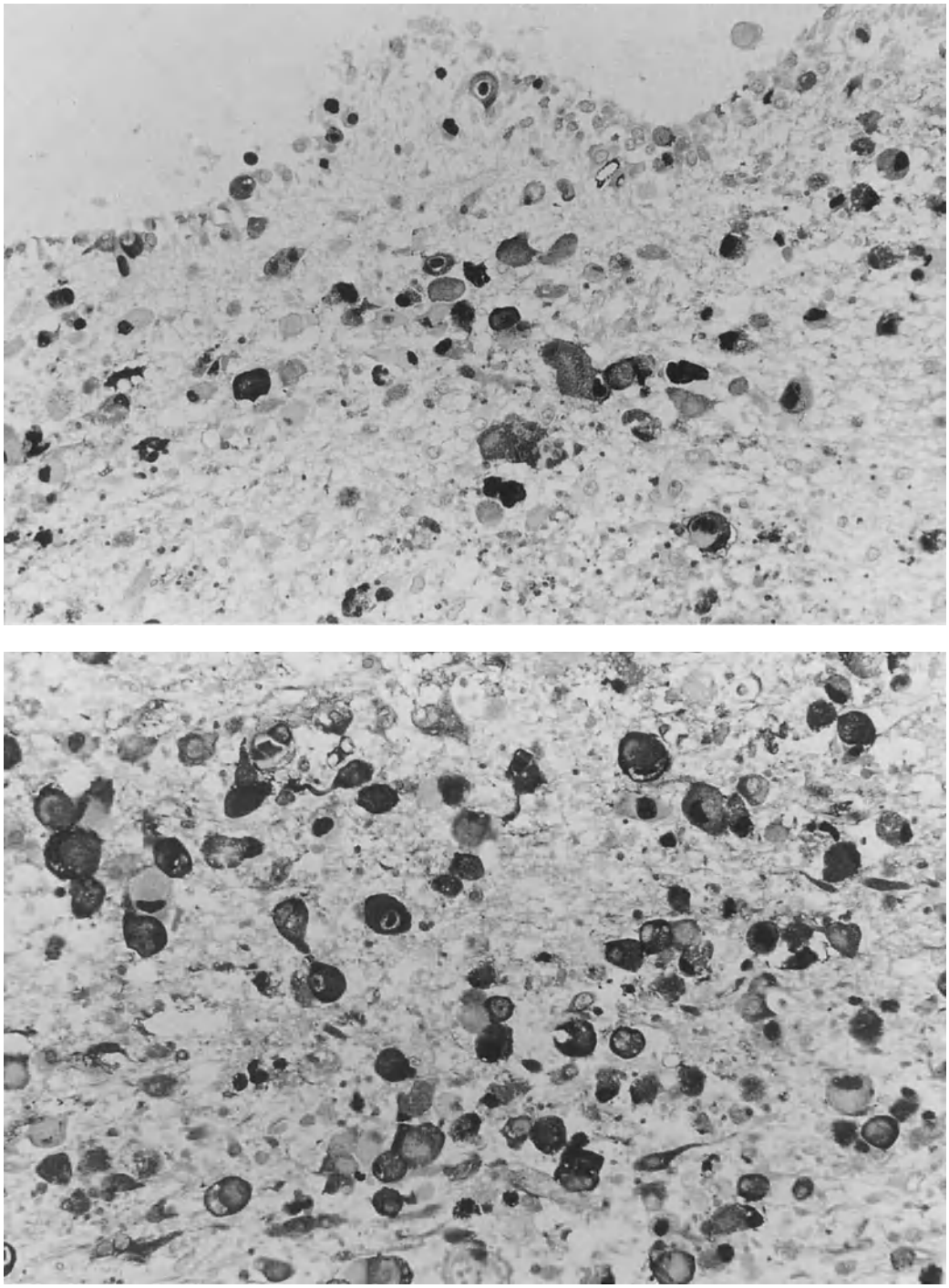


Fig. 3.15. CMV infection of the CNS. Spinal cord, gray matter; loosely structured glia nodule, two large oval CMV-infected cells, already necrotic *(centre)*. H&E

Cases with glial nodule encephalitis that lack inclusion-bearing cells or other associated well-identifiable CMV lesions (e. g., ependymitis), can be considered as CMV encephalitis only in the absence of other identifiable pathogens, especially *Toxoplasma gondii*, and in correlation with systemic CMV infections (Schneck 1965; Dorfman 1973; Morgello et al. 1987). We found glial nodule encephalitis as the sole manifestation of CMV infection in ten cases, without signs of other opportunistic pathogens in the CNS. In all ten cases there was systemic CMV infection.

Ventriculoencephalitis. In most cases with CMV infection a variable number of cytomegalic cells are evident in the ependymal surface. The virus clearly shows a tendency to spread from the ependymal surfaces in a ventriculofugal fashion and to produce laminar necroses of the periventricular white matter (Hawley et al. 1983; Post et al. 1986; Wiley et al. 1986 b; Gray et al. 1988; Burns et al. 1991). In advanced cases a thickened material consisting of abundant CMV-infected cells, necrotic material, an ill-defined infiltrate of macrophages, and acute and chronic inflammation substitutes the ependymal surface of the lateral ventricles, the third ventricle, the cerebral aqueduct, and the floor of the fourth ventricle (Fig. 3.16). In our material there were 16 cases with ventriculoencephalitis. In five of them the changes were severe enough to be detected as ependymitis on computed tomography. However, we have never seen the more severe changes with hemorrhagic ventriculoencephalitis well illustrated by other authors (Morgello et al. 1987; Vinters et al. 1989).

Generally, CMV infection of the CNS in AIDS patients has no consistent clinical picture (Morgello et al. 1987; Vinters et al. 1989; Vinters and Anders 1990). However, in our series ventriculoencephalitis was, as in other cases reported in the literature (Vinters et al. 1989), the major cause of neurological morbidity among the forms of CMV-encephalitis. Lesions of CMV are not anatomically associated with other infections. The unique exception is the superimposed HSV type I and CMV infection repeatedly reported in ventriculoencephalitis in AIDS patients (Pepose et al. 1984; Tucker et al. 1985; Petito et al. 1986; Morgello et al. 1987; Vinters et al. 1989; Lang et al. 1989) and in one immunosupressed patient (Yanagisawa et al. 1975). Occasionally HIV and CMV coinfect MNCs and macrophages, as demonstrated by immunocytochemistry and electron microscopy (Nelson et al. 1988; Bélec et al. 1990). By contrast, we and other authors could not find any significant differences in the



a

b

Fig. 3.16 a, b. CMV infection of the CNS. **a** Paraventricular brain tissue with remnants of the destroyed ependyma *(at top)*. Numerous large CMV-infected cells in addition to vaguely recognizable necrotic cells and detritus. Typical owl's eye cells *(at top, centre)*. **b** Deep subependymal white matter with numerous CMV-infected cells; sometimes owl's eye cells in an necrotic region. Monoclonal CMV antibody; APAAP method, ×20

incidence or severity of white matter lesions in patients with HIV encephalitis and patients with HIV encephalitis and CMV encephalitis.

Focal Parenchymal Necroses. In nine cases we found one or more focal parenchymal necroses. Histologically, the necroses are characterized by multiple cells with CMV inclusions, numerous macrophages, axonal swellings, and absent or minimal inflammatory infiltrates. Though usually of microscopic size, some can be detected macroscopically as zones of softening and gray discoloration (Gonzales and Davis 1988). They have some predilection for the nucleus dentatus, white matter of the cerebellum, and centrum semiovale (Morgello et al. 1987; Vinters et al. 1989). In our material CMV-related necroses were localized in seven cases in the nucleus dentatus and white matter of the cerebellum. In two cases the necroses appeared in the putamen and were macroscopically indistinguishable from toxoplasmic lesions; in two cases necroses were present in the centrum semiovale; and in one case a necrosis was located in the colliculus superior. Similar necroses, usually smaller in size, can be also found in the brain stem and medulla oblongata. Severe necrotizing encephalitis of the brain stem, extensive enough to cause focal neurological symptoms and to be revealed in magnetic resonance imaging but not on computed tomography, has been briefly reported in two cases of AIDS (Masdeu et al. 1988; Reyes 1988).

Necrotizing Myelitis. CMV necrotizing myelopathy has been described in AIDS patients (Dix and Bredesen 1988; Vinters et al. 1989; Mahieux et al. 1989; Bélec et al. 1990; Chimelli et al. 1990; Burns et al. 1991), in one case in association with HSV infection (Tucker et al. 1985). We found CMV infection of the spinal cord in seven cases. Here there were subpial necroses with numerous macrophages and cytomegalic cells. Glial nodules, isolated inclusion-bearing cells, and diffuse microglia proliferation were also present at different levels of the spinal cord.

Plexitis. Inflammation of the plexus choroideus is found in cases with ventriculoencephalitis (Vinters et al. 1989). The choroid plexus shows focal CMV inclusions surrounded by a slight or inconspicuous mononuclear inflammatory infiltrate, and sometimes there are small foci of necrosis. This component of the overall CMV infection may be minimal even in patients with severe ventriculoencephalitis (Vinters and Anders 1990). Thus, the number of cytomegalic cells in very low in comparison with the number of infected cells found in the ependymal surface. This is probably due to prompt and constant desquamation of plexus choroideus infected cells.

Pituitary Pathology. CMV infection of the pituitary gland is relatively rare, even in cases with widespread viral infection. We found only one case with CMV infection of the adenohypophysis, revealed by the presence of a few cytomegalic cells. In another case we found severe atrophy of the gland with multiple necroses in the adenohypophysis and numerous cytomegalic pituicytes in the neurohypophysis. The frequency of CMV infection of the pituitary in pathological AIDS series varies between 3%–10% (Vinters and Anders 1990; Vinters et al. 1989; Sano et al. 1989).

Vasculitis. Sometimes an acute and chronic vasculitis of the leptomeningeal vessels accompanies necrosis in the brain stem, medulla, and spinal cord (Koeppen et al. 1981; Morgello et al. 1987). Vasculitis is not present within neural parenchyma. We found inflammatory changes of the leptomeningeal vessels of the spinal cord in only one case with necrotizing CMV myelitis.

Demyelination. The occurrence of focal demyelination related to CMV in the absence of necrosis has been reported in a few cases (Moskowitz et al. 1984b; Morgello et al. 1987; Vinters et al. 1989). The significance and pathogenesis of these changes remain obscure.

Isolated Inclusion-bearing Cells. In almost every case of CMV infection isolated cells containing CMV inclusions devoid of associated glial nodules or inflammation can be seen (Morgello et al. 1987; Vinters et al. 1989). Usually, these cells may be easily identified, even with hematoxylin-eosin stain, as endothelial cells, astrocytes, ependymal cells, or neurons.

Visual System

In 20 patients with CMV retinopathy we studied the structures of the visual system at different levels. Retina, optic nerve (two levels), chiasma, optic tract (three levels), geniculate body (three levels), radiatio optica, and visual cortex (sulcus calcarinus and area striata at three levels) were examined. Only the retina, optic nerve and chiasma, and occasionally the very proximal part of the optic tract showed CMV infected cells. Atrophy of these structures with astrogliosis and microglia infiltration were common findings in patients severe retinopathy. We did not find signs of transynap-

tic infection in the geniculate lateral and visual cortex. In cases with ventriculoencephalitis CMV-infected neurons and astrocytes may be seen in the outer laminae of the geniculate lateral in the vicinity of the ventricle surface, as seen in our series and also reported by other authors who studied this nucleus in 10 cases of CMV retinopathy (Costanzi et al. 1992).

Immunohistochemistry

Immunocytochemical techniques have demonstrated that morphologically normal but latently infected cells can be found well beyond the site of cells that show viral inclusions (Wiley et al. 1986b, Morgello et al. 1987; Schmidbauer et al. 1989). Immunocytochemical studies conducted in our material with monoclonal CMV late antigen (DAKO) show that many typically infected cells exhibit positivity in the nucleus, cytoplasm, or both. In addition, some cells without inclusion bodies also appear positive. In all cases, however, we observed typical cytomegalic cells that do not show positive stain with the CMV antibody. Inclusion-bearing cells containing cytoplasmic and/or nuclear CMV antigen were demonstrated in all previously mentioned lesions. Well-identified, CMV-labeled cells include neurons, astrocytes, ependymal and plexus choroideus cells, and endothelial cells. The nature of the cells can be demonstrated by double labeling or by staining series of preparations with different antibodies. Oligodendroglial cells are, however, difficult to identify since a definitive marker for these cells is lacking.

In Situ Hybridization

In situ hybridization techniques have demonstrated that morphologically normal but latently infected cells can be found well beyond the site of cells that show cytomegalic changes (Myerson et al. 1984; Wiley et al. 1986b; Morgello et al. 1987; Schmidbauer et al. 1989). We performed in situ hybidrization studies with a biotinylated cDNA probe (Enzo Diagnostics) in a few cases. Our results were similar to those previously reported by other authors. However, since a diagnosis of CMV infection is possible in such cases by conventional histology and immunohistochemistry, we do no discuss this technique further. Immunohistochemistry and in situ hybridization with biotinylated cDNA probes have been shown to be of comparable sensitivity (Schmidbauer et al. 1989). In situ hybridization has been shown to be the method of choice in the diagnosis of cases with glial nodule encephalitis, in which immunocytochemic methods with CMV, *T. gondii,* or HIV antibodies showed negative results (Schmidbauer et al. 1989).

Electron Microscopy

The ultrastructure of CMV infection in the CNS is qualitatively similar to that described in other organs (Donnellan et al. 1966; Mcgavran and Smith 1965; D. G. Munoz et al. 1987). It seems, however, that CMV infection follows patterns that are quantitatively different in cells of the CNS compared with cells of other organs. Infected cells of the CNS produce a reduced number of viruses, the number of defective viral particles is high, and the nuclear chromatin does not completely disappear. These features may be responsible for the extreme difficulty in isolating CMV from the brain, for the absence of minimal inflammatory reaction, and perhaps for the indolent progression of the CMV encephalitis (Munoz et al. 1987).

The virus enters cells either by fusion of the virus envelope with the cellular plasma membrane or by inducing endocytosis (Rosenthal 1979; Smith and de Harven 1974). It then proceeds through the cytoplasma to the nucleus where virogenesis occurs (Rosenthal 1979; Kanich and Craighead 1972). The earliest evidence of CMV infection is the presence of small intranuclear inclusions. With additional replication the number of nucleocapsids increases dramatically. Clusters of naked nucleocapsids are found in the nucleus. Nucleocapsids have an outer diameter of 95–105 nm and may have several different types of appearance: opaque, round core surrounded by lucent and dense shells; a lucent center with one or two dense shells; or entirely dense paticles (Sidhu 1990; Fig. 3.17). There is enlargement of intranuclear inclusions, and the chromatin is displaced to the nuclear membrane or undergoes partial dissolution, leaving only peripheral clumps of normal chromatin. Part of the nucleus becomes filled with an irregular skein of amorphous electron-dense material (Sidhu 1990). The nuclear membrane may show marked protrusions and inden-

Fig. 3.17. Detail of the nucleus of a CMV infected cell. Multiple ▶ uncoated CMV nucleocapsids. (Magnification × 30000)

Fig. 3.18. Cytoplasm of a CMV infected cell. Numerous mature ▶ viruses and dense viral protein material forming aggregates within the endoplasmic reticulum. (Magnification × 20000)

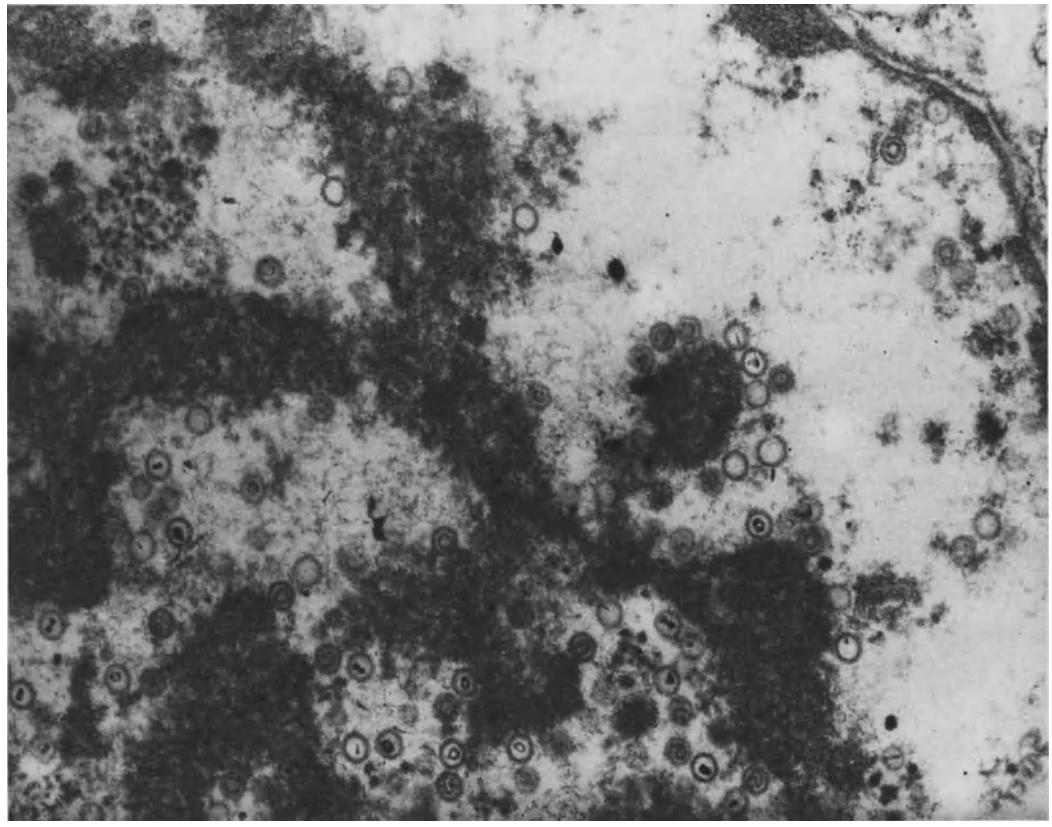


Fig. 3.17

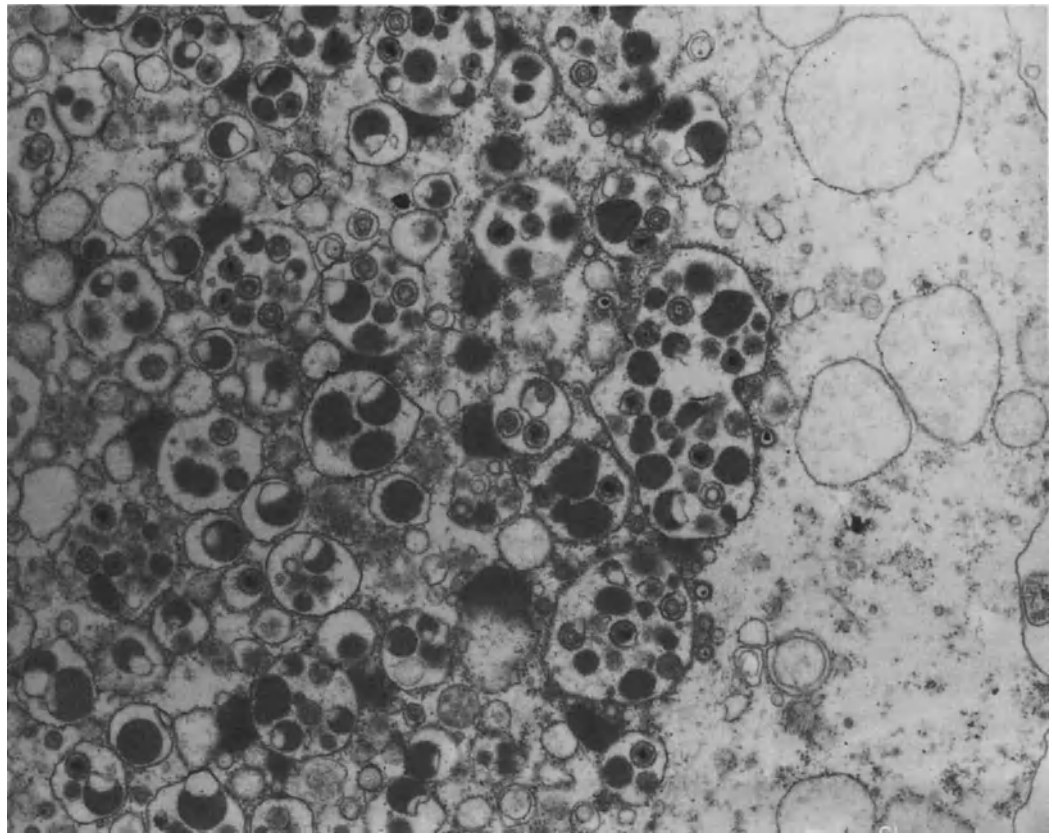


Fig. 3.18

tations. As the nucleocapsids leave the nucleus, they acquire a dense coat, not a true envelope, by budding through the inner nuclear membrane (Kanich and Craighead 1972; Kimura et al. 1976; Kasnic et al. 1982). The viruses acquire the envelope by budding into cytoplasmic vacuoles (Kanich and Craighead 1972; Vonka et al. 1976; Severi et al. 1979; Sidhu 1990). Mature, enveloped viruses are about 200 nm in diameter and have a thick coat that includes dense material from the nuclear membrane, dense material from the cytoplasm, and a true envelope (Sidhu 1990). Mature viruses appear free in the cytoplasm or form aggregates within the endoplasmic reticulum that represent the cytoplasmic inclusions seen in conventional histology (Fig. 3.18). Defective viral particles, consisting of empty envelopes are numerous in infected cells of the CNS.

Frequently, cells with CMV infection show in the cytoplasm the presence of large, rounded aggregates of dense bodies within the endoplasmic reticulum. These dense bodies consist of viral protein, but lack nucleic acid (Kanich and Craighead 1972; Sarov and Abady 1975). They do not appear in cells infected with other herpesviruses (Sidhu 1990).

In one case of AIDS, coinfection of the same cell by HIV and CMV has been illustrated ultrastructurally in macrophages and MNCs (Bélec et al. 1990).

JC Virus Encephalitis, Progressive Multifocal Leukoencephalopathy, Richardson's Disease

Introduction

JC virus encephalitis (JCE) is a rare opportunistic viral disease of the CNS with variable neurological symptoms. The neurological symptoms reflect multifocality of demyelinating lesions that are located in the hemispheres of the cerebrum and/or cerebellum and brain stem. It occurs mainly as a late complication of certain forms of chronic disease, in which the largest group consists of neoplasms of the lymphatic and hematopoietic tissues (Richardson 1970; Walker 1978).

The first unmistakable demonstration of the lesions was given by Hallervorden (1930), who briefly documented two cases in a chapter devoted to unclassifiable neuropathological processes. In the following three decades isolated case reports appeared in which the descriptions of the lesions clearly indicated JCE (Winkelman and Moore 1941; Bateman et al. 1945; Christensen and Fog 1955). In 1958 JCE was first reported as a distinctive clinicopathological entity with the name PML (Åström et al. 1958). Soon it was clearly recognized that JCE occurs in a broader clinical spectrum of patients, including those who have miliary tuberculosis, sarcoidosis, carcinomatosis, and other forms of immunosuppression (Richardson 1961). However, most of the cases have occurred as a complication of disorders affecting the lymphatic or hematopoietic system or in patients therapeutically immunosuppressed for other diseases or organ transplantation (Kimberlin 1984). Some cases of JCE are reported in patients without any other disease, but immunological investigations have often shown a defect in cell-mediated immunity (Silverman and Rubinstein 1965; Fermaglich et al. 1969; Bolton and Rozdilsky 1971; Brooks and Walker 1984; Arthur and Shah 1991). By the beginning of the 1980s only about 200 cases of the disease had been recorded worldwide in over 25 years (Dix and Bredesen 1988). The first case of JCE in AIDS was reported in 1982 (Miller et al. 1982). Soon, JCE was increasingly observed in AIDS patients (Petito et al. 1986; Bedri et al. 1983; Snider et al. 1983a; Bernick and Gregorios 1984; Katlama et al. 1984; Ho et al. 1984; Blum et al. 1985; Berger et al. 1987; Henkes et al. 1989). In 1985 we reported the first case of JCE in an AIDS patient in the FRG (Artigas et al. 1985). JCE may be the initial (Berger and Mucke 1988) and also the unique manifestation of AIDS in HIV-infected patients (Jakobsen et al. 1987). It may occur in isolation or associated with other opportunistic infections of the CNS or with HIV encephalitis (Gray et al. 1987; Scaravilli et al. 1989a; Schmidbauer et al. 1990a; Vazeux et al. 1990). JCE occurs in HIV-infected patients with a much higher frequency than in other disorders associated with immunosuppression. Its estimated incidence among AIDS patients is approximately 4%, which is far greater than previously experienced (Berger et al. 1987). Therefore, as many as 6000 cases of JCE may be expected to develop among the 155000 persons in the United States who have already contracted AIDS by 1991 (Lipton 1991).

Unfortunately, the well-known descriptive term PML does not accurately reflect either clinical or pathological features. In fact, as Richardson (1974) noted, the disease may not always be steadily progressive, and cases with partial recovery (Berger and Mucke 1988) and with complete stabilization (Price et al. 1983) have been described. Furthermore, the lesions are not confined to the white matter, and the spinal cord is at times also affected (Richardson 1974;

De Girolami et al. 1991). Thus it is more truly an encephalomyelopathy than a leukoencephalopathy. This process has been also called Richardson's disease (De Girolami et al. 1990). Here we use the term JCE.

The Causal Agent: JC Virus

The most characteristic feature of the disease is the infected darkly stained nucleus of the oligodendroglial cell. It is three to four times larger than normal and is distended and partially or completely filled by a basophilic, eosinophilic, or amphophilic inclusion which merges imperceptibly with the few remaining specks of chromatin. With increasing experience in the study of cases with JCE, Richardson (1961) became convinced that the distinctive changes in the nuclei of the oligodendrocytes were due to cytopathic effects of a virus. In 1965 Zu Rhein and Chou and, independently, Silverman and Rubinstein showed by electron microscopy that the abnormal oligodendrocyte nuclei were filled with myriads of virus particles that are morphologically typical of one of the papovaviruses. Several years passed before the virus was isolated and cultivated from the brain of a patient with JCE, whose initials were JC (Padgett et al. 1971). This is the origin of the current name of the virus. Subsequent molecular and antigenic studies have now made evident that in all cases PML is the result of infection of the brain by the JC virus (Weiner et al. 1973; Narayan et al. 1973; Walker and Frisque 1986; Aksamit et al. 1987). In some instances the isolation of SV 40 in cases of JCE was reported (Narayan et al. 1973; Scherneck et al. 1980; Weiner et al. 1972). However, restudy of these cases using in situ hybridization or extraction of viral DNA is revealing that these cases were also due to the JC virus (D. L. Walker, personal communication).

The viruses contain double-stranded DNA (molecular weight approximately 3.2–5.2 times 10^6 Da). They have icosahedral nonenveloped capsids and are smaller than the herpesviruses (approximately 40 nm in diameter; Brown 1984). The JC virus is genetically relatively simple, and the regulation of its gene expression may be understood in the context of current molecular biology technology (Frisque et al. 1984).

Pathogenesis

The JC virus is known to induce a naturally occuring disease in humans only. The human being is its only known natural host. It is nearly ubiquitous among adults all over the world. About 65% of the population is latently infected by the age of 14 years, whereas 75% of otherwise healthy adults are seropositive (Padgett and Walker 1983). Conversion from seronegativity to seropositivity for antibodies to the JC virus occurs rapidly during childhood, and in the vast majority of the population the virus apparently acts as a harmless passenger, producing an inapparent disease. Only under conditions of chronic immunosuppression, with the exception of a few cases reported in patients without any known underlying illness (Silverman and Rubinstein 1965; Fermaglich et al. 1969; Bolton and Rozdilsky 1971) does the virus become pathogenic, and JCE is the only disease known to result from infection with it.

The kidney is the recognized site of latent JC virus infection (Loeber and Dorries 1988). During immunosuppression the JC virus may then disseminate through the bloodstream to the brain and occasionally to the lung, bone marrow, and spleen, where the virus can be demonstrated by immunohistochemistry and in situ hybridization in B lymphocytes (Houff et al. 1988). The fact that JCE often begins multifocally, and that lesions tend to concentrate at the gray matter junction, where endarterioles terminate, is consistent with the notion of hematogenous spread. JCV selectively infects human glial cells, with a productive and cytolytic infection of oligodendrocytes and an abortive infection of some astrocytes leading to distinctive morphological alterations (Aksamit et al. 1986). The infection destroys oligodendroglial cells and ultimately myelin sheaths, which are made and maintained by oligodendroglia. The disease truly is an oligodendrocytopathy (Richardson and Webster 1983). Papovavirus usually develops in the following sequence of events within the host cell: viral precursor material assembles in the oligodendroglia cytoplasma and then passes into the nucleus where individual viral assembly occurs, and both round and rod particles are formed. With the increase in the number of mature particles within the nucleus, the nuclear membrane disintegrates; thus the virions reach the cytoplasm. They are enveloped by a new cytoplasmic membrane system from which they are liberated on the final disintegration of the cell (Baker and Rayment 1987; Scaravilli et al. 1989 a).

Pathology

JC virus encephalitis occurs in 1%–5% of autopsy cases in AIDS (Feiden and Möller 1991). In our series we have found eight cases of JCE (4.4%). In four cases the cerebral hemispheres were mostly affected; in two cases the structures of the posterior fossa, cerebellum, and pons were predominantly affected; and in the last one the whole brain was involved. The spinal cord, examined in six cases of our series, did not show pathological findings of JCE.

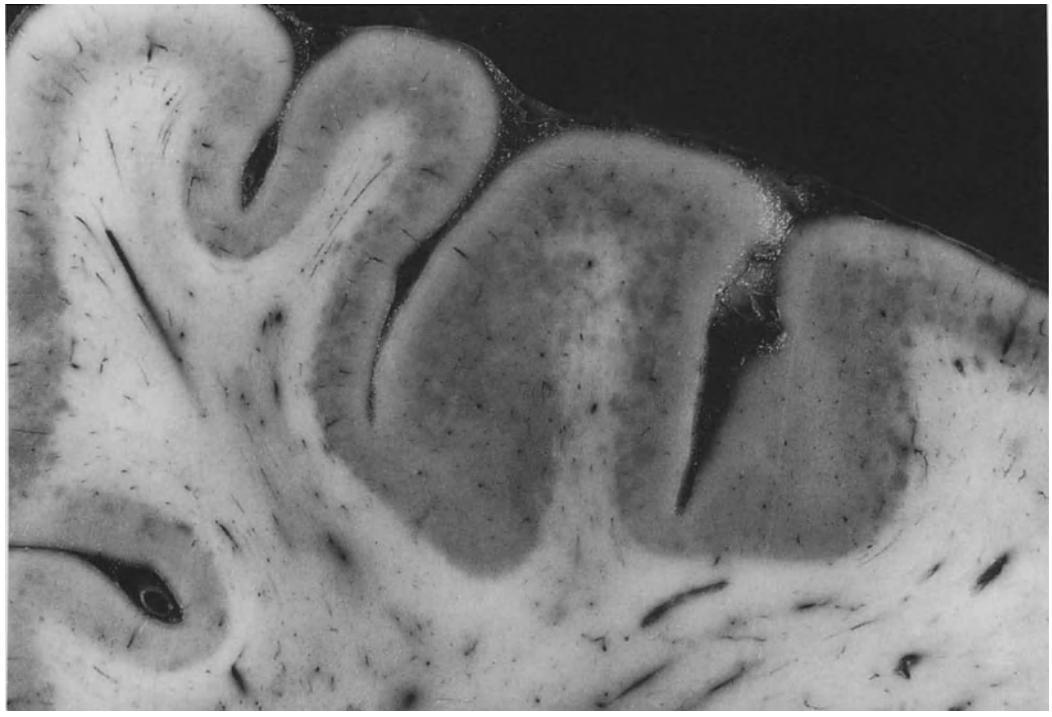
Macroscopy

Macroscopically, different grades of demyelination are observed in all brains studied. The lesions are grossly rounded, well-demarcated, grayish areas that most commonly range from pinpoint size to 1 cm in diameter (Fig. 3.19 a). They are very characteristic in allowing an accurate diagnosis by the macroscopic observation of the brain in almost all cases. The distribution of the lesions seems to be random, but there is a striking tendency for them to cluster in the subcortical white matter and deep layers of the cortex. The cerebral hemispheres are in general more severely affected than the cerebellum and brain stem, although there are cases in which this relationship is reversed. Gross and microscopic appearances of the brain are similar to those of brains affected by the JC virus in other clinical settings (Walker 1985), although a particularly severe, widespread, and necrotizing type of involvement with more numerous and larger demyelinated foci is often observed in AIDS cases (Fig. 3.19 b, Fig. 3.20; Orenstein and Jannotta 1988; Vinters 1990; Aksamit et al. 1990; Kuchelmeister et al. 1993). In our autopsy material we observed no variations in the degree of the lesions as compared with cases without HIV infection. Lesions of the spinal cord have been found in only a few cases in patients with and without HIV infection (Richardson 1974; Hénin et al. 1992; Kuchelmeister et al. 1993).

Microscopy

JCE is one of the few CNS diseases with an almost pathognomonic histology. A characteristic cytological abnormality is present in all cases and is not seen in any other disease; this consists of an enlargement of oligodendroglial nuclei, with effacement of their nuclear structure, which ultimately results in the death of these cells. Viral inclusions are not seen by light microscopy in any other cell kind. Early lesions are characterized by swollen oligodendrocyte nuclei, which are diffusely scattered in the white matter and gray matter without major focal myelin loss (Fig. 3.21). Typical lesions consist of multiple foci of demyelination of varying sizes and stages of evolution. The disappearance of myelin from the lesions is accompanied by a reactive scavenging response by macrophages to the myelin breakdown. The foci of infected oligodendrocytes and demyelination expand circumferentially as contiguous oligodendrocytes at the periphery of the lesions become infected by the JC virus (Richardson 1961). By the time the process has advanced enough for demyelination to be obvious, it becomes possible to distinguish four concentric zones in the lesion (Itoyama et al. 1982; Richardson and Webster 1983). In the outermost one, zone 1, the myelin is histologically intact and stains normally for myelin basic protein (MBP) and myelin-associated glycoprotein (MAG); within this zone, however, there are some infected oligodendrocytes. In zone 2, infected oligodendrocytes are numerous, and there is a decrease in MAG staining while MBP staining is normal. Zone 3, which is relatively narrow, is a region in which myelin breakdown is occurring, as shown by enhanced MBP staining, and macrophages are beginning to be numerous. Zone 4 is the central part of the lesion; here demylination is complete, infected oligodendrocytes are relatively sparse, and macrophages are abundant.

While reactive astrocytosis is present in the periphery of the lesions, bizarre astrocytes may appear in the center of the lesions (Richardson 1961). They are characterized by enlarged nuclei (25–60 μm), lobulated nuclei, multiple nuclei, nuclear hyperchromasia with a coarse chromatin pattern, and occasional mitosis (Åström et al. 1958). In some cases these changes abound whereas in others there are only a few such cells. In most cases the pathology is multifocal from the very beginning. As the individual lesions enlarge, they fuse and form irregularly shaped, demyelinated areas. These typical demyelinative lesions tend to vary greatly in size. We find minute foci, distinguishable only under the microscope, and massive confluent areas occupying large parts of a cerebral hemisphere. In most advanced cases the white matter of an entire lobe can be gray, granular, sunken below the cut surface, and at times cavitated. Areas of HIV-related demyelination are distinguishable from JCE lesions on histological grounds. However, in a few cases the pattern of demyelination in HIV encephalitis may mimic the typical lesions of JCE (Sotrel 1989), as we observed in one case of our series.



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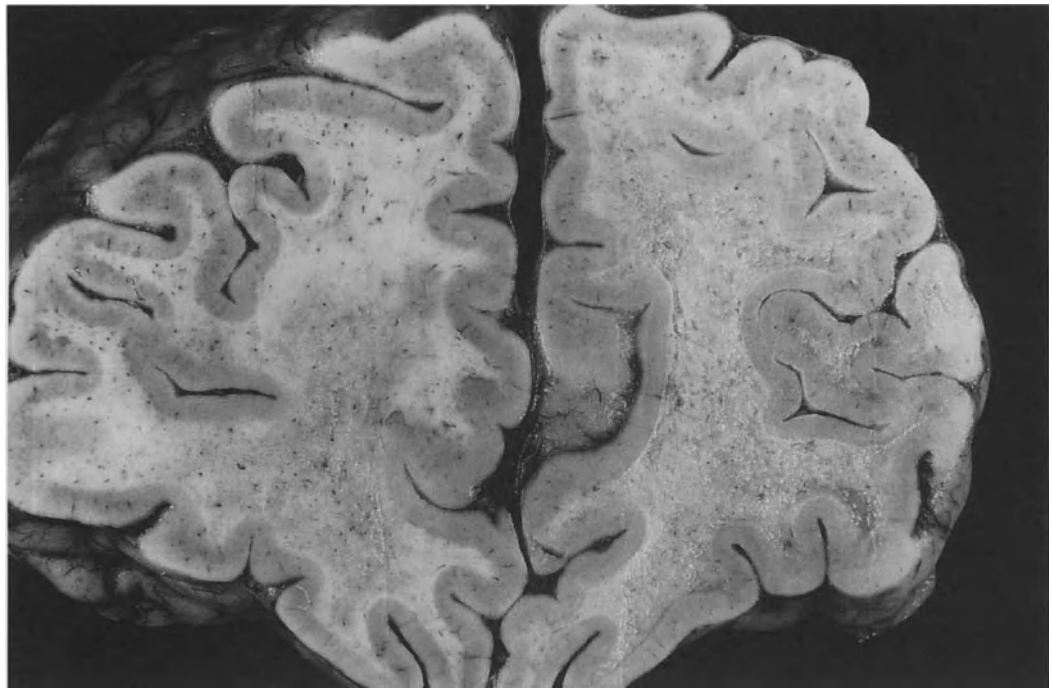

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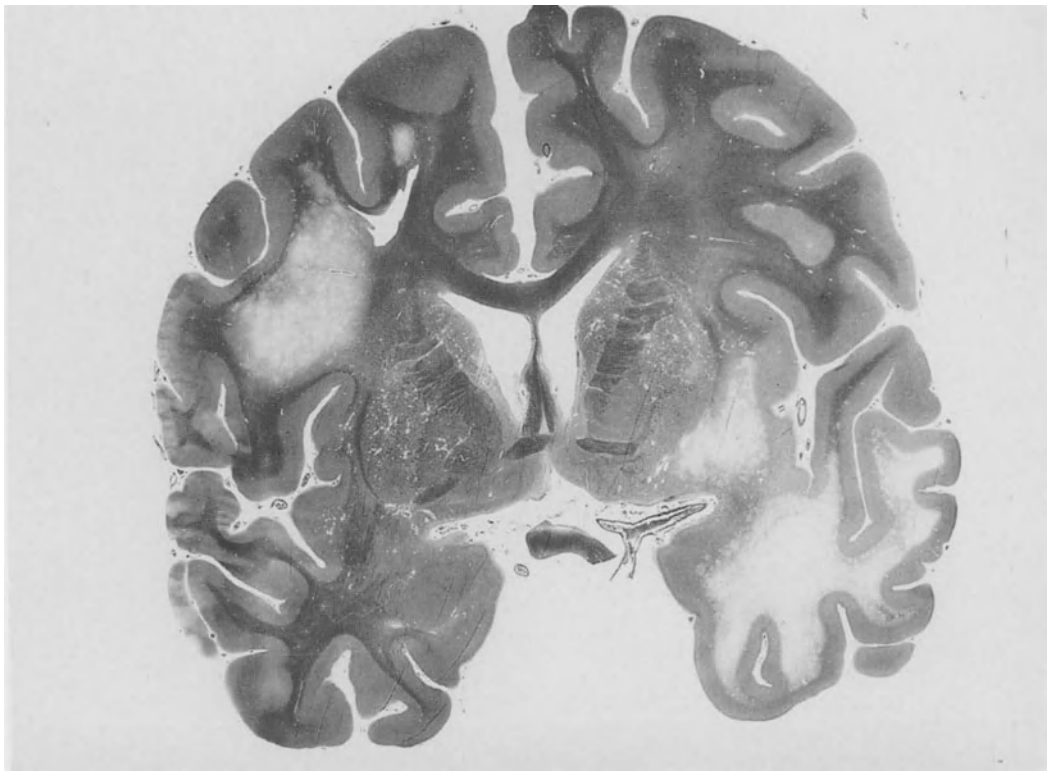
Fig. 3.19 a, b. Progressive multifocal leukoencephalopathy in AIDS. **a** Initial stage of the disease with multiple small demyelination foci within the cerebral cortex and at the cortico-subcortical junction (40-year-old man). **b** Coronal section of the frontal lobes showing a fine granular surface of the white matter caused by enumerable confluent demyelination foci as an advanced stage of the disease. In spite of the severe loss of the white matter substance (especially *right*), the cortex has remained preserved (54-year-old man)



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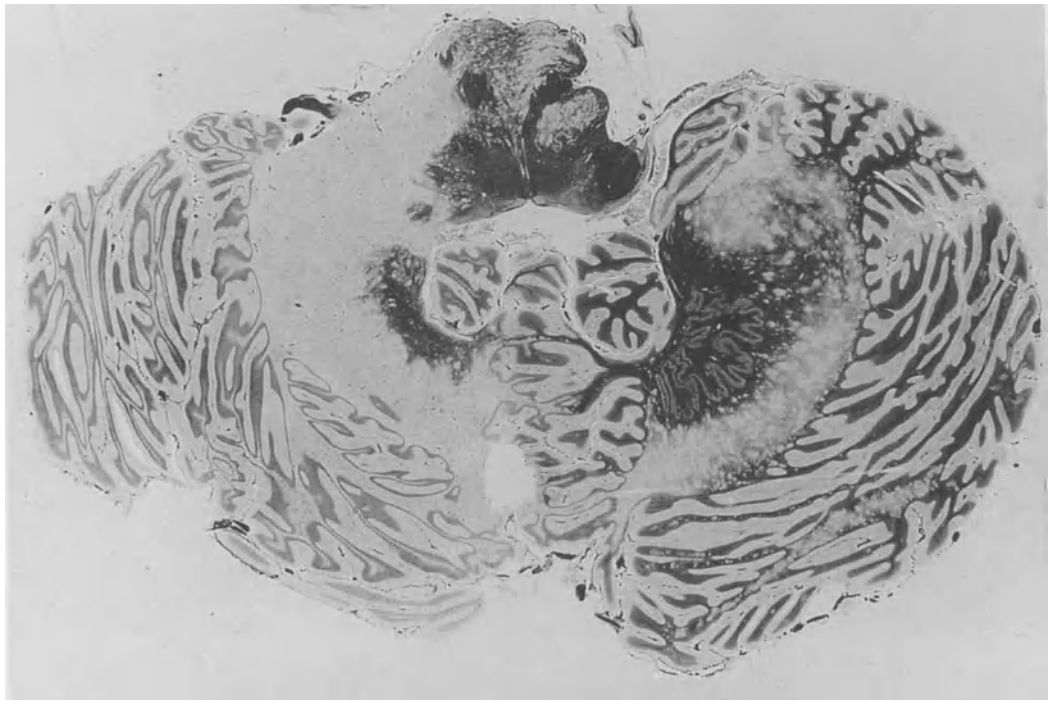

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Fig. 20 a, b. Progressive multifocal leukoencephalopathy in AIDS. **a** Coronal paraffin whole mount section through the cerebral hemispheres showing large demyelination areas, developed from enumerable confluent small foci. The cortex is well preserved even in the areas with most advanced destruction (temporal lobe, *right;*; 30-year-old women). **b** Celloidin whole mount horizontal section of the cerebellar hemispheres and brain stem showing multiple confluent demyelination foci within the brain stem and cerebellar white matter. The white matter of the opposite side shows almost complete loss of myelin (40-year-old man)

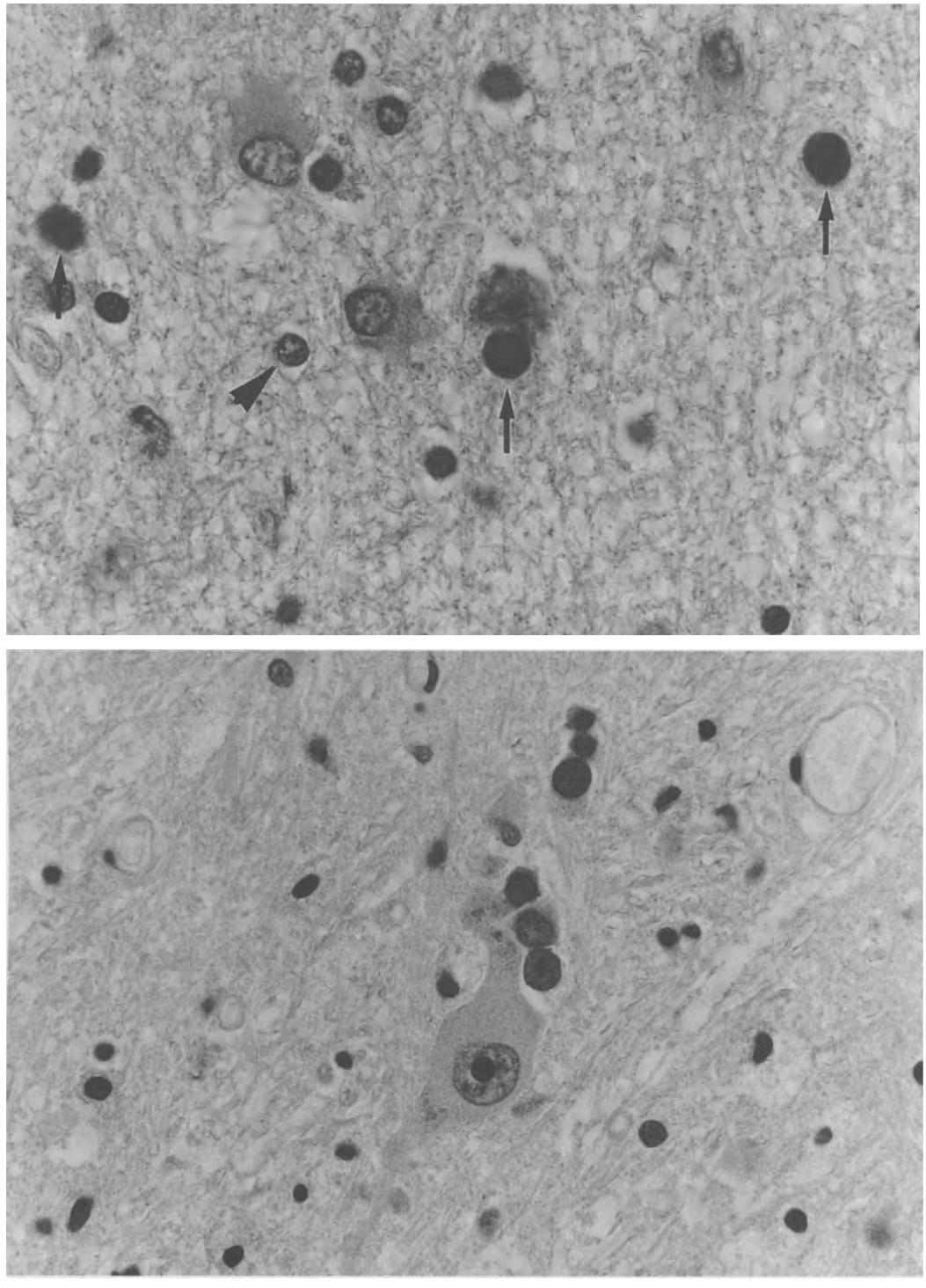
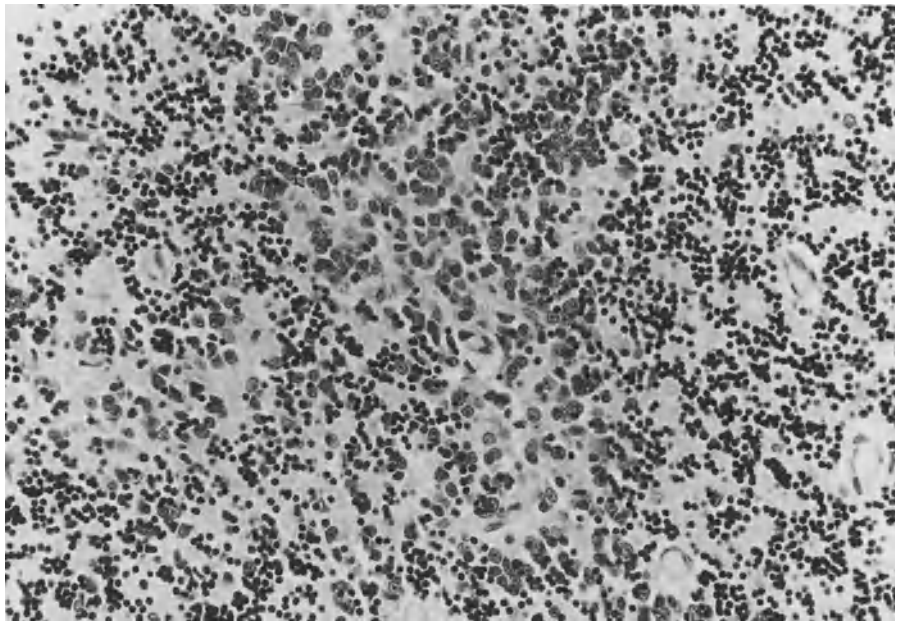


Fig. 3.21 a, b. Progressive multifocal leukoencephalopathy in AIDS. **a** White matter of the brain showing three typically enlarged and darkly stained nuclei of oligodendrocytes *(arrows);* furthermore, some oligodendrocytes with normal chromatin pattern *(arrowhead).* Note two reactive astrocytes. **b** Neuron with three infected satellite oligodendrocytes in the cerebral cortex; another enlarged and obviously infected nucleus *(above).* PAS, ×40



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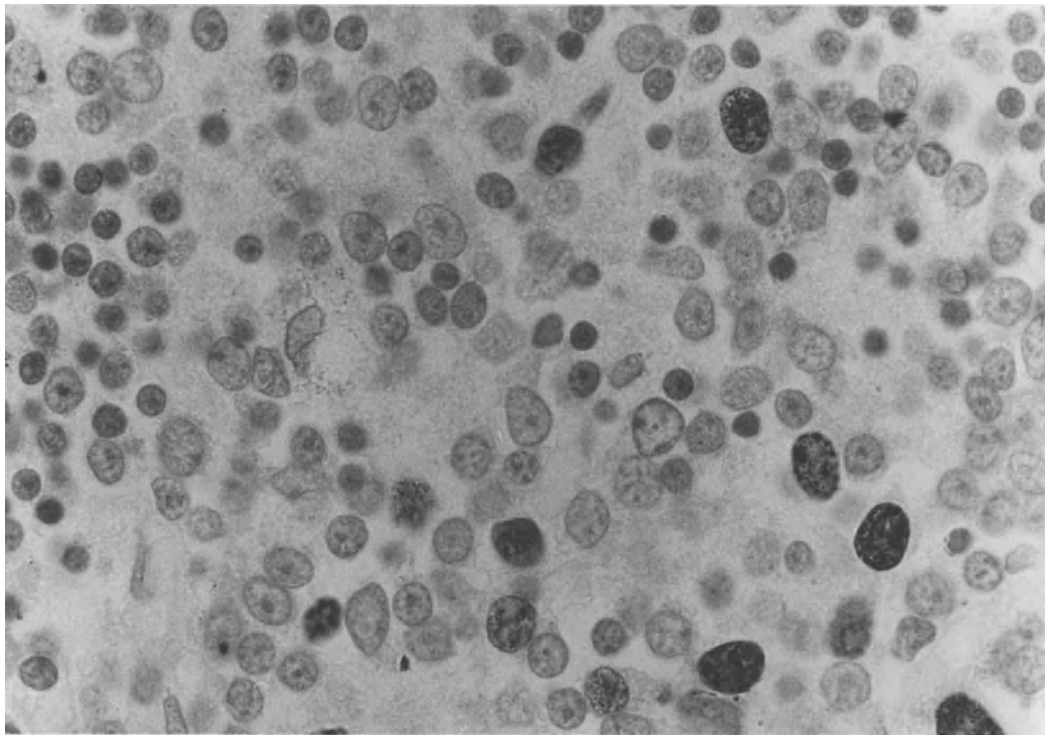

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Fig. 3.22 a, b. Progressive multifocal leukoencephalopathy in AIDS. **a** Granular layer of the cerebellum showing a circumscribed area with larger and less densely stained nuclei. We propose terming these cells "Richardson's cells" after the author of the first description. They are probabely enlarged granule neurons. H&E, ×20. **b** Detail of the immunohistochemical preparation of the same lesion demonstrating numerous enlarged Richardson's cells. Some of these cells are darkly stained as positive reaction of infected cells. Papovavirus antibody (courtesy of Dr. Walker, Wisconsin, USA); ×63

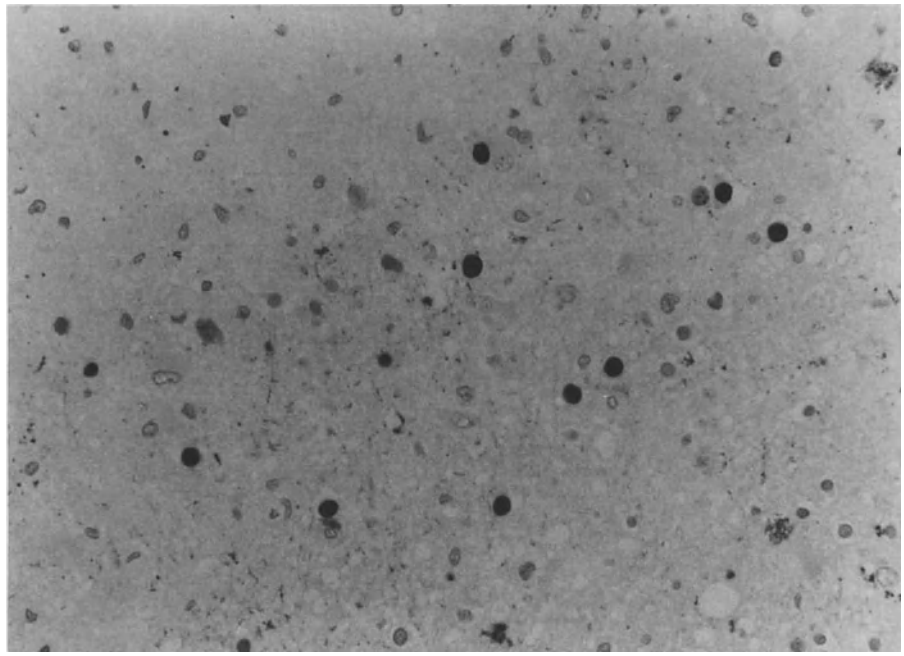


Fig. 3.23. Progressive multifocal leukoencephalopathy in AIDS. Section of frontal white matter of the brain showing immunohistochemical reaction for papovavirus. Multiple enlarged and darkly stained nuclei of infected oligodendrocytes. (Antiserum courtesy of Dr. Walker, Wisconsin, USA); ×20

The neurons themselves remain almost intact, even in the midst of total myelin disappearance (Richardson 1961, 1974). However, we have observed areas with mild to severe neural chromatolysis.

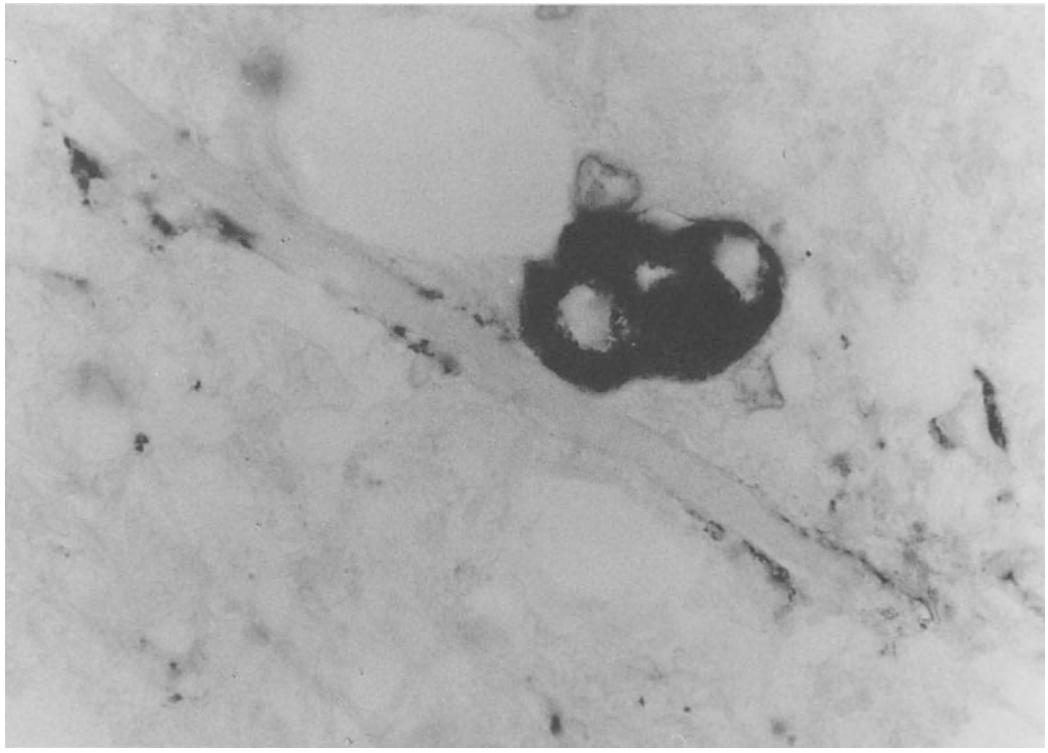
In a review of 83 cases of JCE in 1970, Richardson found in four cases remarkable changes of the granule cell layer of the cerebellum that have not been encountered in any other condition (Richardson 1970). The abnormality consists of scattered foci of partial tissue destruction surrounded by aggregates of enlarged granule neurons. This has subsequently been clearly described in two further cases in patients without HIV infection (Gagné et al. 1977; Richardson and Webster 1983). We found similar findings in two of our cases (Fig. 3.22); in one of the cases there were areas with complete loss of granule cells, remaining only large clusters of the aforementioned cells with enlarged nuclei. Richardson's cells have been described in five other cases, one of them in the absence of nearby foci of demyelination (Kuchelmeister et al. 1993) and in another case with severe loss of granule cells (Weidenheim et al. 1992).

It has been reported that JCE in AIDS shows a more intense inflammatory response (Aksamit et al. 1990, Kuchelmeister et al. 1993), and it has long been known that there is a group of cases in which lymphocytes and especially plasma cells are particularly abundant in the lesions, both in the perivascular spaces and in the parenchyma outside (Richardson and Johnson 1975). In these cases, altered oligodendrocytes are sparse, and giant astrocytes may be absent. We observed one case with this unusual inflammatory response. The inflammatory infiltration was composed of B- and T-lymphocytes, while in the other cases perivascular cuffings were scarce.

We also found in our cases, as reported by Aksamit et al. (1990), microglia activation and proliferation in the white matter, this being very frequent in AIDS brains with any kind of opportunistic infection, even in areas far from the lesions.

Immunohistochemistry

We carried out immunohistochemical studies with polyvalent antiserum directed against the genus-specific antigen common to all polyomaviruses. (This antibody was generously supplied by Dr. D.L. Walker, Department of Medical Microbiology and Immunology, University of Wisconsin.) Affected oligodendrocytes with swollen nuclei show the most intense staining for JC virus capsid antigen (Fig. 3.23). These



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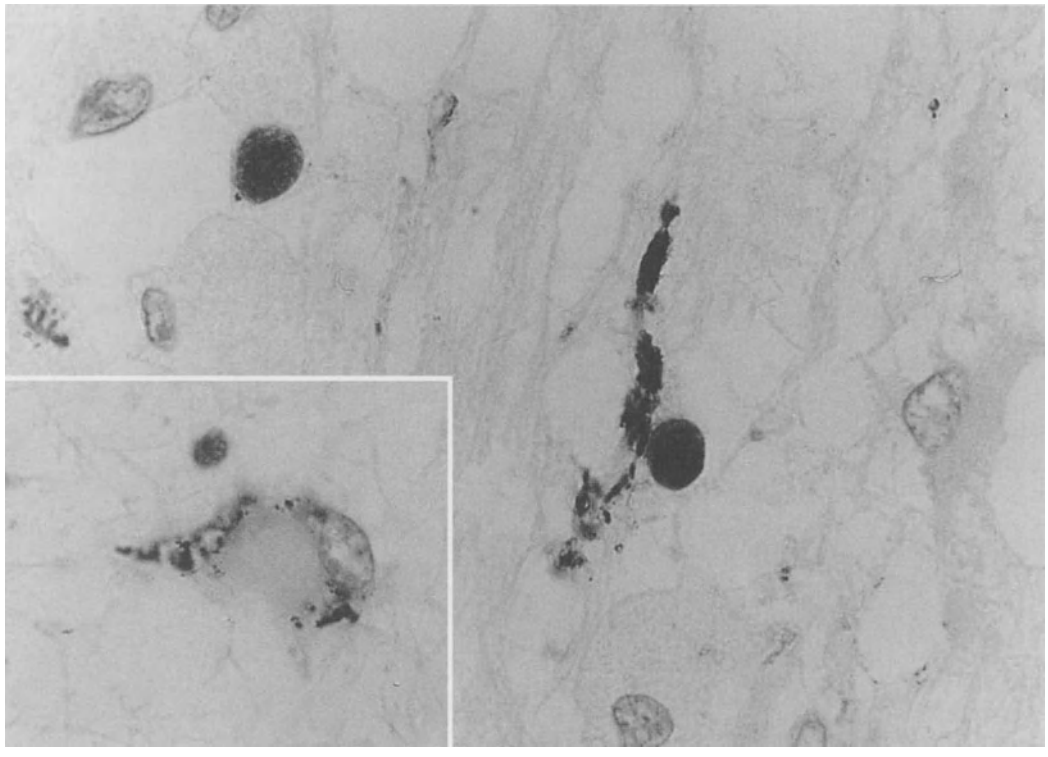

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◀ **Fig. 3.24 a, b.** Progressive multifocal leukoencephalopathy in AIDS. **a** Enlarged oligodendrocyte with darkly stained nucleus and cytoplasm as positive immunohistological reaction for papovavirus. Myelin remnants surrounding an axon are also positively labeled. **b** Typically enlarged nuclei of oligodendocytes with strong positivity in the immunohistochemical reaction. Note the clearly stained remnants of a myelin sheath adjacent to one of the infected oligodendrocytes. *Inset,* granular immunohistochemical staining of the cytoplasm of a reactive astrocyte. Papovavirus antibody (courtesy of Dr. Walker, Wisconsin, USA); ×100

oligodendrocytes are typically situated at the margin of demyelinated foci or, less commonly, diffusely through demyelinated areas (Aksamit et al. 1986, 1990; Wiley et al. 1988; Schmidbauer et al. 1990a). Nuclear staining of reactive astrocytes is rare (Aksamit et al. 1986; Schmidbauer et al. 1990a). Large bizarre astrocytes are sometimes labeled in the nuclei (Aksamit et al. 1986). A few enlarged glial cells within the granule cell layer contain JC virus antigen (Aksamit et al. 1990). Neurons, endothelial cells, ependymal cells, and inflammatory cells around blood vessels do not stain for JC virus (Schmidbauer et al. 1990a; Aksamit et al. 1990).

In addition, we observed in two cases numerous oligodendrocytes with strong positivity in the cytoplasma (Fig. 3.24). We also observed long trajects of myelin sheaths with JC virus positivity. Fine ramified cell processes were seen in areas of demyelination, and with another pattern, in the granule cell layer of the cerebellum. We also found clusters of small positive granules in the cytoplasm of reactive astrocytes. Sometimes in our material macrophages showed a fine granular positivity in the cytoplasm. In cases with cerebellar affection some of the nuclei in cell clusters with enlarged nuclei showed JC virus positivity. The number of positive cells clearly increases in areas with severe loss of granular cells.

In a few cases it has been described that macrophages that infiltrate the demyelinating lesions of JCE may also be infected by HIV. (Wiley et al. 1988; Schmidbauer et al. 1990a). We observed in only one case large amounts of HIV proteins in macrophages and MNCs in a demyelinated area in the pons. In this case, there was no further evidence of HIV encephalitis in the brain. Macrophages showing HIV positivity normally do not stain for JC virus antigen (Aksamit et al. 1990), so that synergistic effects of the two viruses from coinfection of the same cell, as has been suggested, seems unlikely.

Electron Microscopy

Ultrastructurally, JC virions are usually seen in tightly packed, crystalloid aggregates that fill the nucleus. The virions are present in the form of ovoid, round, or hexagonal particles, 30–40 nm in diameter, and filamentous structures about 15–27 nm wide and of indeterminate length (ZuRhein and Chou 1965; Aksamit et al. 1985). A transverse periodicity may be visible in these latter forms. Smaller, rounded particles corresponding to cross-sections of the filamentous forms are also to be seen. The filamentous particles may represent improperly assembled virions or virions in the process of assembly (Sidhu 1990). Virus particles may occasionally also be found in oligodendroglial cytoplasm. In our own material we have observed virus particles within the processes of oligodendrocytes and even within the myelin lamellae (Fig. 3.25).

Intranuclear virions in astrocytes are present in remarkably fewer numbers as compared with those in infected oligodendroglial cells but, when present, have the same spherical and filamentous forms (Mazlo and Herndon 1977; Mazlo and Tariska 1982). When virions are present in the cytoplasm of astrocytes, they appear singly or in clusters; the former are surrounded by a membrane suggesting endocytosis, and the latter are surrounded as a group by an endoplasmic reticulum membrane. Furthermore, papovavirus appears in the endoplasmic reticulum of large pleomorphic astrocytes (Aksamit et al. 1986). Occasionally, papovavirus can be observed in the cytoplasma of macrophages, where it appears to be replicating from phagocyted myelin. Large numbers of papovavirus are to be seen both free and associated with cellular debris in the interstitium. Unusual findings with abnormal and florid modes of viral replication were reported in a case by Scaravilli et al. (1989a).

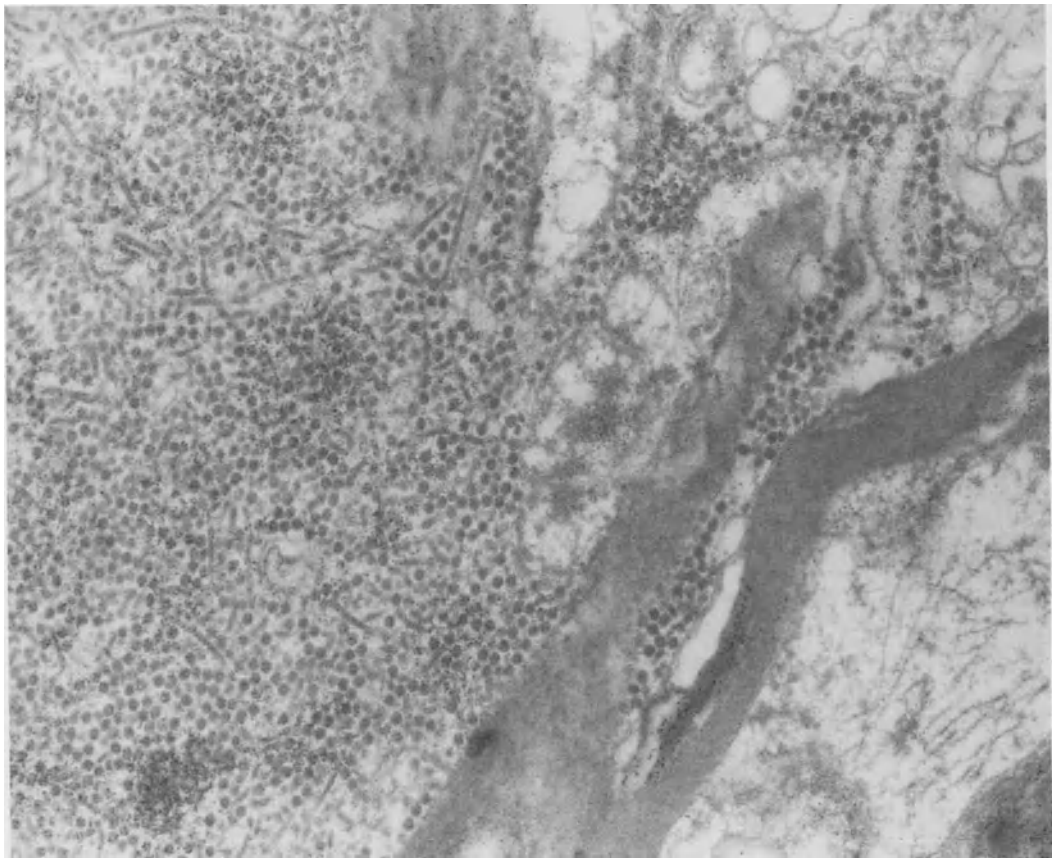


Fig. 3.25. Progressive multifocal leukoencephalopathy in AIDS. Electron microscopic picture showing numerous filamentous and round viral particles within the cytoplasm and the process of an oligodendrocyte partly surrounding lamellae of myelin. × 20000

■ Toxoplasmosis

Introduction

Since the recognition of AIDS, cerebral toxoplasmosis (CT), once a rare disease even in immunocompromised adults, has become one of the most common causes of encephalitis in the United States and Europe (Luft and Remington 1988). Before 1980 CT occurred only sporadically in immunocompromised patients, predominantly in those with malignancies of the reticuloendothelial system and heart transplant recipients (Feldman 1968; Hooper et al. 1982; Hakes and Armstrong 1983). In 1941 Pinkerton and Henderson reported the first case of postnatally acquired CNS toxoplasmosis. Between 1940 and 1980 CT was found in 31 out of 36 autopsy cases of disseminated toxoplasmosis (Yermakov et al. 1982). The incidence of infection increases with age and varies geographically. Immunoglobulin G (IgG) antibodies to *T. gondii* are found in 40%–50% of healthy young American adults (Remington and Desmonts 1983), compared with only 20% of British adults and 90% of adults in France and in underdeveloped countries (World Health Organization 1984).

More than 90% of primary infections with *T. gondii* are subclinical but result in seropositivity (Pons et al. 1988). Immunocompetent hosts with symptomatic toxoplasmosis have one of four clinical syndromes: congenital infection with intracerebral or ocular involvement, uveitis with chorioretinitis, acute mononucleosis like syndrome, or chronic regional lymphadenopathy (Pons et al. 1988). Disseminated disease and/or neurological manifestations occur in fewer than 1% of normal hosts with symptomatic disease (Velimirovic 1984), whereas among patients with AIDS or other immunosuppressive conditions, CNS

Table 3.12. CNS toxoplasmosis (56/180 autopsies)

	n
Focal encephalitic form	43
Necrotizing	15
Organizing	30
Chronic	18
Diffuse encephalitic form	5
Ventriculoencephalitis	2
Acute disseminated anergic form	1
Resting bradycystic form	4
Necrotizing myelitis	2

In a few cases there were more than one morphological form in the same patient.

involvement is common. The first case of CT in an AIDS patient was reported by French authors in 1980 (Rutsaert et al. 1980). Today, infection with *T. gondii* is the most common cause of intracerebral mass lesions (Navia et al. 1986b; Vinters and Anders 1990) and, after CMV, the most common opportunistic infection of the CNS in patients with AIDS (Luft and Remington 1988). *T. gondii* is distributed worldwide, with an increased incidence of infection in warmer climates.

Along with important geographical variations in the incidence of the infection, there are also regional variations in the clinic and pathological features. CT is rare in New York (Petito et al. 1986), for instance, but is common in Florida (Moskowitz et al. 1984a, b) and in Europa (Gray et al. 1988; Lang et al. 1989).

In our series of 180 autopsy cases 56 (31%) were found to have CNS toxoplasmosis. The distribution of forms of toxoplasmosis in our material is presented in Table 3.12.

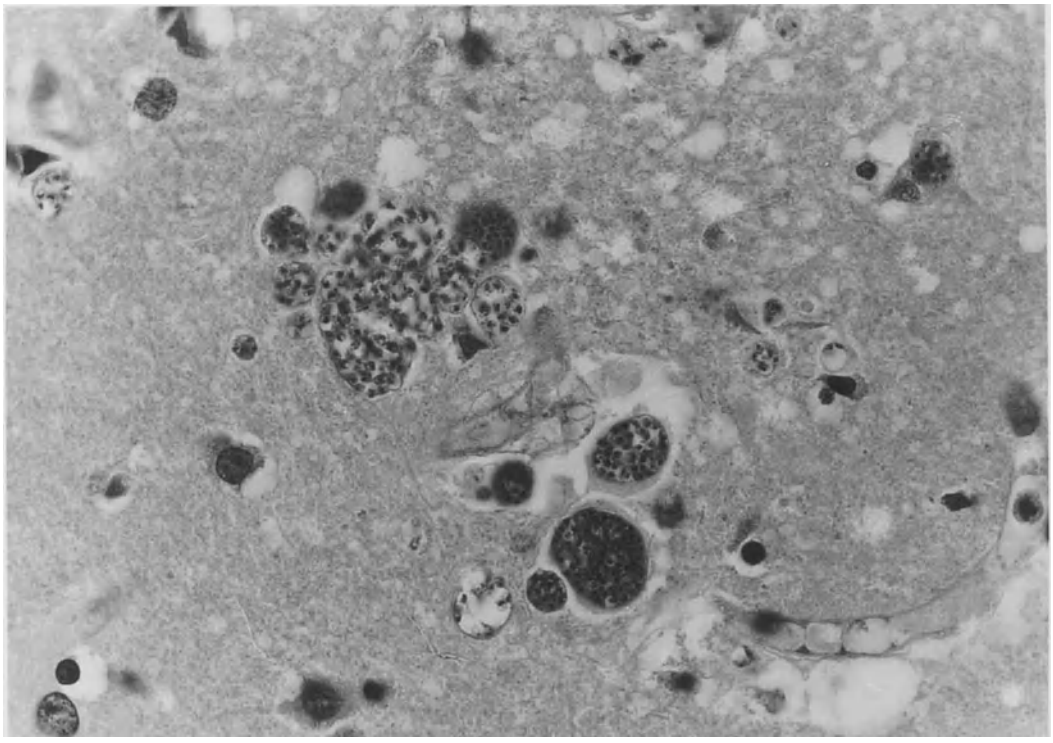
Pathogenesis

The most common routes of infection by *T. gondii* are: ingestion of raw, poorly cooked, or not previously frozen beef, pork, and lamb; ingestion of substances contaminated by cat feces containing oocysts; transplacental blood-borne transmission to the fetus from an acutely infected mother; very rarely, transplantation of infected human organs; blood transfusion; and laboratory accidents during handling of infected laboratory animals (Krick and Remington 1978; Ryning et al. 1979). Ingestion of toxoplasma cysts or oocysts leads to digestion of the cyst capsule in the gastrointestinal tract, freeing the organisms which then invade the epithelial cells. Free tachyzoites measure 4–7 μm in length and 2–4 μm in width and have small nuclei with nucleoli. They represent the proliferating active forms of the parasite (Hoare 1972). The organism invades the gut, with dissemination to all organs and the establishment of persistent inactive infection (latent infection). Although each parasite seems to be equipped with all the structures needed for sustaining life and multiplication, its replication depends absolutely on the host cell and cannot take place extracellularly (Jones et al. 1972; Powell et al. 1978). Tachyzoites can infect, replicate, and form cysts within nucleated cells of all tissues. A competent humoral and cell-mediated immune system prevents any major tissue damage by destroying free organisms and promoting formation of true cysts (bradycysts) from pseudocysts (groups of tachyzoites which are encased by the remnants of the host cell membrane). The bradycysts are formed by a new membrane replacing the host cell membrane around the pseudocyst. These measure between 20 and 100 μm and contain slowly multiplying bradyzoites (Fig. 3.26). Bradycysts reside latently as encysted forms confined to the lymph nodes, heart, lung, skeletal muscles, and brain. They persist for the life of the host and are considered the likely cause of recrudescence of disease.

In the brain, tachyzoites focally invade all types of cells, including neurons, glia and their processes, and endothelial and plexus choroideus cells. The mass of intracellular parasites enlarges by division and eventually bursts from the host cell, freeing motile tachyzoites to establish new infections in neighboring cells. Once this process of cell invasion and cell destruction is initiated in a patient with severely impaired cellular immunity, it progresses very rapidly even in the absence of inflammatory cells or overt thrombosing angiitis (Ghatak and Sawyer 1978).

Pathology

In addition to geographical variations in the distribution of *T. gondii*, there are also some differences in the frequency of CT found in autopsy series. American authors found CT in 10.5% of AIDS patients at autopsy in New York (Petito et al. 1986), 14% in San Francisco (Levy et al. 1985a), 7% in Los Angeles (Anders et al. 1986a, b), and 31% in Florida (Moskowitz et al. 1984b). Whereas in Switzerland the frequency is 26% (Lang et al. 1989), in the FRG the frequency of CT in autopsy series varies between 14% in Munich (Möller and Backmund 1991), and 31% in Berlin (our series). In our series of autopsies in AIDS patients, we found



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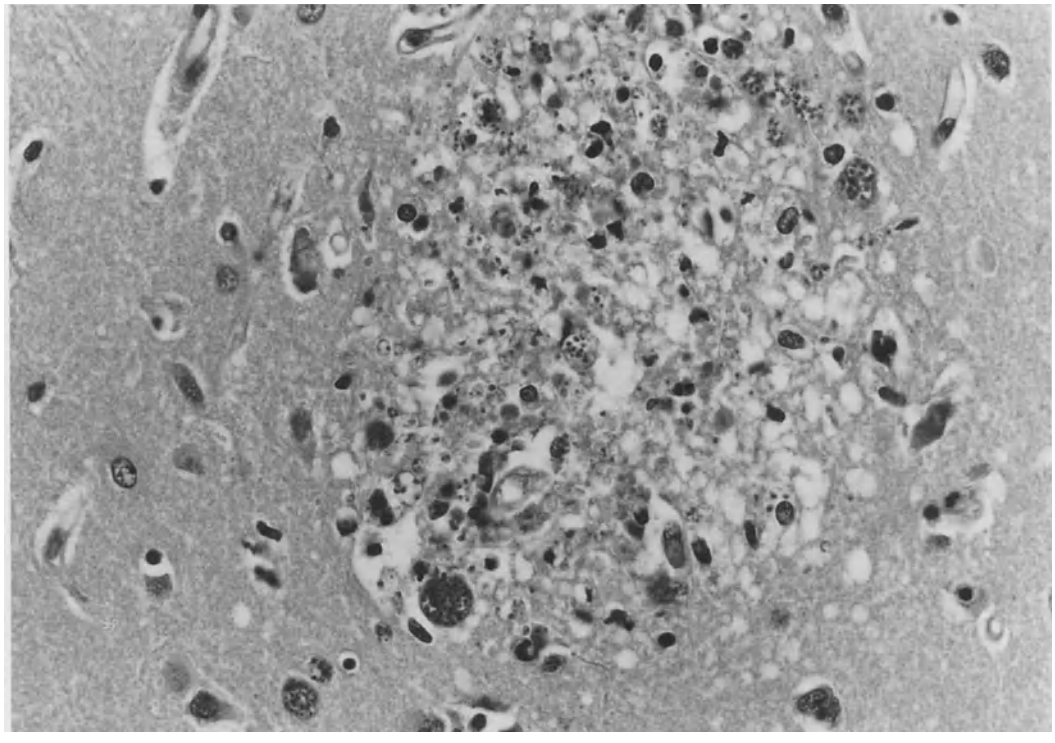


b

Fig. 3.26 a, b. Cerebral toxoplasmosis in AIDS. **a** Bradycysts with well-defined rims and clearly discernible capsule *(lower half);* ruptured cysts with released tachyzoites *(centre).* H&E, ×60. **b** Small fresh necrosis focus in the cerebral cortex with a bradycyst, ruptured cyst *(top right)* and numerous tachyzoites. H&E, ×60

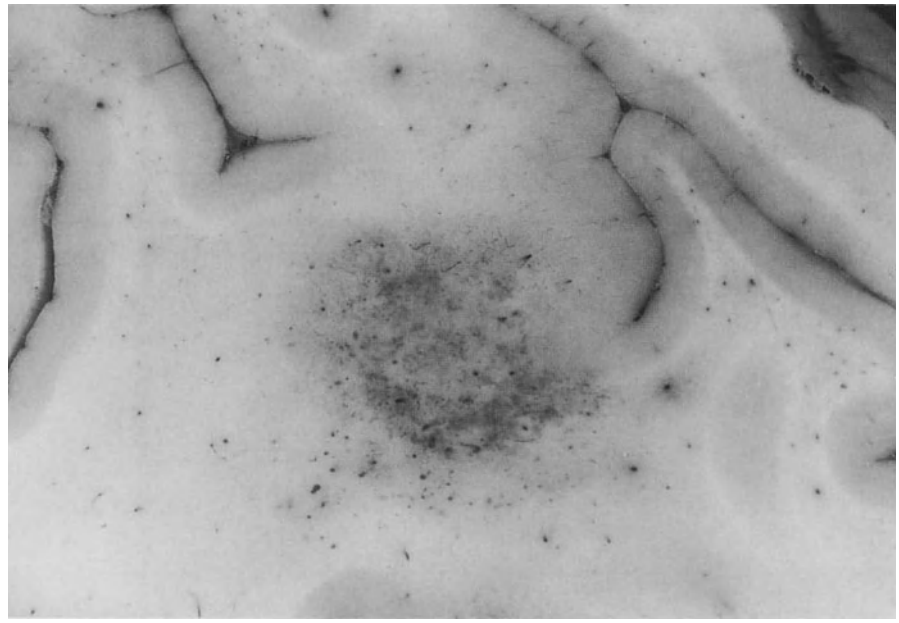
56 cases (31%) of CT (Table 3.12). CT has been characterized as a profoundly destructive but well-demarcated necrotizing encephalitis (Gerberding 1988). In the majority of the cases, the lesions are accompanied by a diffuse glial nodular encephalitis. In addition, a diffuse encephalitic form (Gray et al. 1989), a severe ventriculoencephalitis, and an acute disseminated anergic form (our series) has been observed among AIDS patients.

Macroscopic Findings

The gross appearance of the focal lesions in CT depends on the stage of evolution. Brains with acute *T. gondii* infection often show external features reflecting the presence of a mass effect, with uncal and cerebellar tonsillar herniation. Sectioning of the brain reveals several large, poorly delineated necrotic lesions which are usually soft and gray-white (Fig. 3.27), but sometimes hemorrhagic; very recent lesions may be macroscopically indistinguishable from an acute infarction. Minute hemorrhages are occasionally present within and around the lesions. The surrounding brain tissue is conspicuously edematous. Thus, the heaviest brains in our AIDS series, sometimes weighing over 1650 g, were invariably in cases of acute toxoplasmosis. The lesions are frequently multiple and have a predilection for the deep cerebral gray matter (Fig. 3.28), especially the putamen, the corticosubcortical junction, most commonly the frontal (Fig. 3.29), and occipital lobes, and the centrum semiovale. The cerebellum and brain stem are less often affected. The leptomeninges are almost always spared.

Older, better organized focal lesions are round or oval, measuring 1–2 cm in diameter, and have yellow-tan, cheesy centers due to coagulative necrosis of infected tissue. Areas of coagulative necroses are surrounded by an ill-defined rim of dusky red tissue which blends with the surrounding brain parenchyma. Chronic lesions are rarely found. They are represented by small tissue cysts or cavitary lesions with ragged margins up to 0.5 cm in diameter (Fig. 3.30).

Fig. 3.27. Cerebral toxoplasmosis in AIDS. Fresh focus with ill-defined rim in the subcortical white matter with pronounced perifocal edema (35-year-old man)



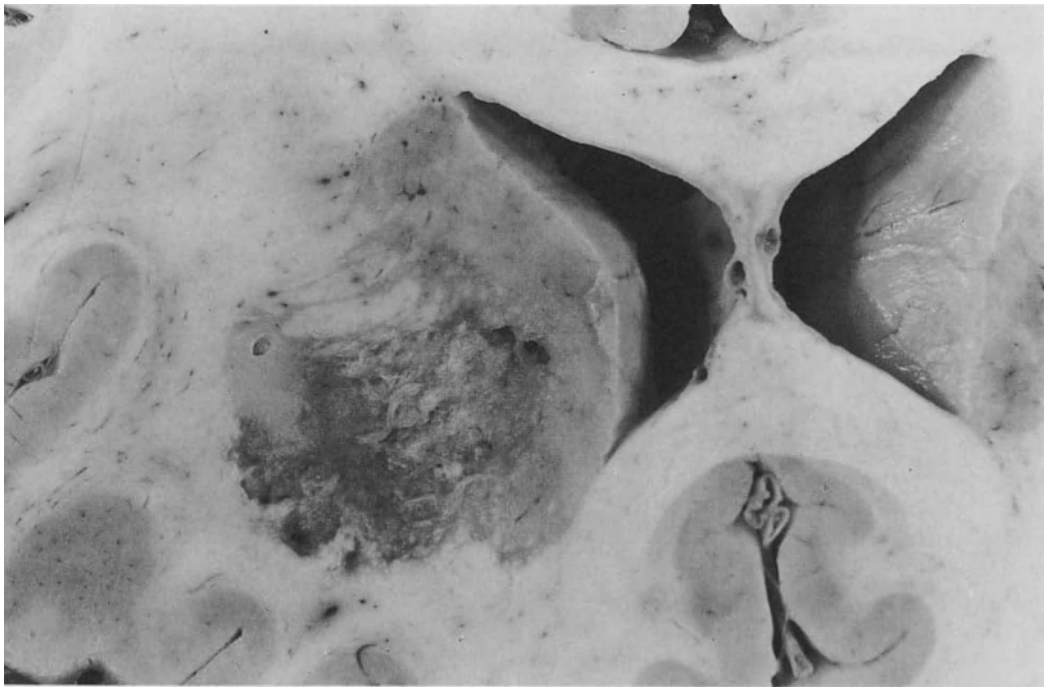


Fig. 3.28. Cerebral toxoplasmosis in AIDS. Large focus with ill-defined rim with varyingly old, partly already cystic lesions in putamen, internal capsule, and head of the caudate nucleus (43-year-old man)

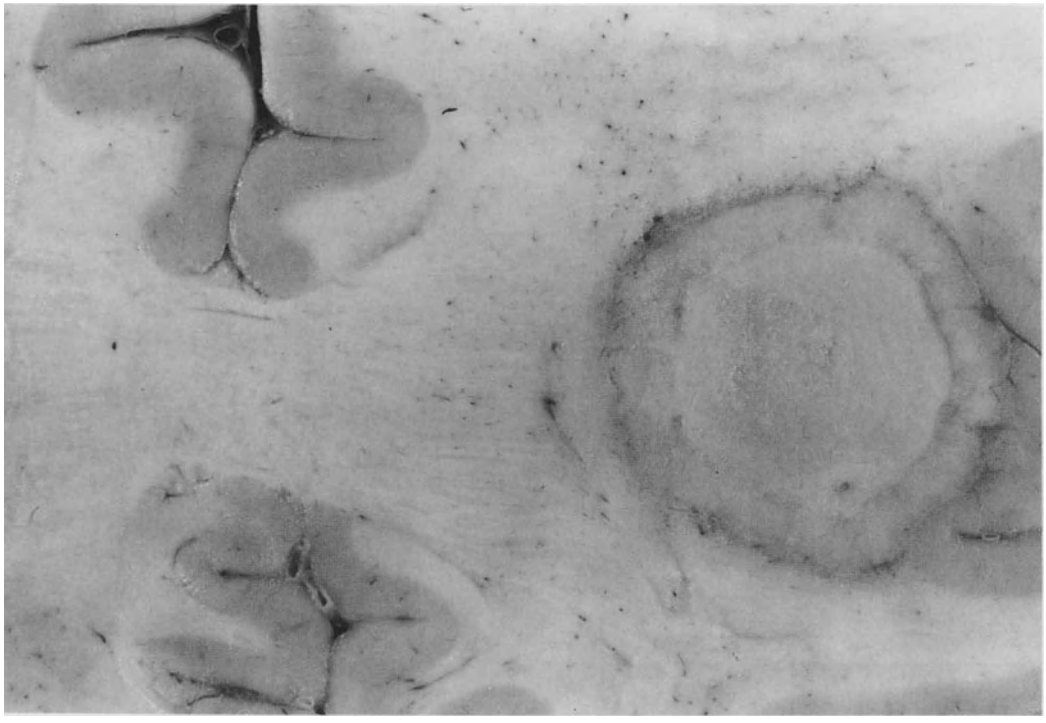
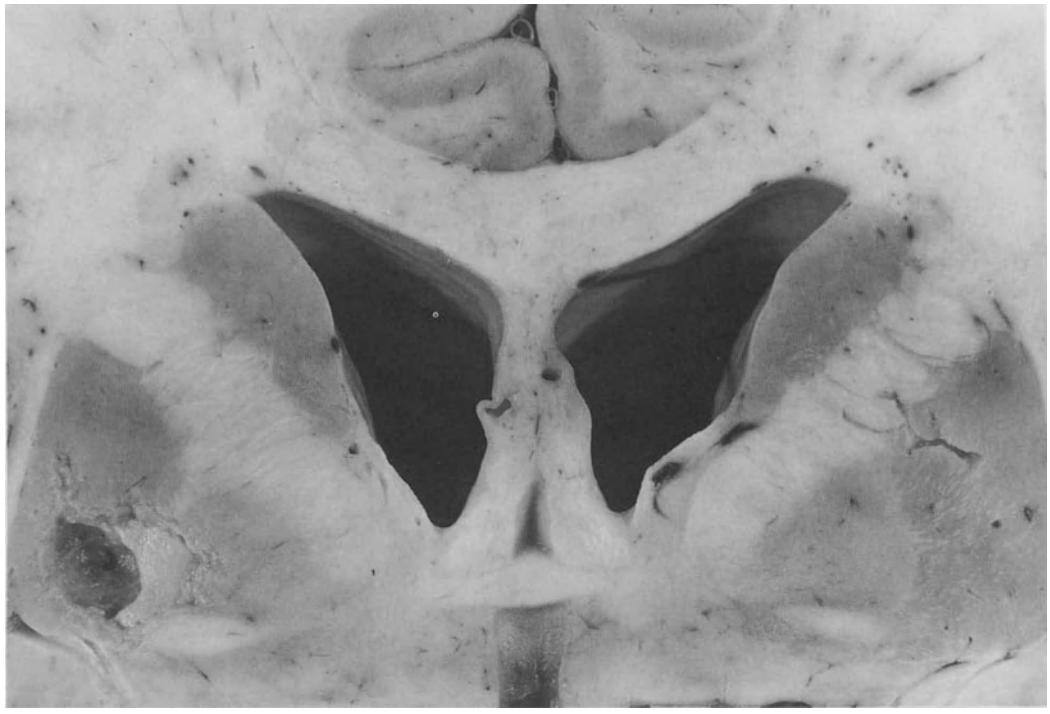


Fig. 3.29. Cerebral toxoplasmosis in AIDS. Large, rounded, relatively old focus with relatively well-defined rim and central coagulation necrosis (43-year-old man)

Fig. 3.30. Cerebral toxoplasmosis in AIDS. Relatively old, partly already cystic focus in putamen, relatively well defined rim (56-year-old man) ▶



Microscopic Findings

The essential histological features of CT are densely cellular microglial infiltrates, along with necrotizing thrombo-occlusive vasculitis (Huang and Chou 1988; Sotrel 1989). The microglial infiltrates appear in the form of microglial nodules, small clusters, or large irregular collections. Large lesions seem to be formed as a result of a centrifugal propagation of cellular destruction by the tachyzoites, eliciting more expansive microglial and other mononuclear infiltrates. Thus, neighboring lesions coalesce and form large, densely cellular foci of infection whose centers ultimately undergo coagulative necrosis, through the destructive action of the organism and ischemic changes caused by the vasculitic processes. Regardless of their age, toxoplasmic lesions are neither encased in a connective tissue capsule nor do they contain pus (Huang and Chou 1988); thus the term toxoplasma abscess is a misnomer (Sotrel 1989).

Focal Encephalitic Form

Petito and colleagues (Navia et al. 1986 c) grouped the lesions into three histological types based on the degree of tissue reaction: necrotizing, organizing, and chronic. All of these types may coexist in the same patient. The earliest stage of CNS infection includes necrotizing lesions containing a variable amount of inflammation and vascular reaction (Ghatak et al. 1970; Ghatak and Sawyer 1978; Navia et al. 1986 c). This necrotizing phase is said to be characteristic of acute infections of less than a few weeks duration. It is distinguished by three zones. The central zone contains abundant necrotic and cellular debris, where the free tachyzoites are difficult to visualize with conventional staining methods. The necrotic area is heavily infiltrated with neutrophils and histiocystes. An intermediate zone of vascular proliferation and congestion shows endothelial hyperplasia, vasculitis, and fibrin thrombi. Myofibroblastic hyperplasia of small or medium-sized blood vessels is a useful clue, suggesting the presence of nearby tachyzoites and scattered cysts, which are most easily found in this region (Moskowitz et al. 1984 a). The outer zone is characterized by relatively little inflammation and vascular changes, fewer tachyzoites, and more common bradycysts. Scattered microglial nodules may also be present (Luft et al. 1984).

Following acute necrotizing inflammation the lesions enter a phase of resolution that may persist for

many months (Navia et al. 1986c; Gonzales and Davis 1988). Organizing lesions consist of large, well-demarcated areas of central coagulation necrosis; they are usually basophilic and contain ghosts of former cellular infiltrates and diseased vessels but no viable organisms. These areas of coagulative necrosis are better delineated than in the acute lesion by densely aggregated lipid- and hemosiderin-filled macrophages. They are surrounded by a thick irregular ring of actively expanding inflammatory and microglial infiltrates intermixed with numerous organisms and blood vessels, many of which show inflammatory features corresponding to those of vasculitis or necrotizing vasculitis. Organisms are best seen adjacent to the lesion. The organizing phase occurs in several weeks to months.

The chronic phase occurs after many months and is characterized by small cystic brain lesions usually less than 0.5 cm in diameter. These contain small numbers of lipid-laden and occasionally hemosiderin-laden macrophages with surrounding astrogliosis but no fibrosis. Only very few bradycysts are seen in the surrounding brain at this stage, and free tachyzoites are not identified. These nonspecific features are usually seen at postmortem examination in patients who have responded to chemotherapy for toxoplasmosis but have succumbed to other complications of AIDS (Gonzales and Davis 1988).

Prolonged treatment with antitoxoplasma drugs usually eliminates the tachyzoites and makes the encysted forms very rare, although in some cases both forms may be found in the viable edge of the lesions (Navia et al. 1986e; Sotrel 1989). Subsequent organization noted in patients treated for at least 2–4 weeks involved the formation of cystic cavities without the development of a fibrous capsule, as occurs with bacterial abscesses (Hakes and Armstrong 1983; Navia et al. 1986c). At times, both necrotic debris and viable brain parenchyma and blood vessels may contain finely granular, diffuse, basophilic, calcified deposits (Sotrel 1989).

It has been reported that the most striking histological difference between patients with and without AIDS is that neutrophils represent a substantial component of the inflammatory cell infiltrate in patients with AIDS, while the infiltrate in patients without AIDS consists primarily of mononuclear cells (Luft et al. 1984; Townsend et al. 1975). In our experience, however, mononuclear cells and microglial cells constitute the inflammatory cell elements in all cases of CT in AIDS patients.

Glial Nodule Encephalitis

In most cases of CT in AIDS patients, in addition to the focal necrotizing lesions, there is a more widespread, subtle pathology in the form of small scattered collections of microglial cells intermingling with various forms of *T. gondii*. Although microglial nodules are one of the hallmarks of virus diseases of the CNS, including CMV infection, they are frequently seen in CT (Townsend et al. 1975; Sharer and Kapila 1985; Matthiessen et al. 1988; Sotrel 1989). Glial nodules can be seen at any stage of toxoplasmosis (Figs. 3.31, 3.32).

Diffuse Encephalitic Form

A massive form of microglial nodular encephalitis in the absence of large necrotic lesions has been described as a new form of CT. This diffuse "encephalitic" form of cerebral toxoplasmosis has been reported in four cases of AIDS (Gray et al. 1989). We also found this form in five cases in our series. The microscopic examination shows widespread microglial nodules, mostly containing toxoplasmic cysts or free tachyzoites, in the cerebral hemispheres, brain stem, and cerebellum. They are more numerous in the gray matter, but the white matter is also involved. A few nodules show central necrosis, and a few others are devoid of parasites. Toxoplasmic cysts are also present in the leptomeninges, accompanied by a fibrous reaction, and in or under the ependymal lining, where some are associated with granular ependymitis. Multiple disseminated parasitic cysts without inflammatory reaction or neighboring gliosis are also observed in the cerebral parenchyma. These changes may represent a prenecrotic acute form of CT and may be related to the short survival of the patients (Gray et al. 1989).

Plexitis

Little attention has been paid to the examination of the plexus choroideus in CT. We observed in five cases focal to extensive necrosis of the plexus choroideus epithelium. The process was accompanied by inflammatory changes in the vascular stroma. We found tachyzoites and cysts in the plexus choroideus, in ependymal cells, and in the subependymal tissue. The morphological changes ranged from the presence of a few organisms without inflammation or tissular damage to a severe ventriculitis (Fig. 3.33).

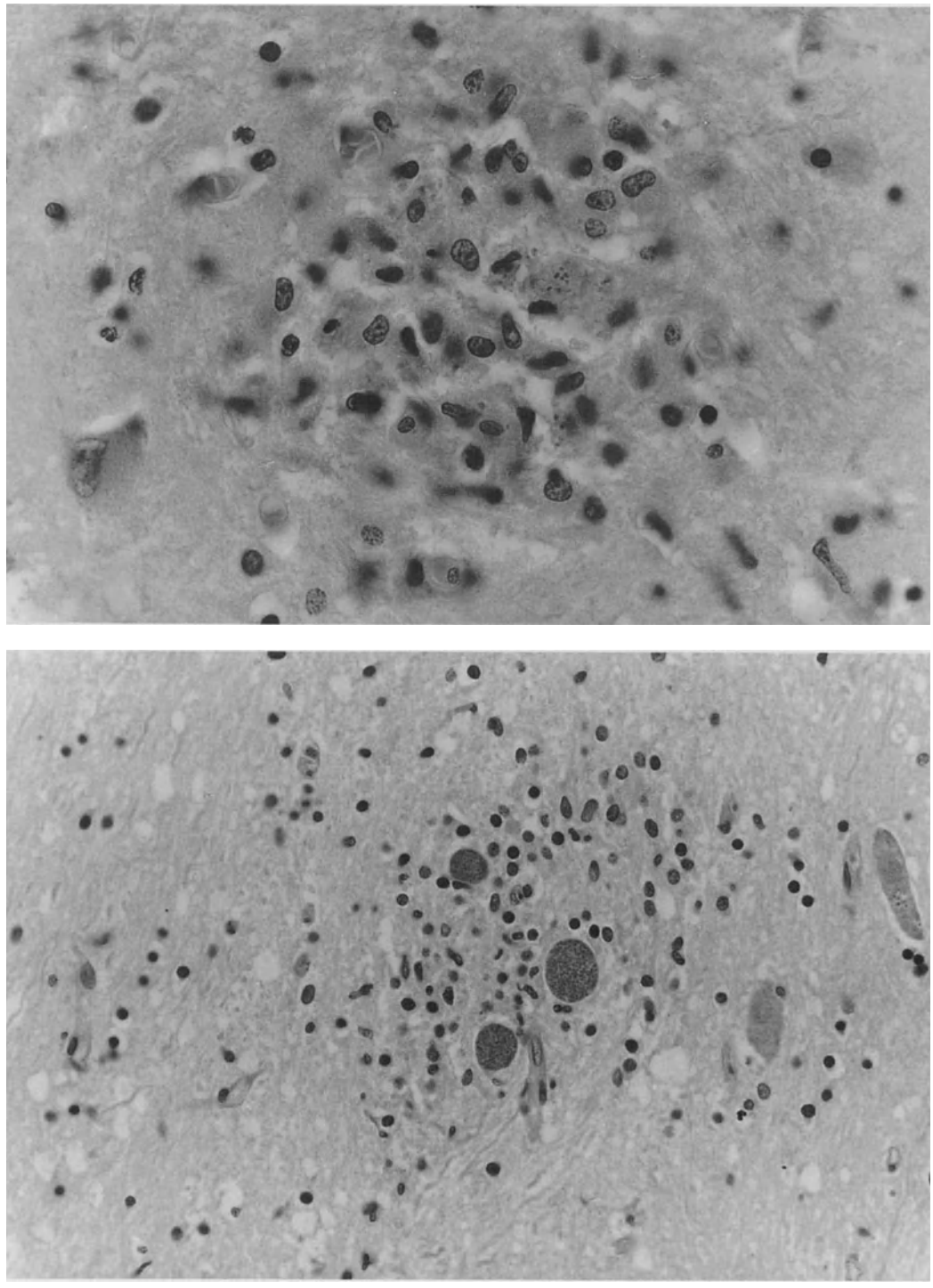
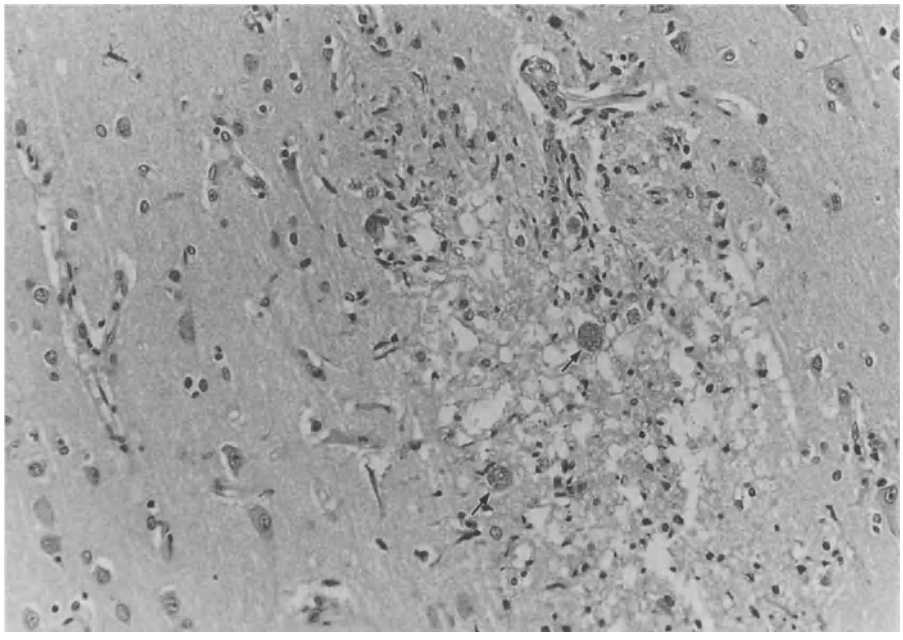


Fig. 3.31 a, b. Cerebral toxoplasmosis in AIDS. **a** Mixed-cellular glia nodule with numerous free tachyzoites. H&E, ×60. **b** Loosely structured mixed-cellular glia nodules with three bradycysts. PAS, ×40



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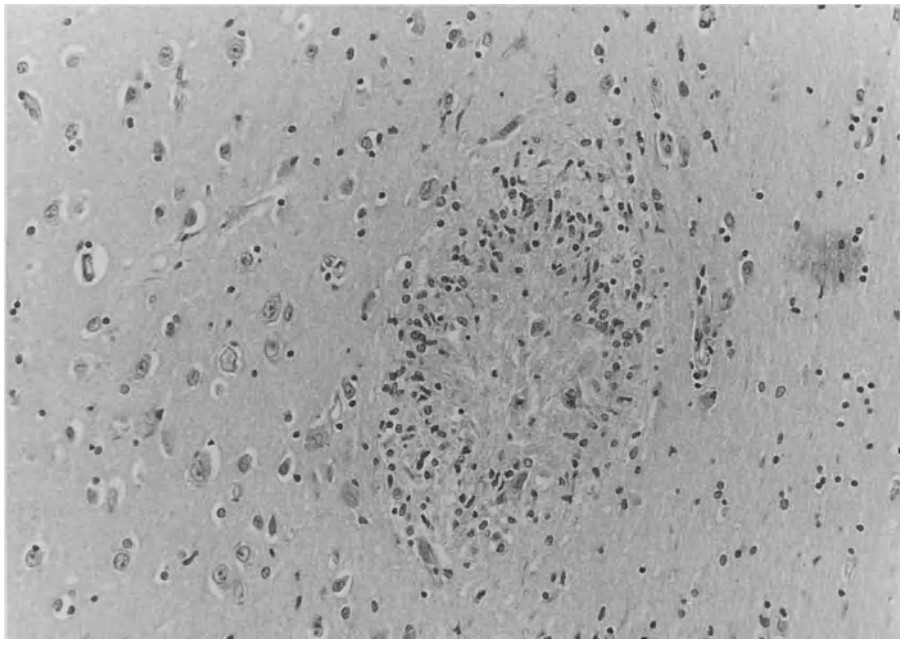


b

Fig. 3.32 a, b. Cerebral toxoplasmosis in AIDS. **a** Fresh toxoplasmosis focus in the cortex with edema, sponginess of the neurophil and the beginning of glia reaction. Two bradycysts in the focal area (tachyzoites not visible in this picture). **b** Small circumscribed cerebral-tissue necrosis with coronalike margin of microglia cells and monocytes on the white matter cortex border. H&E, ×20

Fig. 3.34. Cerebral toxoplasmosis in AIDS. Severe ventriculoencephalitis with fine fibrinous membranes in the ventricular lumen; uneven ventricular wall with extensive erosion of the ependyma and the neighboring layer of brain tissue. Multiple petechial bleeding in the corpus callosum and in the cerebral white matter ▶

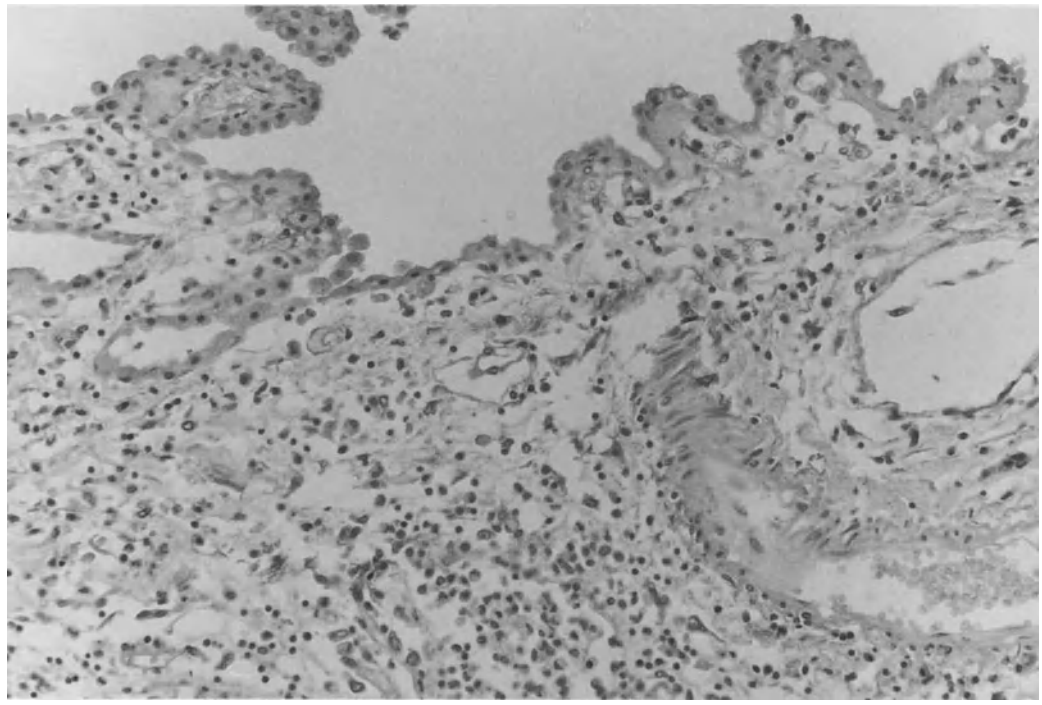
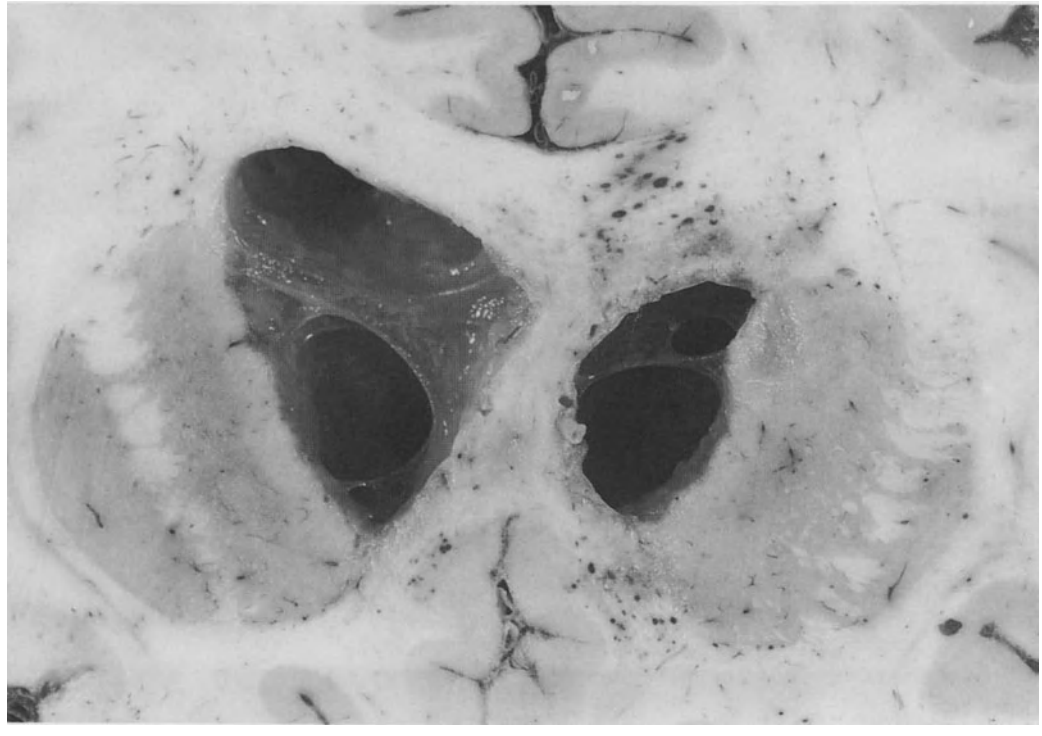
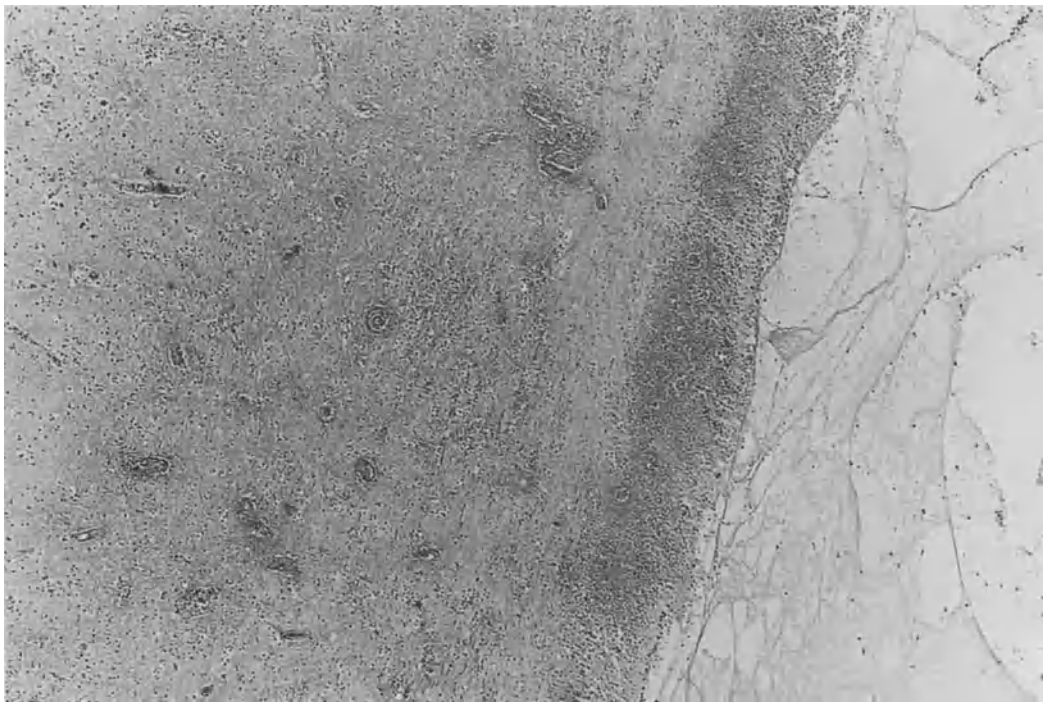


Fig. 3.33. Cerebral toxoplasmosis in AIDS. Choroid plexus in lateral ventricle with edema and loose inflammatory cell infiltration. H&E, ×20





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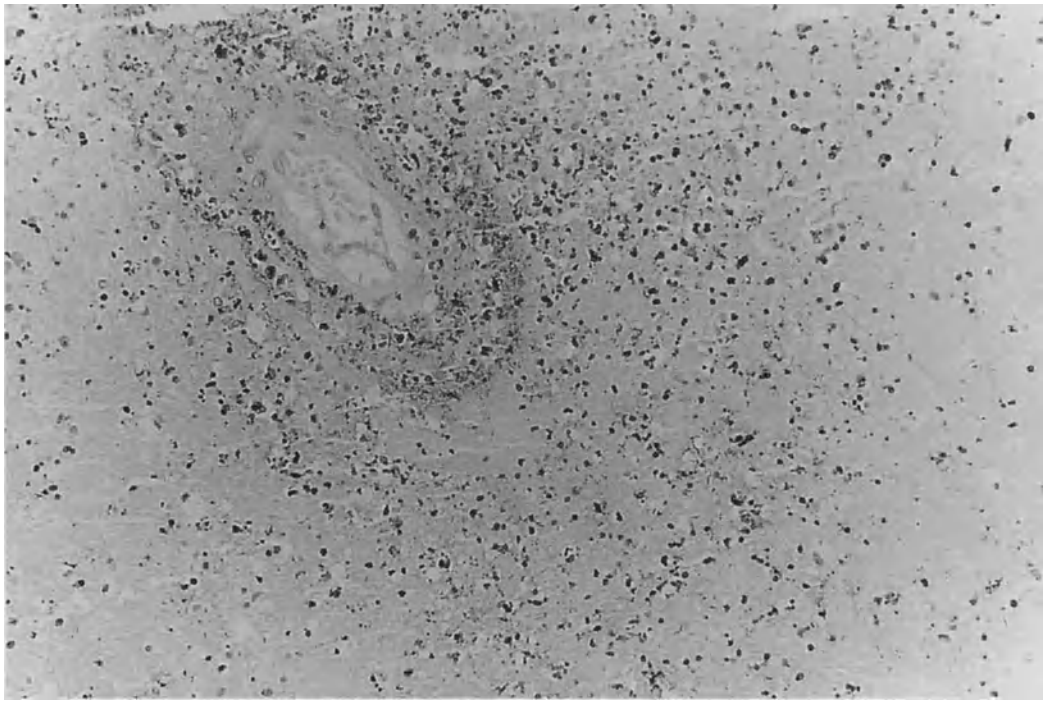


b

Fig. 3.35 a, b. Cerebral toxoplasmosis in AIDS. **a** Severe ventriculoencephalitis. Streaky necrosis of ependyma and subependymal brain tissue. Dilated blood vessels and loose inflammatory cell infiltration. Loose fibrinous membranes in the ventricular lumen. H&E, ×10. **b** Same subependymal region. Numerous tachyzoites in the ventricular wall and in the vicinity. Toxoplasma antibody, biogenesis; ABC method, ×20

Ventriculoencephalitis

In two cases we observed a severe ventriculoencephalitis with a large, variegated, gelatinous mass containing remnants of plexus tissue occupying the occipital horns of the lateral ventricles, and with the formation of pseudomembranes along the lateral ventricles (Fig. 3.34) and the third ventricle (Artigas et al. in press). Only Sharer and Kapila (1985) have described a similar gelatinous mass occupying the right lateral ventricle in a case of cerebral toxoplasmosis. Microscopically, there was, in our cases, destruction of the ependymal layer and deep necrosis of the subventricular tissue accompanied by necrotizing vasculitis along the lateral, third, and fourth ventricles. Immunohistochemical staining demonstrated the presence of numerous tachyzoites, whereas bradycysts were very rare (Figs. 3.35).

Acute Disseminated Anergic Form

We have had the opportunity to examine a unique case of a lethal acute form of disseminated toxoplasmosis. Almost all organs, including the brain and the hypophysis, were affected after massive hematogenous dissemination of the organisms. Microscopically, there were multiple foci of cysts and tachyzoite infiltration in all organs, sometimes with minute areas of necrosis, but no cellular reaction (Fig. 3.36; Artigas et al. 1993).

Case Report. This 24-year-old woman had been HIV positive for years. She had been hospitalized twice because of pneumocystis carinii pneumonia. In April 1991 she presented with diarrhea and fever. Despite antibiotic treatment her condition progressively worsened. She developed septic shock and died 3 weeks after the beginning of the symptoms. Macroscopic postmortem examination revealed onyl the typical signs of "shock lungs". Histological and immunohistochemical examinations showed a peracute anergic septic toxoplasmosis with dissemination in the bone marrow, lungs, heart, liver, kidneys, spleen, lymph nodes, hypophysis, and brain. In all examined organs, there were multiple foci of toxoplasmic cysts and free tachyzoites, sometimes with minute areas of necrosis, but no inflammatory reaction.

Resting Bradycystic Form

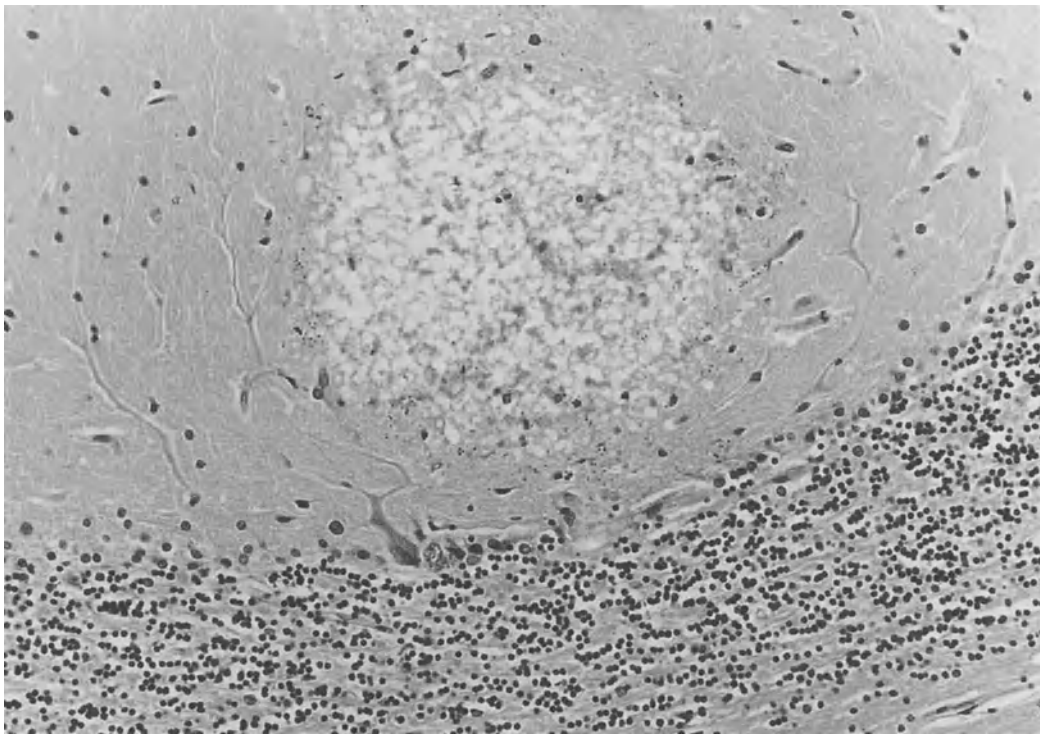
Widely disseminated bradycysts without a parenchymal reaction are frequently observed (Anders et al. 1986a, b; Navia et al. 1986c; Hénin et al. 1987) and may be the only manifestation of CT (Gray et al. 1988). This form was found in four cases in our series (Fig. 3.37).

Necrotizing Myelitis

Rarely, the spinal cord is involved, showing necrotizing myelitis with bradycysts and tachyzoites. We found necrotizing myelitis with multiple small foci of necrosis under the pia mater along the spinal cord in the two cases with severe ventriculitis (Fig. 3.38). In all reported cases with necrotizing myelitis there have been concomitant toxoplasmosis lesions in the brain (Navia et al. 1986c; Mehren et al. 1988; Herskovitz et al. 1989; Emskötter 1991a).

Pathological Findings of the Pituitary

We found in eight cases of CT one or more small necroses in the adenohypophysis. Around the necroses there was minimal inflammation. Immunohistochemical staining revealed the presence of numerous tachyzoites in the periphery of the necroses. Similar changes have been described in a few cases of cerebral toxoplasmosis in patients with and without AIDS (Yermakov et al. 1982; Milligan et al. 1984; Sano et al. 1989)



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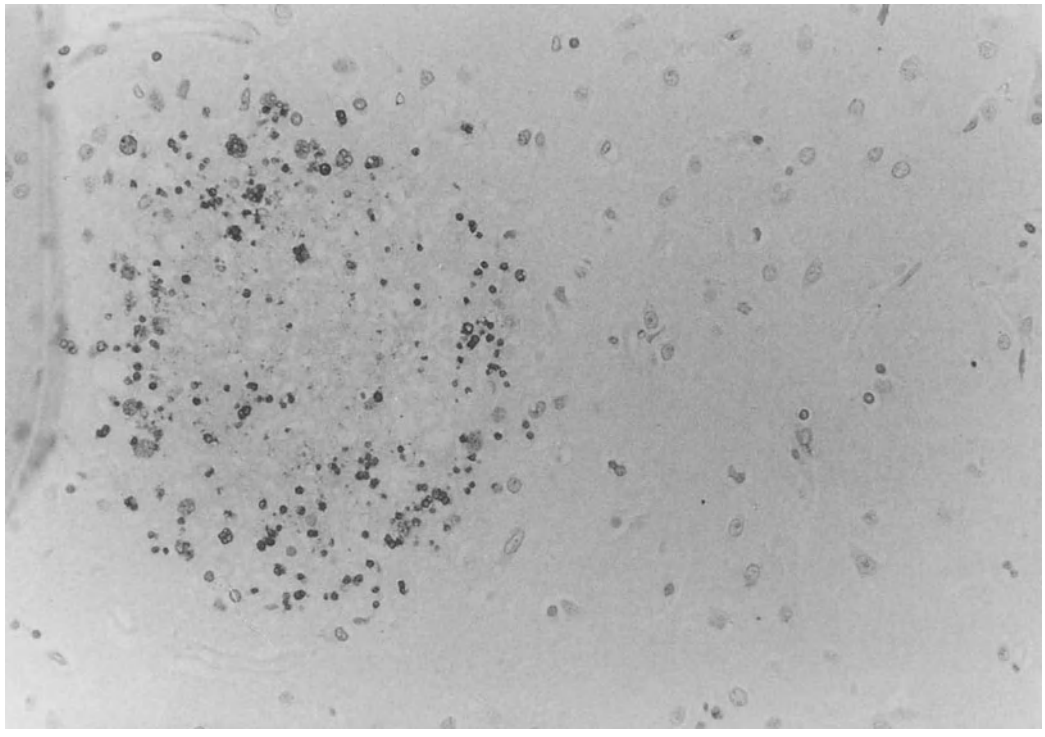


b

Fig. 3.36 a, b. Cerebral toxoplasmosis in AIDS. **a** Small fresh toxoplasmosis focus in the cerebellar cortex with edema and numerous tachyzoites in the periphery (visible as extremely fine points). No cellular reaction. H&E, × 20. **b** Small fresh toxoplasmosis focus in the cerebral cortex. Numerous tachyzoites. Toxoplasma antibody, biogenesis; ABC method, × 20

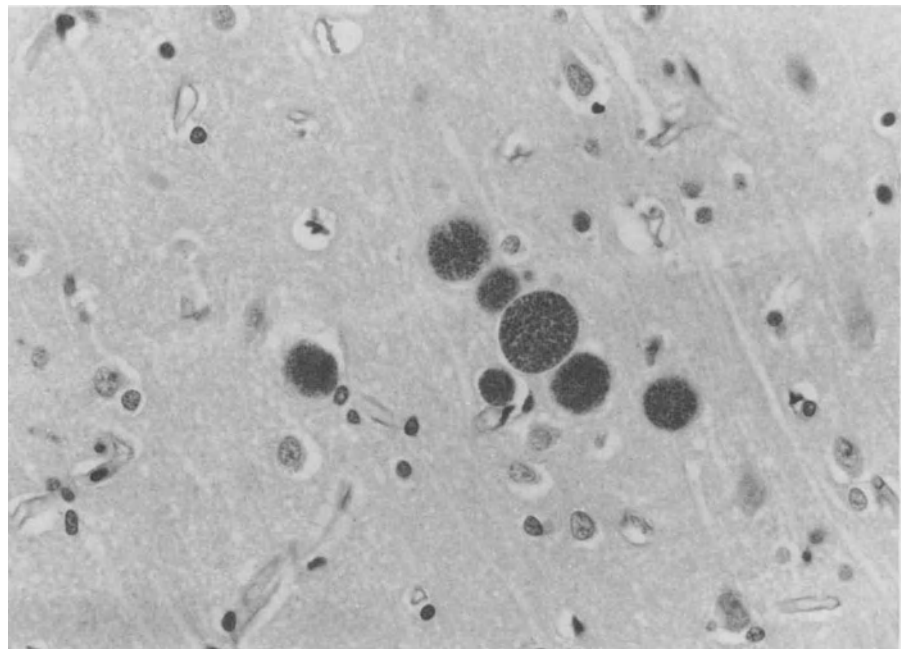


Fig. 3.37. Cerebral toxoplasmosis in AIDS. Seven bradycysts of various sizes in the brain cortex with no identifiable tissue damage and with no cellular reaction. H&E, × 40

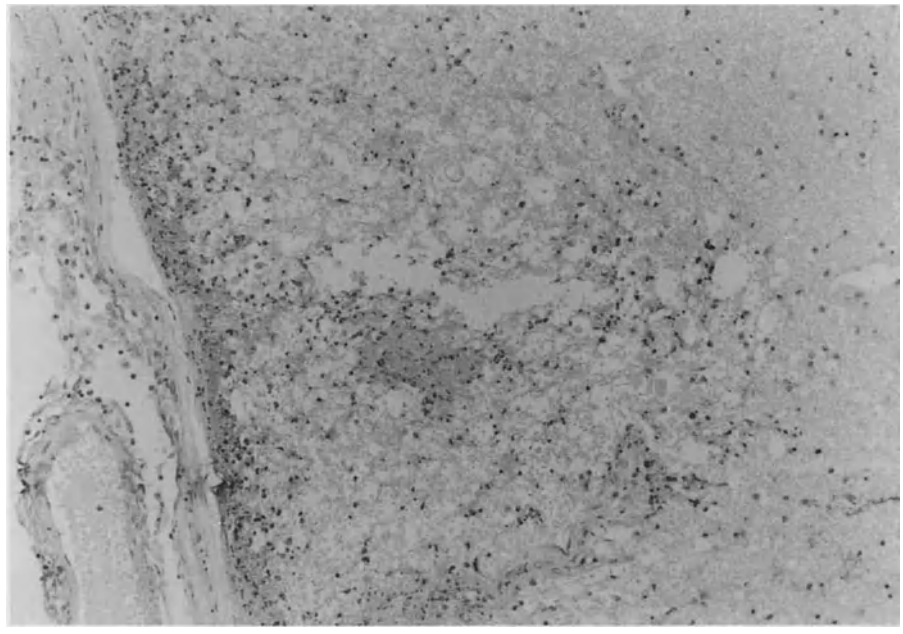
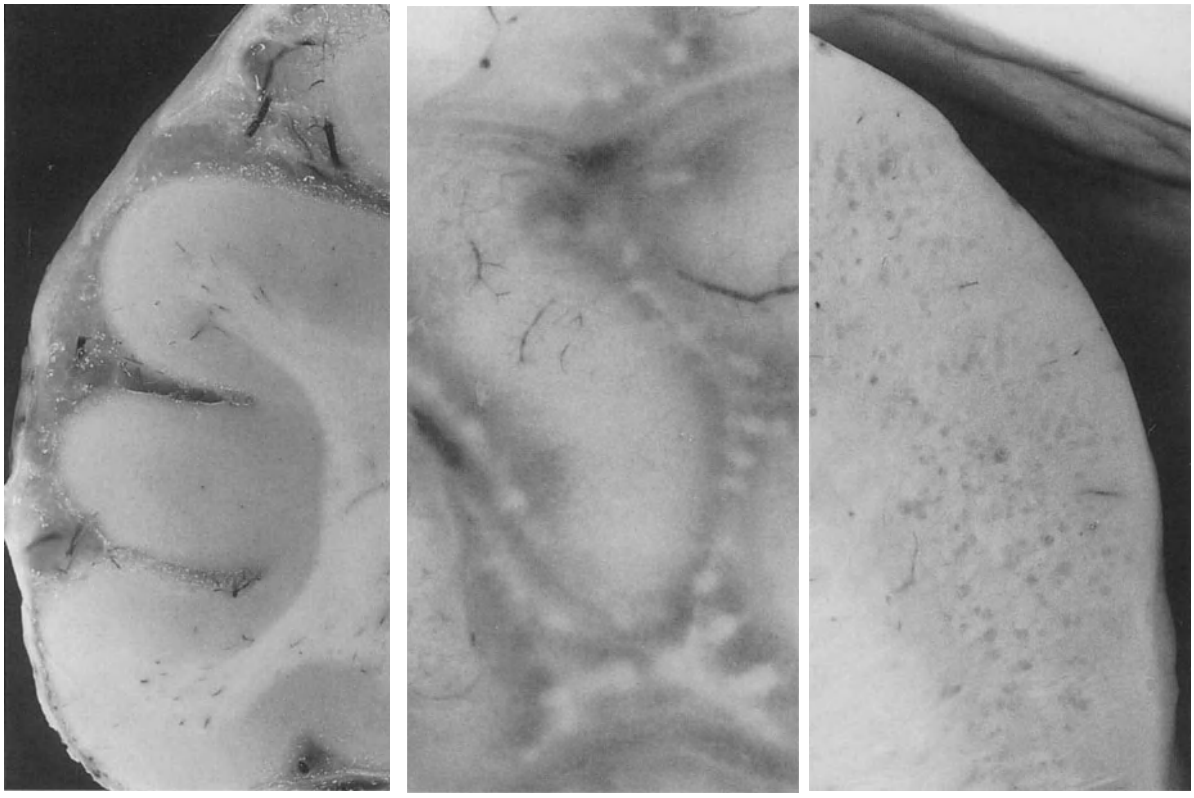


Fig. 3.38. Necrotizing Myelitis in toxoplasmosis. Small cuneate necrosis with edematous loosening of this tissue in the area of the anterior pyramidal tracts. Numerous tachyzoites visible as extremely fine points. Toxoplasma antibody; ABC method, × 10



a–c

Fig. 3.39 a–c. Cerebral toxoplasmosis in AIDS. **a** Immunohistochemical representation of pathogens and pathogen fragments in a necrosis in the vicinity of an arteriole. Toxoplasma antibody, biogenesis; ABC method, × 40. **b** Immunohistochemical representation of a few tachyzoites in a glia nodule. Toxoplasma antibody, biogenesis; ABC method, × 40. **c** Branched activated microglia cells with granular positivity for toxoplasmosis in cytoplasm (phagocytosed pathogen fragments). Brain cortex near a necrosis focus. Toxoplasma antibody (courtesy of Dr. Deschlein, Berlin); ABC method, × 40

Immunohistochemistry

Free tachyzoites and encysted bradyzoites may be demonstrated by immunocytochemical staining using *Toxoplasma*-specific antisera (Conley et al. 1981). Immunohistochemistry greatly facilitates the detection of tachyzoites, which are difficult to see when present in small numbers, and when not associated with the encysted forms of the organisms (Petito et al. 1986; Fig. 3.39). Tachyzoites have small nuclei with nucleoli, and morphologically they are variously described as being round, elongated, comma-shaped, crescent-shaped, or droplike (the name *Toxoplasma gondii* derives from *toxon* = bow shape, *plasma* = body, and *gondi* from the northern African rodent in which it was first discovered). In our series we used three anti *Toxoplasma* antibodies (Dr. Deschlein, Berlin; Biogenesis). The first antibody (Dr. Deschlein) stained cysts, rupturated cysts, and free tachyzoites. It also demonstrated a conspicuous granular positivity of numerous microglia cells in the periphery of necrotizing and, sometimes, organizing lesions. We believe that this reaction shows phagocytosed fragments of tachyzoites. The two other antibodies (Biogenesis) are monoclonal antibodies any yielded cysts and tachyzoites, both extracellularly and intracellularly within the cytoplasm of macrophages.

Electron Microscopy

The ultrastructure of the individual organisms is highly characteristic and quite uniform (Ghatak and Sawyer 1978; Powell et al. 1978; Yermakov et al. 1982; Cerezo et al. 1985). The tachyzoite is a crescent-shaped, elongated structure, 4–7 µm long and 2–4 µm wide, bounded by a double-layered 40-nm-thick pelli-

cle, with a narrowed anterior end containing a hollow, conelike structure, the conoid, and a wider, more rounded posterior end (Ghatak et al. 1970; Tang et al. 1986; Sidhu 1990). The apparatus for entering the host cell is located in the anterior end. Each organism is surrounded by a continuous outer membrane, while the inner membrane is interrupted, having a wide gap at the slightly pointed anterior pole (conoid end). The most prominent organelles, the rhoptries, are longitudinally arranged saccular profiles of unknown function located near the apical end of the parasite. The nucleus, with quite prominent nucleolus, is located near the posterior end of the parasite whereas mitochondria, glycogen granules, endoplasmic reticulum, and Golgi apparatus are scattered throughout the cytoplasm.

■ Opportunistic Fungal Infections

Cryptococcosis

Introduction

Cryptococcosis is a typical infectious complication of the AIDS patient, the second most common mycosis, the most important generalized mycotic complication, and the most common mycosis of the CNS in AIDS (Anders et al. 1986a; Budka et al. 1987; Burns et al. 1991; Chandler 1985; De La Monte et al. 1987; Grosse et al. 1987, Kato et al. 1987b; Lang et al. 1989; Levy et al. 1986, 1988; Morace et al. 1990; Patterson and Andriole 1989; Petito et al. 1986; Sharer and Kapila 1985; Staib 1987, 1991, 1992; Sugar 1991; Zuger et al. 1986). Before the AIDS era cryptococcosis was very rare, and the CNS was predominantly involved by the airborne fungal infection of chronic course (Chandler et al. 1980; Grosse 1991; Grosse et al. 1987; MacKenzie 1989; Salaki et al. 1984; Staib 1987, 1991, 1992). Under the irreversible and progressive immunodeficiency the course of infection of cryptococcosis is more rapid, and the CNS involvement is not predominant in all cases (Chuck and Sande 1989; Clark et al. 1990; Dismukes 1988; Grosse et al. 1987; Grosse 1990; Michelone et al. 1989; Quirino et al. 1990; Staib 1987, 1990; Zuger et al. 1986).

Cryptococcus neoformans var. neoformans is an obligatory pathogen for the AIDS patient because of the deficient cell-dependent immunity (Grosse et al. 1987; Grosse 1990, 1991; Staib 1987, 1991, 1992). Cryptococcosis can be found less frequently than other complications typical of AIDS (4%–9%) because of the relatively rare exposure (Anders et al. 1986a; Budka et al. 1987; Chandler 1980; Chandler et al. 1985; Chuck and Sande 1989; Cohen et al. 1992; Grosse et al. 1987; Kovacs et al. 1985; Lang et al. 1989; Levy et al. 1988; MacKenzie 1989; Petito et al. 1986; Staib and Heissenhuber 1989; Staib 1992; Zuger et al. 1986). Cryptococcosis may be the first or an early infection in the course of AIDS or may arise in the advanced stage of AIDS in combination with other infective or neoplastic complications. In individual cases a circumscribed lung focus can be found as an initial stage of cryptococcosis and an unimportant secondary finding among various other serious infections in the terminal stage of AIDS (Cameron et al. 1991; Chechani and Kamholz 1990; Chuck and Sande 1989; Clark et al. 1990; Gal et al. 1986; Grosse et al. 1987; Staib 1991, 1992).

The following stages are distinguished in the cryptococcosis of AIDS:

Stage I: local cryptococcosis of the lung (AG 0)
- Ia: focal lung involvement as associated finding among further, more severe AIDS complications
- Ib: lung involvement as first opportunistic AIDS complication

Stage I–II: initial generalization (AG +)
Cryptococcosis of the lung and pulmohilar lymphnodes

Stage II: generalized cryptococcosis (AG ++)
- IIa: focal lung involvement of little importance, predominant CNS involvement (no further recognizable extrapulmonary manifestation)
- IIb: lymphomalike infiltration of the lymphnodes, massive generalization, and massive CNS involvement
- IIc: lymphomalike infiltration of the lymphnodes, generalization, and relatively moderate CNS involvement

AG antigen in body fluids
- 0 no titre
- + low titre
- ++ high titre

Data on the seven cases of cryptococcosis in our series of 180 autopsy cases is presented in Table 3.13.

Table 3.13 Cryptococcosis in AIDS autopsy cases (n = 180)

No.	Patient	Age (years)	Sex	Cryptococcosis		Further AIDS complications
				Stage	CNS	
1	H.J.	43	M	IIc	+	0
2	M.J.	28	M	I–II*	0	Pcp, KS (disseminated)
3	S.B.	32	F	IIa	+++	0
4	S.W.	29	M	IIb	+++	0
5	L.M.	27	M	IIc	++	Pc (disseminated)
6	B.W.	40	M	I–II*	0	PcP(+++) CMV (lung +++)
7	S.K.	35	M	IIb	+++	MAI (lymph nodes, liver, spleen)

CNS, Central nervous system; CMV, cytomegalovirus infection; KS, Kaposi's sarcoma; MAI, atypical mycobacterial infection; Pc(p), *pneumocystis carinii* (pneumonia); + small, sporadical; ++ some infiltrates; +++ massive infiltration.
* Lung, lymph nodes (low antigen titre in body fluids)

Pathogenesis

Cryptococcosis is an airborne infection. Therefore the respiratory tract is the primary portal of entry for the respirable basidiospores of the perfect state of *C. neoformans, Filobasidiella neoformans* (Chandler et al. 1980; Know-Chung 1975; Staib 1989). The only known habitat of the basidiomycete in the environment of man is bird manure (Staib and Heissenhuber 1989). In the lung of the susceptible patient a circumscribed and symptomless colonization of *C. neoformans* cells develops. The round fungus cells are of varying size and surrounded by a polysaccharide capsule. There is only a minimal cell reaction of macrophages and perhaps some lymphocytes. The cells of *C. neoformans* are able to traverse the capillary wall without destruction and without thrombosis of the blood vessel (Schnoy 1991). The lung is therefore the source of the hematogenous dissemination of viable fungus cells into all organs, especially into the CNS. Within the foci of dissemination there also is a minimal cell reaction (Chandler et al. 1980; Chandler 1985; Grosse et al. 1987; Grosse 1990, 1991; Hawkins and Armstrong 1984; Salfelder 1971). In AIDS patients atrophic lymphnodes can be completely infiltrated by encapsulated fungus cells. Some reticulohistiocytic cells, or macrophages, show a weak reaction visible by an immunohistochemical macrophage marker. The lymphocytes can disappear extensively.

The macroscopic aspect of a generalized lymphoma corresponds to the histological picture of the so-called cryptococcoma. On the one hand, the weak cell reaction depends mainly on the immunodeficiency; on the other, the polysaccharide capsule of the fungus reduces the cell reaction (Grosse et al. 1987; Grosse 1990, 1991; Hawkins and Armstrong 1984). In the colonization of *C. neoformans* the capillary network remains mostly intact. In large tumorlike fungus colonizations there may be bland necroses (Chandler 1985; Grosse 1990). In connection with the intact blood vessels large masses of antigen enter the blood circulation as a sign of generalized cryptococcosis (Grosse 1990, 1991; Staib 1991). The circumscribed colonization of cryptococci only in the lung characterizes stage I of cryptococcosis and the generalization stage II (Grosse et al. 1987; Grosse 1990, 1991; Staib 1991, 1992). Involvement of the CNS belongs to stage II, the stage of generalization. Some cases show a massive involvement of the CNS without apparent manifestation of other extrapulmonary organs, and a relatively small, circumscribed infiltration of the lung can be overlooked. However, cerebral involvement does not predominante in all cases of cryptococcosis in AIDS. Meningeal cryptococcosis is the most frequent CNS manifestation. Furthermore, small cystlike intracerebral foci can be found (Chandler et al. 1980; Chandler 1985; Dismukes 1988; Grosse et al. 1987; Grosse 1990; Hawkins and Armstrong 1984; Quirino et al. 1990; Salfelder 1971; Staib 1991, 1992; Sugar 1991; Weinke et al. 1989; Zoller et al. 1989; Zuger et al. 1986).

Pathology

Macroscopic Findings

The meningeal affection of CNS cryptococcosis shows in some cases a thickening of the meninges by a grayish and glassy infiltration of the subarachnoid space of the brain. In some cases a weak meningeal involvement is invisible, or almost invisible, in the macroscopic examination. In other cases small nodules are evident within the thickened leptomeninx (Fig. 3.40 a,

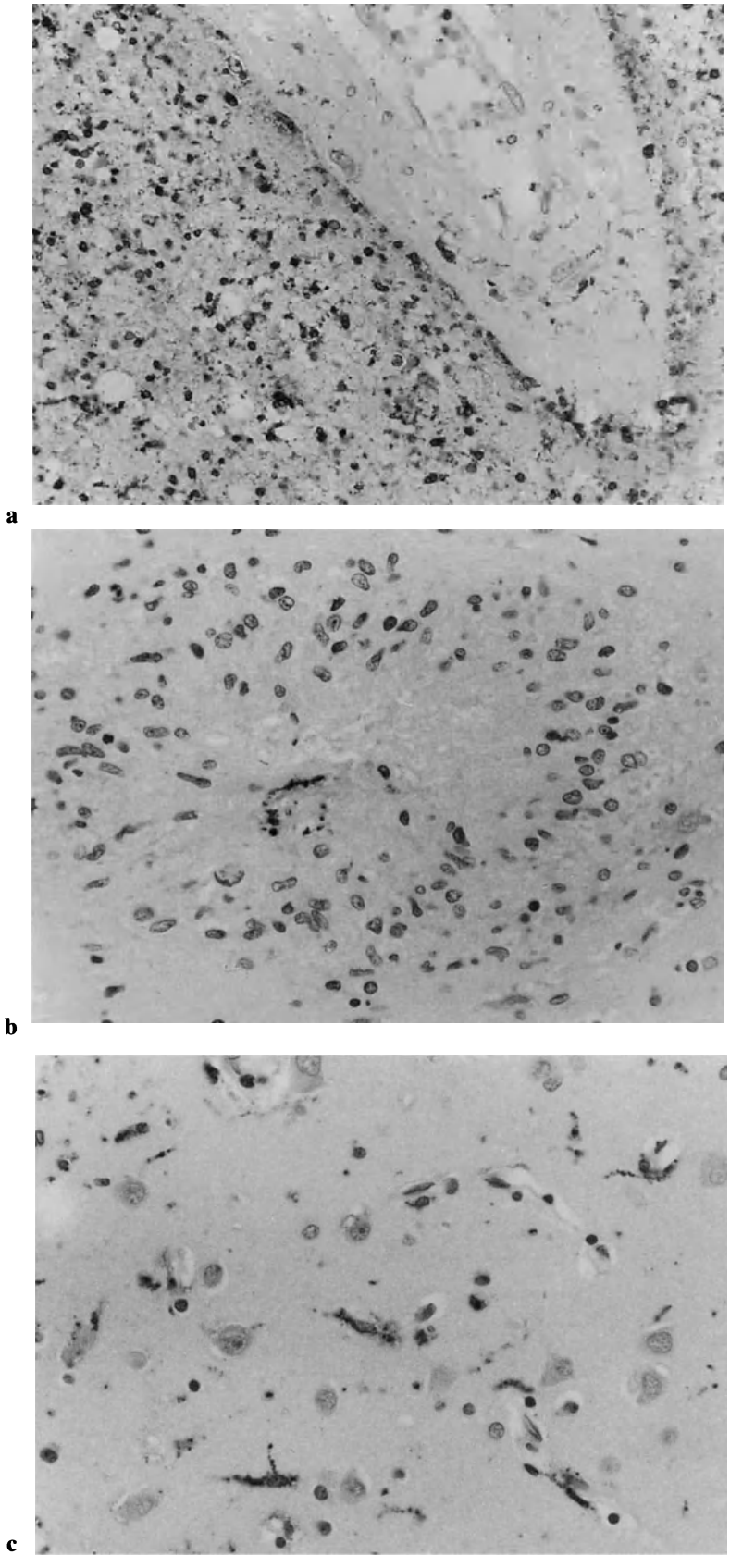
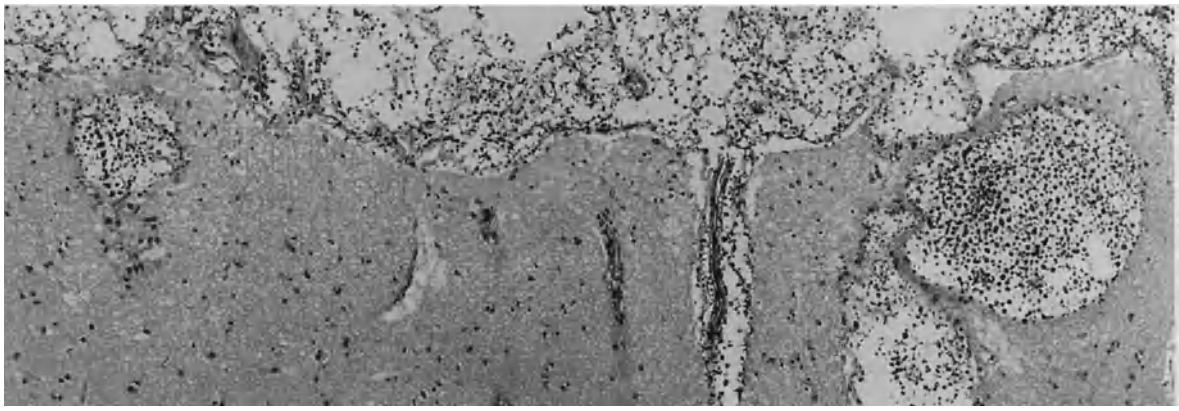


Fig. 3.40 a–c. Crytococcosis of the CNS in AIDS. Meningeal infiltration with thickening of the subarachnoid space by grayish and glassy masses. **b** Meningeal cryptococcosis with very small nodular foci *(white)* within the subarachnoid space. **c** Intracerebral cryptococcosis with multiple microcystic foci *(dark)* in the nucleus caudatus beside the capsula interna



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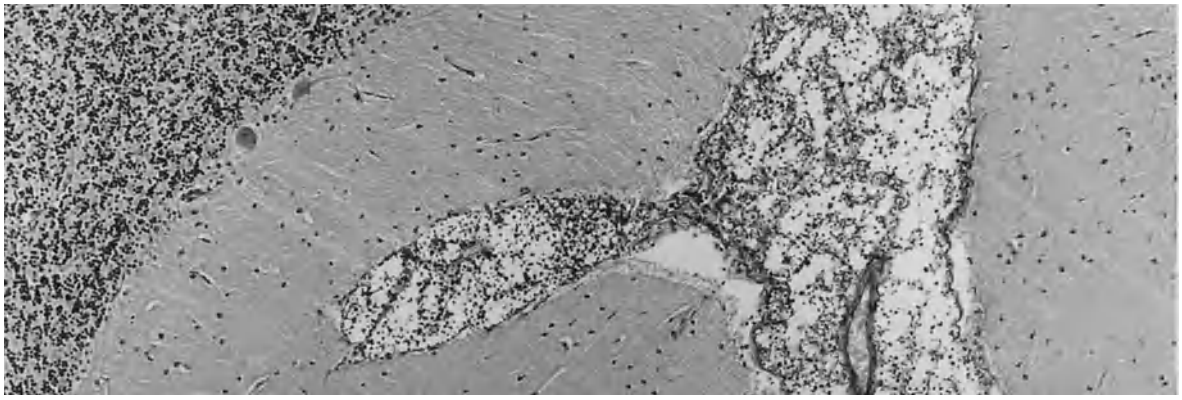

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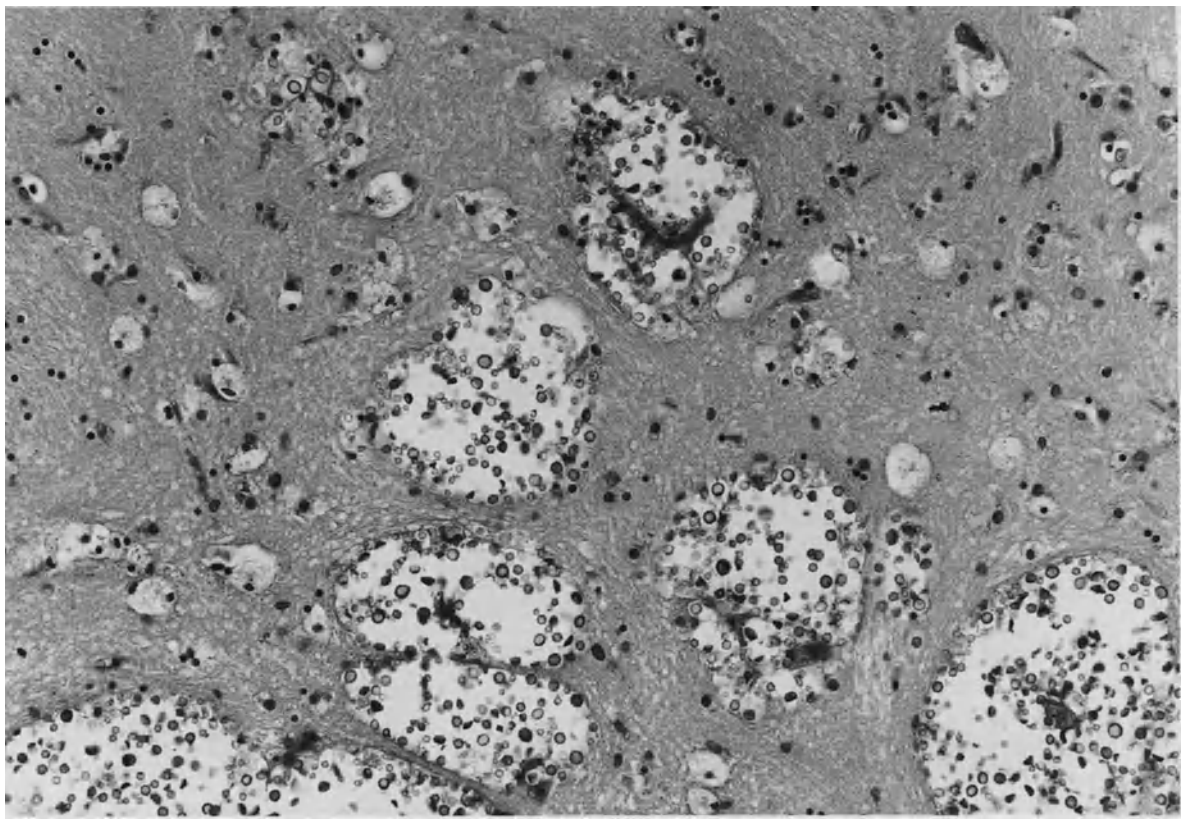
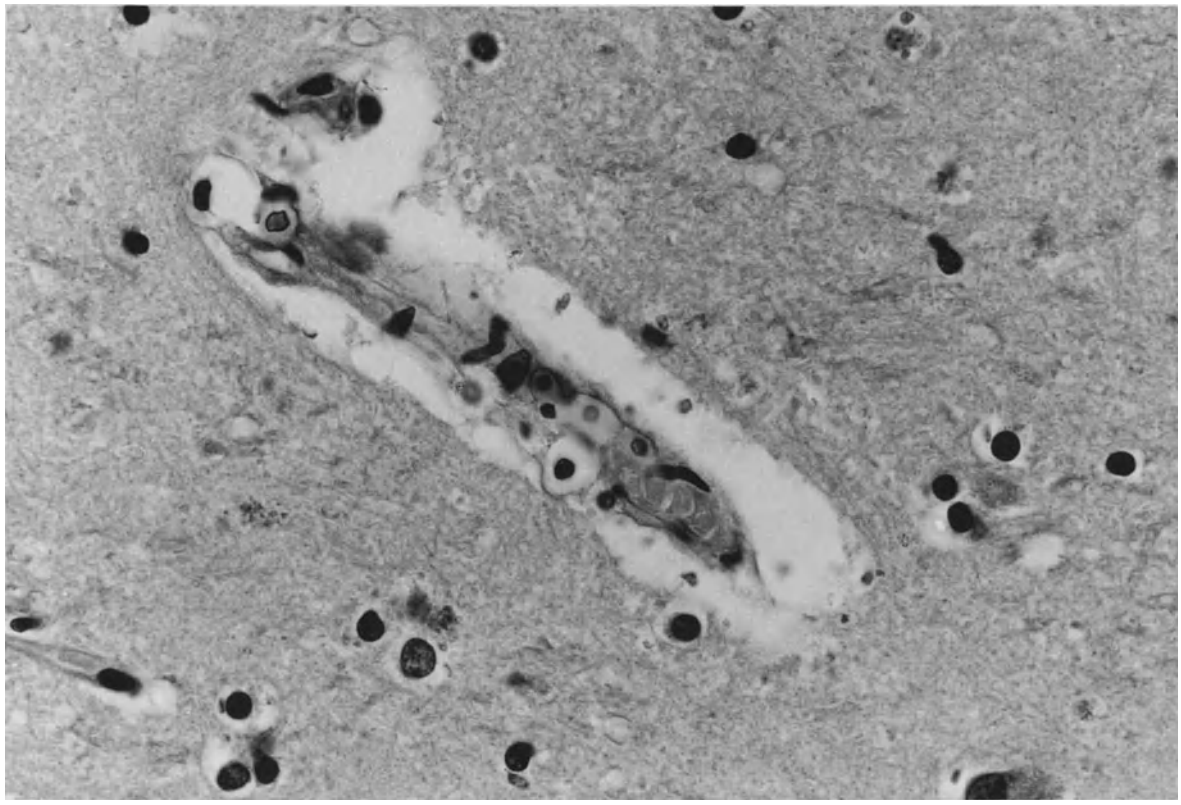




◀ **Fig. 3.41 a, b.** Meningeal cryptococcosis in AIDS. **a** Countless *C. neoformans* cells within the subarachnoid space and within the (blood vessel accompanying) Virchow-Robin space of the brain without recognizable cell reaction. PAS, ×10. **b** Masses of *C. neoformans* cells within the cerebellar subarachnoid space. PAS, ×10

◀ **Fig. 3.42.** Intracerebral cryptococcosis in AIDS. Multiple (pseudo-)cystic foci within the brain containing many encapsulated cells of *C. neoformans* with minmal cell reaction. In the centre of some cysts a capillary. PAS, ×20

Fig. 3.43. Intracerebral cryptococcosis in AIDS. Initial cystic focus within the brain with some encapsulated cryptococci directly pericapillar without recognizable cell reaction. PAS, ×63

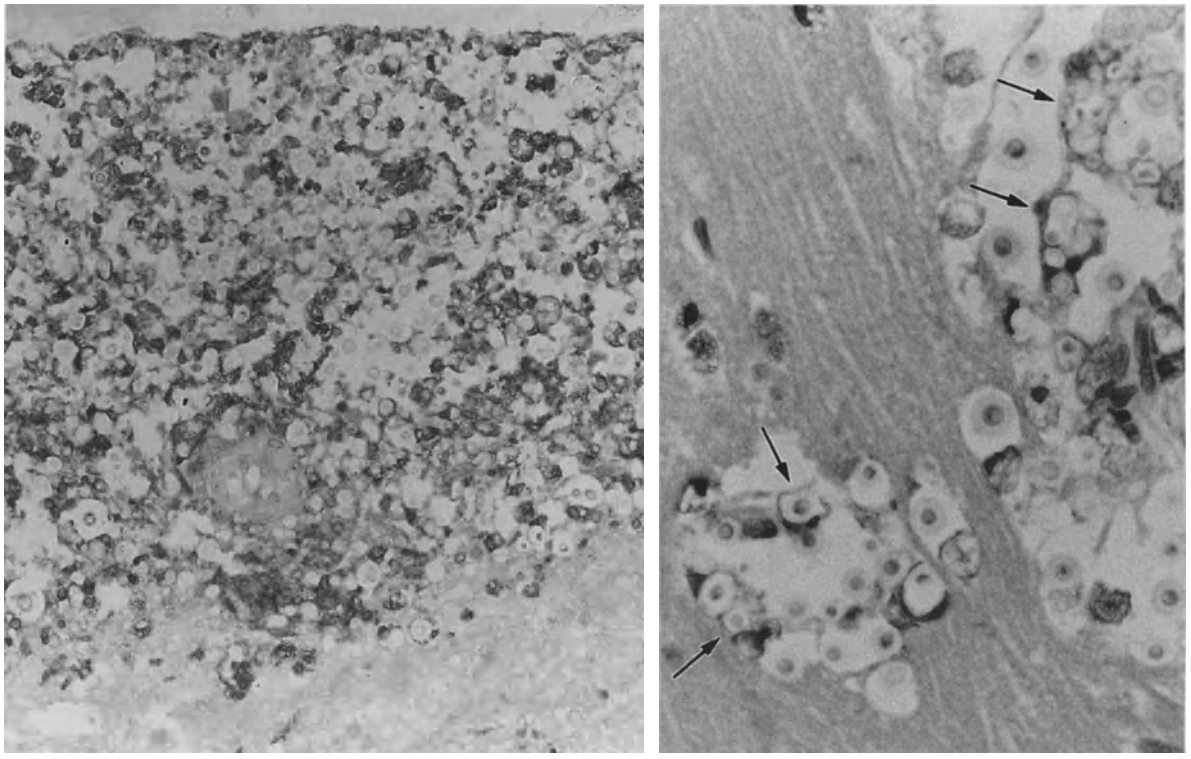
b). The intracerebral infiltrates generally cannot be seen macroscopically; only in individual cases it is possible to see relatively large cystic foci even with the naked eye (Fig. 3.40 c).

Microscopic Findings

The meningeal involvement of cryptococcosis generally shows a massive infiltration of countless round, encapsulated fungus cells within the thickened cerebral and cerebellar subarachnoid space and within the perivascular Virchow-Robin space (Fig. 3.41). A minimal cell reaction of macrophages can sometimes be seen, only with immunohistochemical markers. Some lymphocytes may be among the macrophages. The intracerebral involvement shows small cystlike foci as pericapillary colonization of fungus cells rich in capsule material with only minimal macrophage reaction, sometimes visible only when immunohistochemically marked (Fig. 3.42–3.44). The cells of *C. neoformans* are round, of variable size (mostly 2–20 µm) and surrounded by a polysaccharide capsule. Budding can sometimes be seen. Sickle or bell forms, bloated or bursted cells are degeneration forms.

Immunohistochemistry

The immunohistochemical characterization of *C. neoformans* is unnecessary in nearly all cases because of the diagnostic polysaccharide capsule, the only one among the pathogenic fungi of man, and this capsule can be shown by mucin stainings. In stage II the fungi of the numerous foci can be interpreted without difficulty. In stage I there is little chance to make the diag-



a b

nosis microscopically. In none of these cases do we need immunohistochemical examination. In cases with multiple infections, for example, in the combination of *Pneumocystis carinii* and infections with other yeastlike fungi, the immunohistochemical diagnosis may be desirable. The interesting question of the viability of the fungi under antimycotic therapy cannot be answered by immunohistochemistry. This is possible only with culture examination using Staib's agar (syn. bird seed agar; Staib 1987, 1991, 1992). Immunohistochemical macrophage markers demonstrate the mostly weak cell reaction within the meningeal and intracerebral infiltrations (Fig. 3.43).

Electron Microscopy

In the ultramicroscopic dimension one can see interesting structural variations of the polysaccharide capsule. The capsule material may be important for the passage of the capillary wall (Fig. 3.45 b; Schnoy 1991). One can find morphologically intact fungus cells with capsules (Fig. 3.45 a) and apparently destroyed fungus cells without capsules or shrunken cell fragments within the macrophages (Fig. 3.46).

▲ **Fig. 3.44 a, b.** Cryptococcosis of the CNS in AIDS. **a** Meningeal cryptococcosis of the brain with striking phagocytosis in an older process. KP-1, immunohistochemical, ×20. **b** Intracerebral cryptococcosis with weak phagocytosis of encapsulated cryptococci (→). KP-1, immunohistochemical, ×40

Fig. 3.45 a, b. Cryptococcosis of the CNS in AIDS. **a** The electron-microscopic picture shows a round cell of *C. neoformans* surrounded by the polysaccharide capsule containing very fine filaments in close connection with the cell wall. The fungus cell is lying near the capillary endothelium (→). ×7000. **b** *C. neoformans* cell with partly shrunken capsule and tubular junction between the capsule and an endothelial cell with microcystic cytoplasm (the fungus cell, for example) before the passage through the capillary wall (→). ×12000 ▶

Fig. 3.46 a, b. Cryptococcosis of the brain in AIDS. Phagocytosis of *C. neoformans* cells in the electron-microscopic picture. The fungus cells are partly deformed and with a residual capsule (▶), partly sickle shaped (→). ×4400 ▶

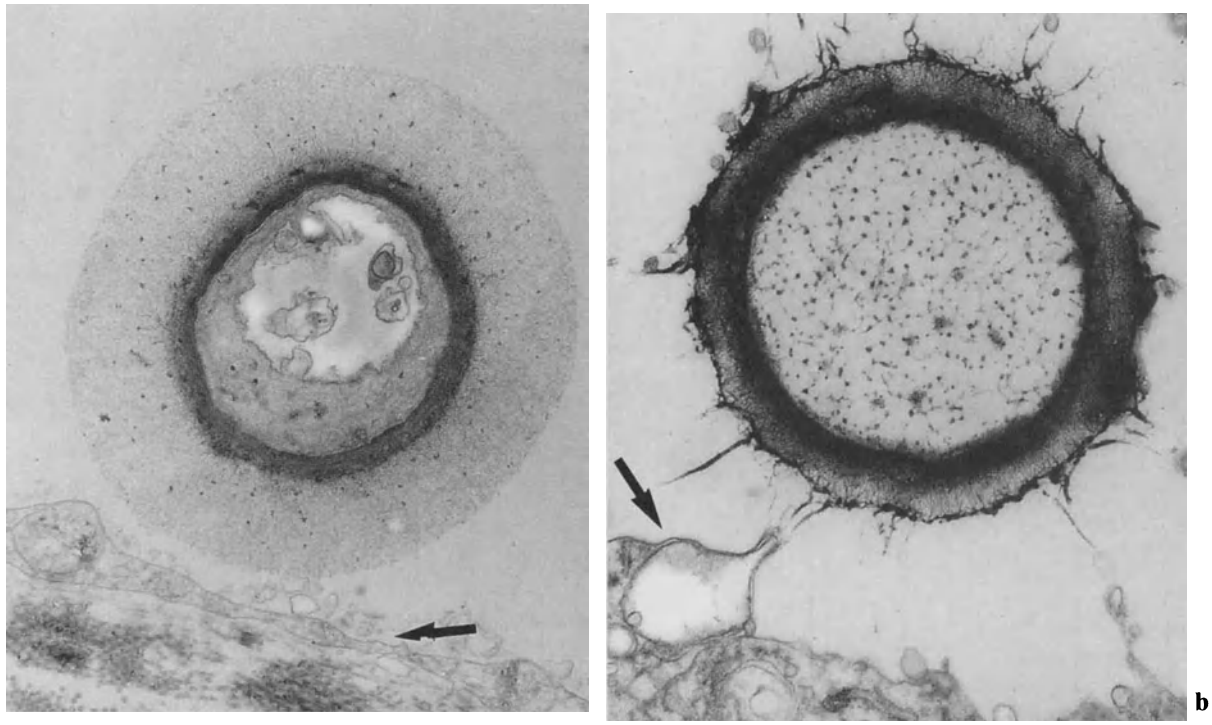


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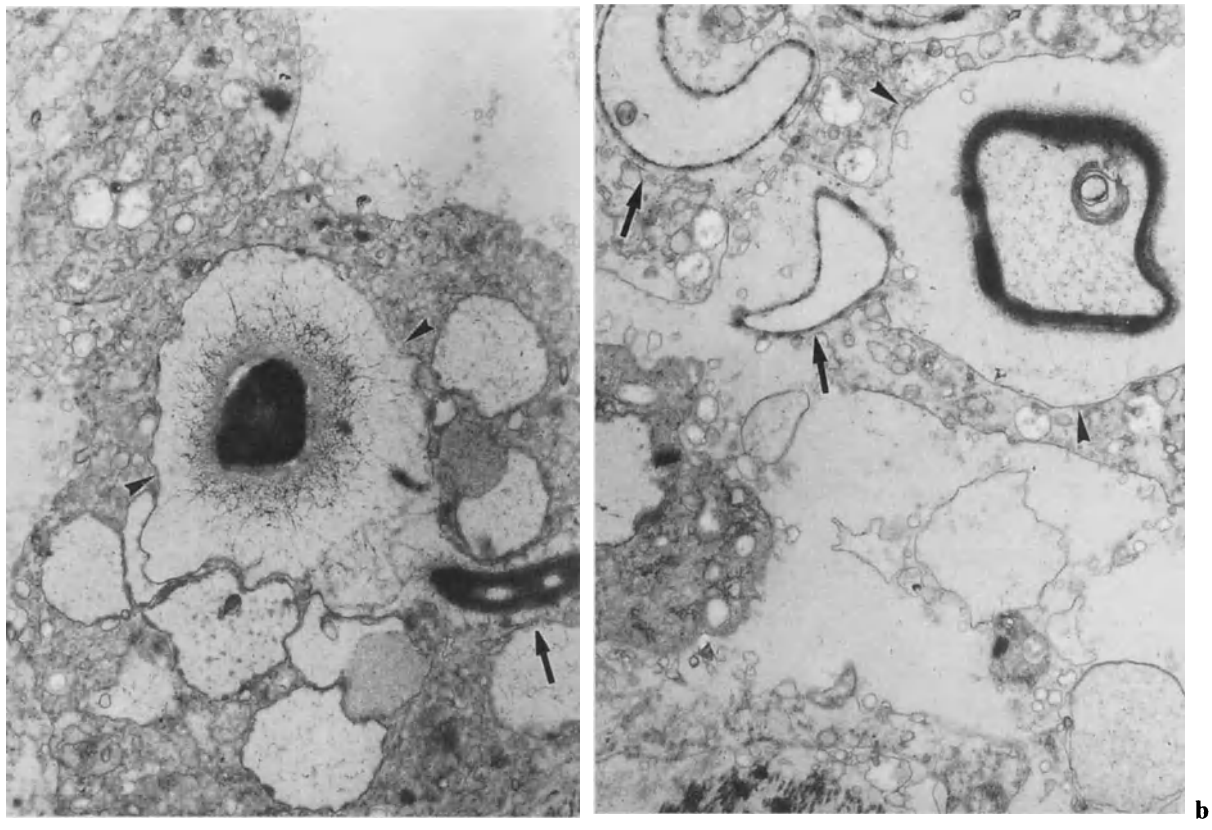
Fig. 3.45

Fig. 3.46



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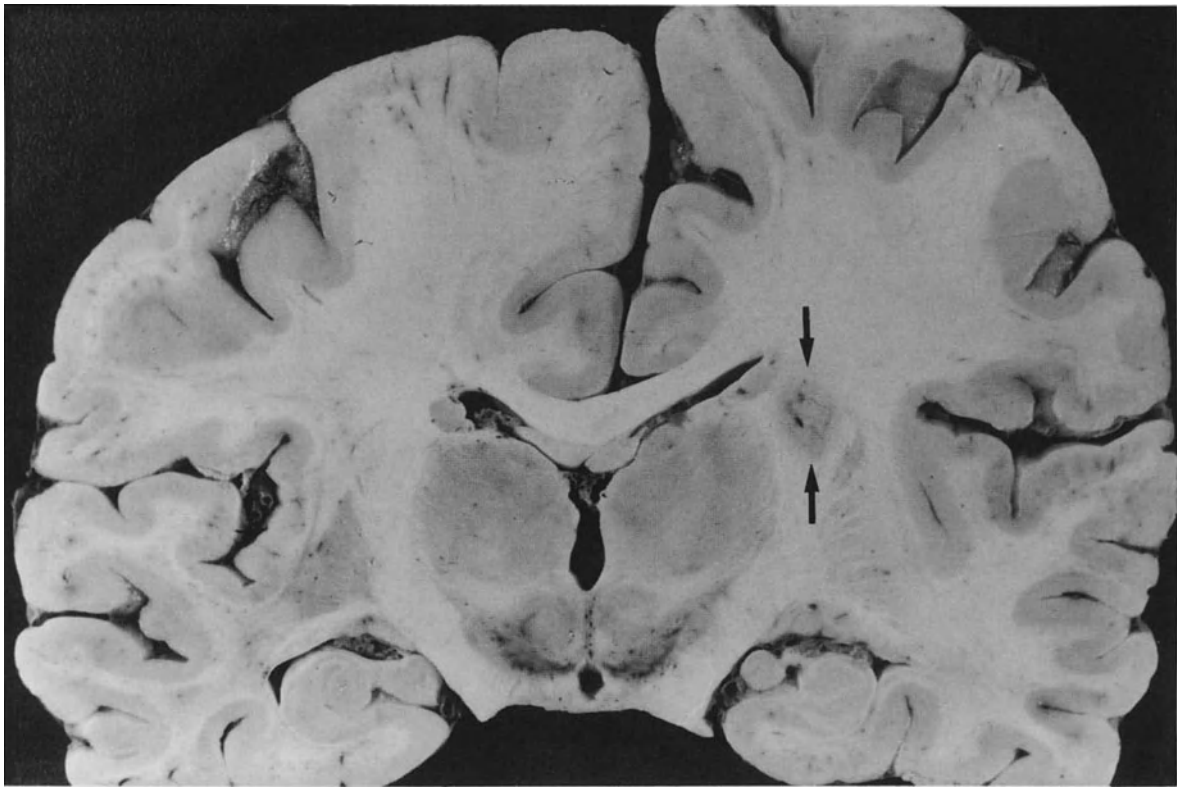


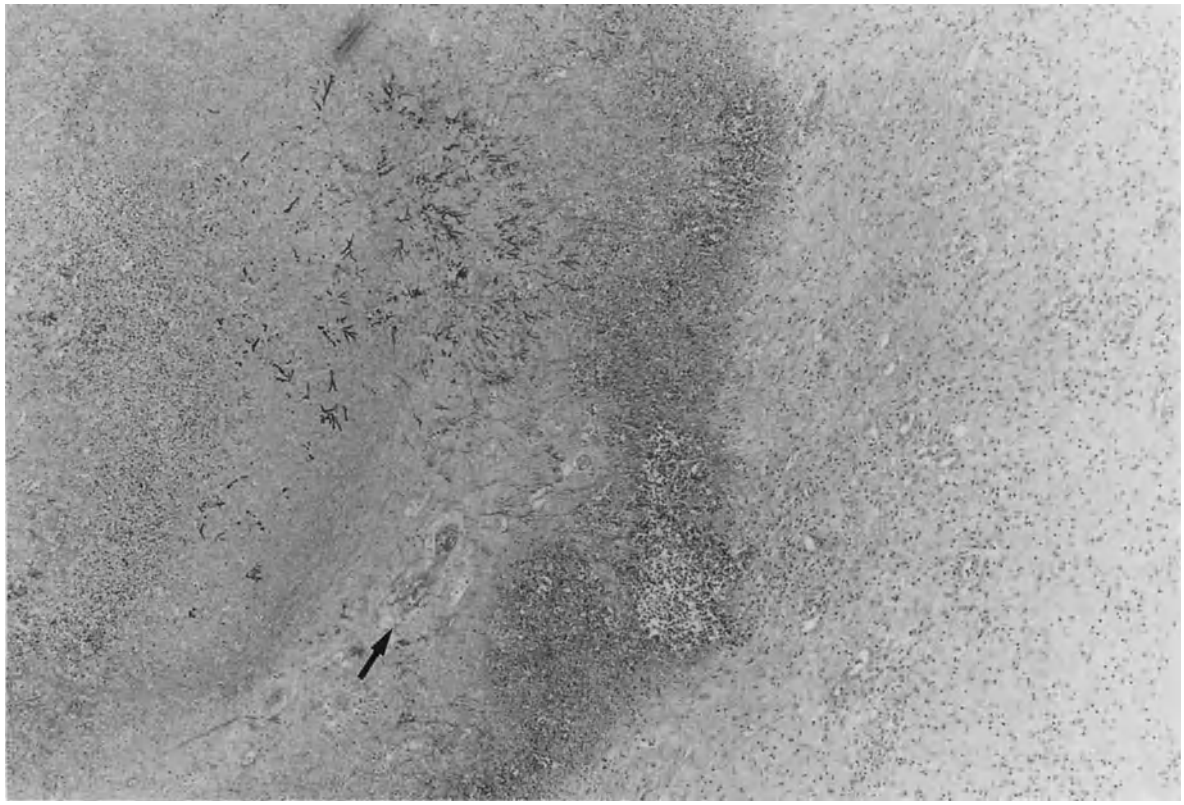
Fig. 3.47. Invasive aspergillosis of the CNS in AIDS. Frontal section of the brain with a disseminated *Aspergillus* focus within the region of the nucleus lentiformis (→)

Aspergillosis

Introduction

Aspergillosis is not an infection that directly and exclusively depends on AIDS (Chandler 1985; Denning et al. 1991; Grosse et al. 1989; Singh et al. 1991; Staib 1991, 1992) although it is often seen in AIDS autopsies (Decker and Parenti 1991; Klapholz et al. 1991). In the statistical synopsis of 1983–1984 from the United States (Center for Disease Control), invasive aspergillosis was found in 0.16% of cases (Chandler 1985). Chronic pulmonary changes in connection with a recurrent *P. carinii* pneumonia and also side effects from the therapy of various AIDS complications may be the reason that we have detected more cases of invasive aspergillosis now (about 8%) (Decker and Parenti 1991; Grosse et al. 1989; Torrents et al. 1991). Dispositional factors other than AIDS are important for the pathogenesis of aspergillosis, such as leukopenia, corticoid therapy, and further pulmonary alterations. Invasive aspergillosis is a complication of the terminal stage of AIDS without any real chance of successful therapy. Because of the wide spread occurrence of *Aspergillus* spores the genesis of aspergillosis does not depend essentially on the exposure but on the severe alteration of the host (Chandler 1985; Cohen et al. 1992; Denning et al. 1991; Grosse et al. 1989; Minamoto, Barlam and Vander 1992; Singh et al. 1991, Staib 1991, 1992). Aspergillosis is an airborne mycosis, and mainly the lungs are involved (Chandler 1985; Chandler et al. 1980; Cox et al. 1990; Denning et al. 1991; Staib 1989, 1991, 1992). Other organs such as the CNS may be affected by dissemination (Gapen 1982; Grosse et al. 1989; Singh et al. 1991; Woods and Goldsmith 1990). The most important species are *As-*

Fig. 3.48 a, b. Invasive aspergillosis of the CNS in AIDS. **a** Focal necrosis with fragments of *Aspergillus* mycelium *(black)* and cell debris; furthermore, a minimal cell reaction without proper abscess formation because of a striking leukopenia. Within the necrosis a small thrombotically closed blood vessel (→) in connection with the disseminated *Aspergillus* infection. PAS, objective, ×4. **b** Mycelium of *A. fumigatus* with typical branching of the knobby hyphae in the necrosis of the brain tissue. No abscess formation because of an AIDS-independent leukopenia. PAS, ×20 ▶



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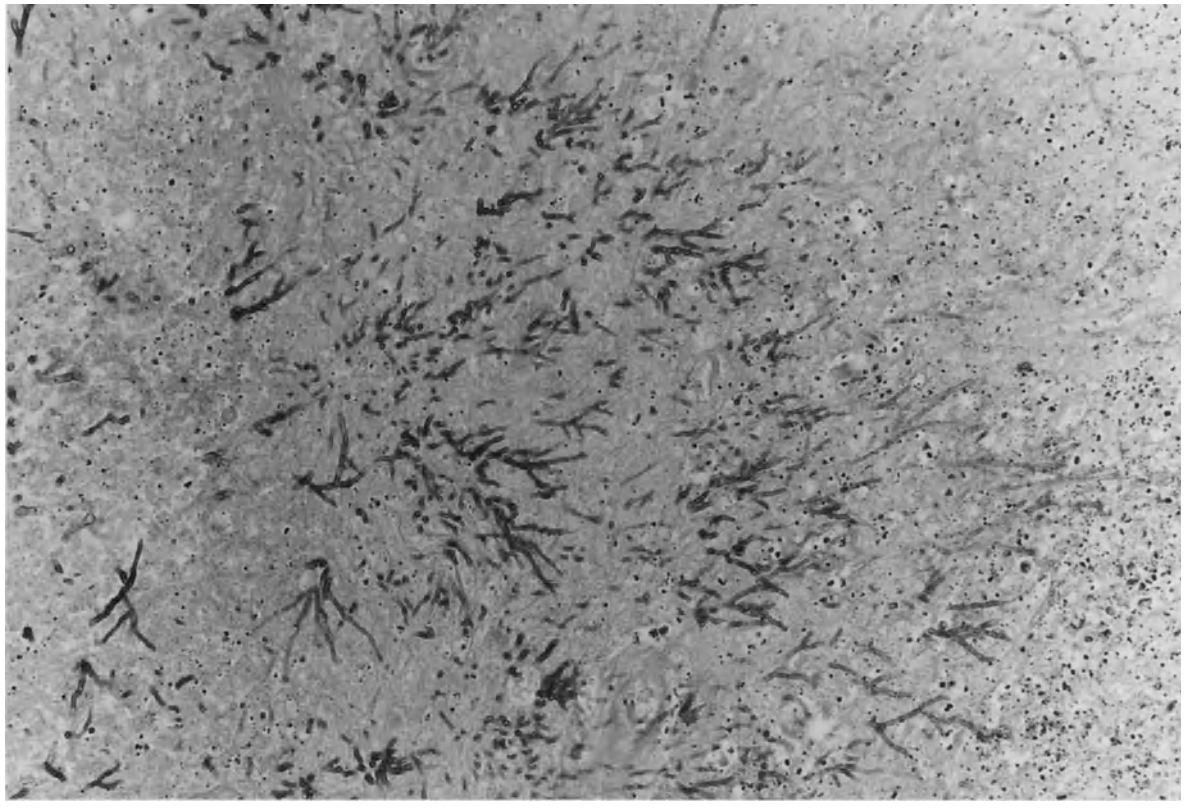


b

pergillus fumigatus and *A. flavus* (Hawkins and Armstrong 1984; Salaki et al. 1984; Woods and Goldsmith 1990). The soil of ornamental plants is the most important habitat of *A. fumigatus* in the direct environment of man and a special source of masses of respirable conidia (spores) (Grosse et al. 1985; Staib 1984, 1991, 1992).

Pathogenesis

The airborne infection of aspergillosis is caused by spores from the fruit heads of fructifying aspergilli. These spores are ubiquitious, but an important habitat producing masses of spores may be the soil of ornamental plants for *A. fumigatus* (and toasted or salted nuts for *A. flavus*; Staib 1984; 1989; 1991, 1992). The lungs of the susceptible patients – for example, patients with a severe leukopenia – show infarctionlike or hemorrhagic necroses or a necrotic pneumonia. The generally granulocytic cell reaction is often minimal or absent because of the more or less serious leukopenia. Within the necroses blood vessels are thrombotically closed. The mycelium of the aspergilli infiltrates the necrotic tissue, the wall of the vessels, and the thrombotic material with their strong proteases, inducing the thrombosis and the thrombolytic invasion (Chandler 1985; Chandler et al. 1980; Grosse et al. 1985; Grosse 1991; Staib 1985, 1991, 1992). Thrombotic particles with fragments of mycelium can be embolized into organs such as the CNS, kidney, heart, thyroid, liver, or spleen. In the extrapulmonary foci of the dissemination we also find circumscribed hemorrhagic necroses with little or minimal cell reaction, depending on the leukopenia (Chandler 1985; Cox et al. 1990; Gapen 1982; Grosse et al. 1985; 1989; Singh et al. 1991; Woods and Goldsmith 1990). In connection with a chronic or relapsing *P. carinii* pneumonia there are caverns of the lungs which can become moldy, i. e., the inner wall may be covered by a turf of fungi with many fruit heads (Grosse et al. 1989; Torrents et al. 1991). However, a real aspergilloma does not develop. In principle, here is a difference with the chronic noninvasive aspergillus infection. The aspergilloma is a long-existing lung cavern filled by a socalled fungus ball in an immunocompetent patient without invasion and dissemination (Chandler et al. 1980; Torrents et al. 1991).

Pathology

Macroscopic Findings

Foci of dissemination of invasive aspergillosis in the brain appear as red points or globular bleeding up to cherry size. These foci can be found mostly as single foci and more often in the white than the gray matter surrounded by a focal edema (Fig. 3.47; Staib 1991; Woods and Goldsmith 1990).

Microscopic Findings

Within the circumscribed hemorrhagic necroses the aspergillus mycelium can be predominantly found at the border of the lesion, sometimes as basophilic knobby fragments of mycelium which can be seen in the hematoxylin-eosin staining quite well. The hemorrhagic necrosis shows a little or almost absent reaction of leukocytes without abscess formation (Fig. 3.48). In rare cases a meningeal infiltration can be found (Gapen 1982; Klapholz et al. 1991; Minamoto, Barlam and Vander 1992). In the PAS reaction the mycelium sometimes reacts positively and can sometimes be basophilic. In Grocott's silver staining the fungal elements are optimally marked. Mostly, the morphology of the *Aspergillus* mycelium is so typical that the diagnosis of aspergillosis is possible without immunohistochemical reaction. Only more degenerate, swollen mycelium fragments can simulate phycomycetes. The mycelial phase of yeastlike fungi can usually be differentiated, especially if the yeast phase is present as the second form.

Immunohistochemistry

The immunohistochemical reaction is not necessary for the diagnosis of aspergillosis. The diagnosis of more degeneratively changed fragments of the mycelium in a broad necrosis could be difficult. In AIDS patients with aspergillosis there is usually no diagnostic problem in the conventional histology because of the extensive involvement. The decision about whether the aspergilli are viable is possible only with culture methods of diagnosis. Culture should always be tried in order to detect or to exclude fungi of other genera.

Electron Microscopy

In the coarse, destroyed tissue of invasive aspergillosis one does not need ultramicroscopic exploration.

Phycomycosis/Mucormycosis

Like aspergillosis, phycomycosis does not depend directly on AIDS. These mycoses, caused by various mucoraceae, are very rare in AIDS patients (Hawkins and Armstrong 1984; Staib 1992). Phycomycetes and aspergilli are very different fungi, but they share some qualities: nearly the same habitat on vegetable material in the soil of ornamental plants, the production of masses of respirable spores, and the airborne infection (Staib 1992). Within the hemorrhagic necroses of the primary lung affection the thrombosis of blood vessels is characteristic. The mycelium of this hyphomycete differs histologically from the *Aspergillus* mycelium. The Mucoraceae show thin-walled hyphae of various caliber without septae. PAS reaction and silver staining make the fungus clearly visible. A reduced cell reaction depends on the degree of leukopenia (Chandler et al. 1980; Hawkins and Armstrong 1984; Salaki et al. 1984; Staib 1992). In the lungs or the organs secondarily involved as a result of dissemination there are progressive infiltrations by the rapidly growing fungus. The involvement of the CNS can be found in connection with the dissemination. The cell-dependent immunodeficiency is not the decisive disposition for phycomycosis. Further pathogenetic factors such as leukopenia, corticoid therapy, diabetes mellitus, or other destructive lung processes cause this mycotic infection in the terminal stage of AIDS. The only case of mucormycosis among the AIDS autopsies of our series did not show the typical picture of a serious progressive invasive fungal disease with fatal dissemination but was a relapsing local problem within the nasal sinuses without dissemination. Mycosis was not the cause of death.

Candida Mycosis/Candidiasis

Introduction

Candida mycosis is the most frequent mycosis of AIDS patients. In the HIV-positive person soor or thrush may indicate the beginning of immunodeficiency. Nearly all AIDS patients are more or less affected by *Candida albicans,* the cause of thrush of the oropharynx or esophagus, without prophylaxis and local therapy (Blatchford 1990; Bluhm and Bickerstaff 1990; Bonacini et al. 1990; Chandler et al. 1980; Chandler 1985; De Wit et al. 1991; Gil et al. 1991; Hay 1990; Korting 1989; Leen et al. 1990; Plettenberg et al. 1990; Staib 1991, 1992; Viviani 1991). Consequently, thrush is rarely seen now at autopsy. Some other species of yeastlike fungi of minor importance can generally be found in AIDS patients (Sanchez-Rodriguez et al. 1990). The natural habitat of *C. albicans* as a saprophyte is the mucosa of the oropharynx. The pathological colonization of the mucosa depends on AIDS, but interestingly it does not become an invasive *Candida* mycosis or septicemia without further dispositional factors (Chandler 1985; Cohen et al. 1992; Hawkins and Armstrong 1984; Korting 1989; Munoz et al. 1990; Staib 1991, 1992; Whelan et al. 1990). First of all, a leukopenia in the terminal stage of AIDS may induce a hematogenous dissemination also involving the CNS (Bruinsma-Adams 1991; Del Arco-Galan et al. 1990; Hawkins and Armstrong 1984; Munoz et al. 1990; Sanchez-Rodriguez et al. 1990).

Pathogenesis

The typical mycotic manifestation of the yeastlike fungus *C. albicans* is thrush of the oropharyngeal mucosa or of the esophagus; it is generally superficial pseudomembraneous affection of the mucosa of the upper digestive canal. In these areas of the mucosa with a squamous epithelium, where *C. albicans* exists saprophytically, thrush of the mucosa may endogenously arise under the pathogenic constellation of AIDS. The pseudomembranes, which are of varying size, consist of fibrin and detached surface epithelia or cell debris interspersed with fungus cells. The dense fungal colonization predominantly contains the filamentous elements of the mycelial phase and, less frequently, the yeastlike round oval cells. Beneath the fungal colonization there is a mixed bacterial flora within the pseudomembranes. Without prophylaxis and therapeutic influences thrush of the mucosa may be an indicator of initial stages of AIDS in the HIV infection. In the later stages of AIDS a deep mycotic process of the mucosa can arise from a superficial thrush. The destruction of the deep layer of the squamous epithelium leads to a real membranous inflammation or an ulcer of the mucosa. The ulceration may be caused by a superinfection with herpesvirus or CMV. A deep fungal invasion with vascular penetration of *C. albicans* in the lamina propria of the mucosa may arise under the additional condition of a severe leukopenia. The proteolytic activity of *C. albicans* causes a thrombosis of blood vessels and a fungus invasion of the vessels. In connection with the consequent dissemination there can be cerebral involvement (Bruinsma-Adams 1991; Del Arco-Galan et al.

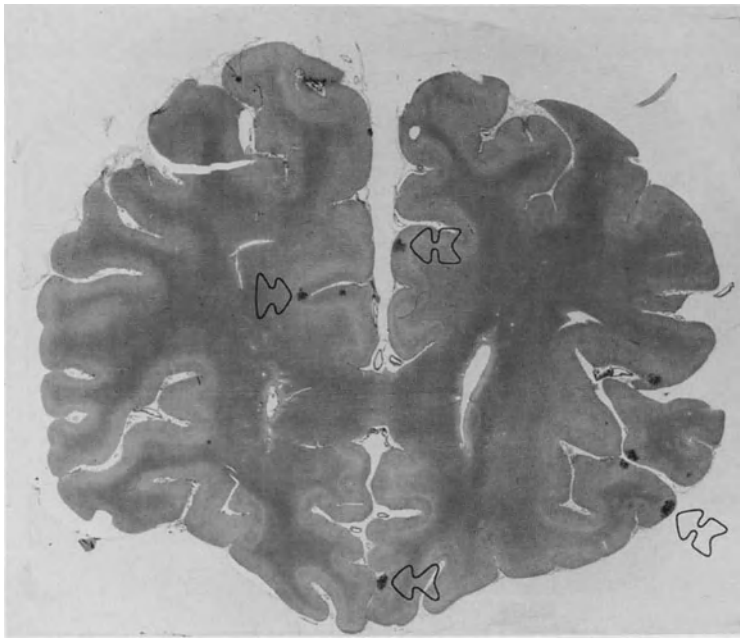


Fig. 3.49. *Candida* mycosis of the CNS in AIDS. Coronal section of the frontal lobes showing some small hemorrhagic points *(arrows)* as foci of *candida* septicemia. (PAS)

Fig. 3.50 a, b. *Candida* mycosis of the CNS in AIDS. **a** Circumscribed necrosis within the brain cortex containg *C. albicans* predominantly in the filamentous mycelial phase without abscess formation because of an AIDS-independent leukopenia. PAS, ×4 **b** In the higher magnification the filamentous fungal elements of the mycelial phase are shown. In the centre of the necrosis a thrombotically closed blood vessel; furthermore, minimal cell reaction within the hemorrhagic necrosis. PAS, ×10 ▶

1990; Hawkins and Armstrong 1984; Staib 1991, 1992). Leukopenia is the most important dispositional factor for deep *Candida* mycosis or mycotic dissemination. On the other hand, such a deep mycosis indicates the final stage of AIDS with further complications not directly depending on AIDS. A focal lung infiltration with massive colonization of yeastlike fungi may arise in connection with a preexsistent lung alteration, such as chronic *P. carinii* pneumonia in combination with a CMV infection. A pneumonia with less numerous fungus elements may point to an aspiration. In these cases other species of yeastlike fungi also can be found (Chandler et al. 1980; Chandler 1985; Staib 1991, 1992).

Pathology

Macroscopic Findings

Brain foci caused by a *Candida* septicemia generally cannot be seen macroscopically. Sometimes small hemorrhagic points can be found within the cerebral tissue (Fig. 3.49).

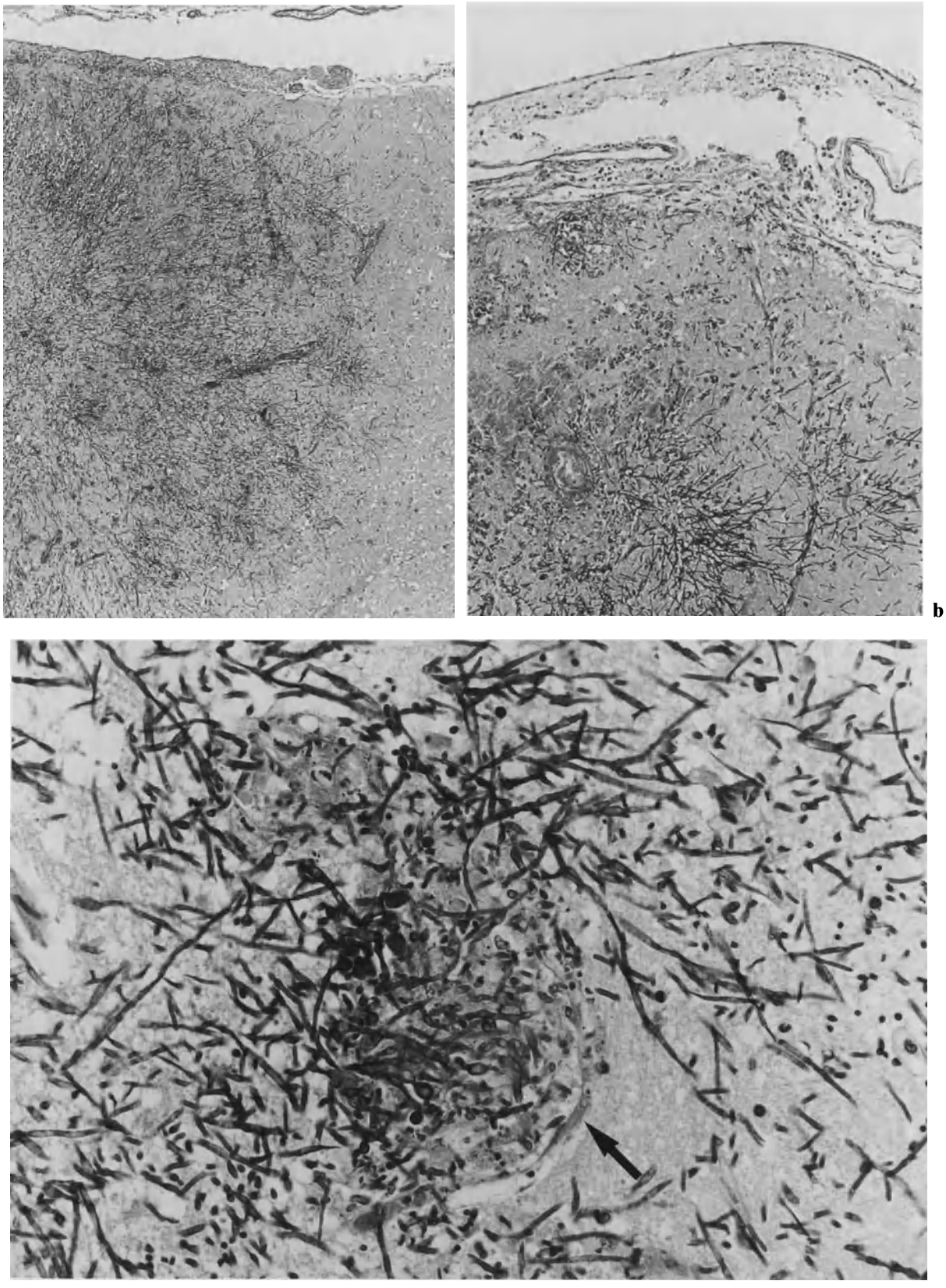
Microscopic Findings

Small disseminated foci contain a varying number of fungus cells. The cell infiltration depends on the degree of leukopenia. In severe cases we find small necroses with fungus cells and without a leukocytic reaction (Fig. 3.50). *C. albicans* as the decisive species can be found in two morphological stages: round oval budding blastospores of 2–6 μm diameter as the yeast phase or filamentous elements as the mycelial phase (Fig. 3.50 b). The yeastlike fungi can barely be seen in the hematoxylin-eosin staining but excellently in the PAS reaction or with Grocott's silver stain. The CNS foci may contain fungus elements only in the yeast phase as blastospores or single elements of the mycelial phase (Figs. 3.50 b, 3.51; Chandler et al. 1980; Chandler 1985; Staib 1991, 1992).

Immunohistochemistry

The immunohistochemistry identification of the *Candida* species is not clearcut because of possible cross-reactions. Experience shows that the CNS foci contain *C. albicans.*

Fig. 3.51. *Candida* mycosis of the CNS in AIDS. *C. albicans* predominant as filamentous elements of the mycelial phase and with less frequent round oval blastospores of the yeast phase. Minimal cell reaction without abscess formation because of a (primary AIDS-independent) leukopenia. Within the centre of the necrotic focus a small blood vessel with fungi-containing thrombotic material (→). PAS, ×40 ▶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Electron Microscopy

The ultramicroscopy dimension is not important in determining the identification of the fungi, the description of the tissue lesion, or the cell reaction.

Extra-European Systemic Mycoses

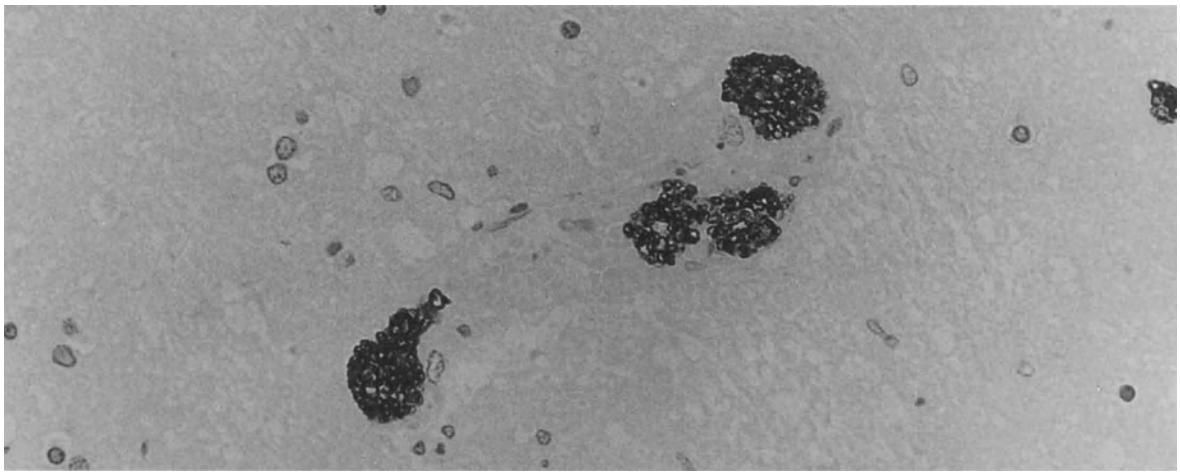
Cases of extra-European systemic mycoses are very rare outside the endemic regions. We have no experience of these mycoses, especially with regard to the CNS. In addition to histoplasmosis (Ankobiah et al. 1990; Gottlieb and Mariott 1990; Heyligenberg et al. 1990; Machado et al. 1991; Marshall et al. 1990; Nightingale et al. 1990; Rockstroh et al. 1991; Sarosi and Johnson 1990; Tomita et al. 1990; Wheat et al. 1990; Zarabi, Thomas and Adesokan 1992), coccidioidomycosis (Antoniskis et al. 1990; Byrne and Dietrich 1989; Fish et al. 1990) is mentioned as a possible AIDS complication with individual cases of CNS involvement in connection with a disseminated infection.

Supplement

Pneumocystis carinii Infections

Recently, a discussion has arisen about whether *P. carinii* is a protozoon or a fungus because new aspects have been discovered in connection with ribosomal RNA (Edman et al. 1988). Irrespective of this question we did not find a real CNS involvement in our cases of disseminated extrapulmonary *P. carinii* infection. (Mayayo et al. 1990). In connection with

Fig. 3.52 a, b. ***Pneumocystis carinii*** in the CNS in AIDS. *P. carinii* exclusively intravascular without invasion of the brain tissue. **a** Immunohistochemically stained *P. carinii (black complexes)* within the lumen of a brain capillary beneath shadowlike erythrocytes. A perivascular edema may point to the *P. carinii* manifestation. *P. carinii* antiserum, ×63. **b** PAS-positive *P. carinii* complexes within the capillary lumen beneath some erythrocytes. Note the perivascular hydropic changes of the brain parenchyma. PAS, ×40. (The paraffin embedded brain tissue of an AIDS patient courtesy of Dr. Iglesias, Institute of Pathology, Katharinenhospital, Stuttgart, Prof. Dr. B. Kraus)



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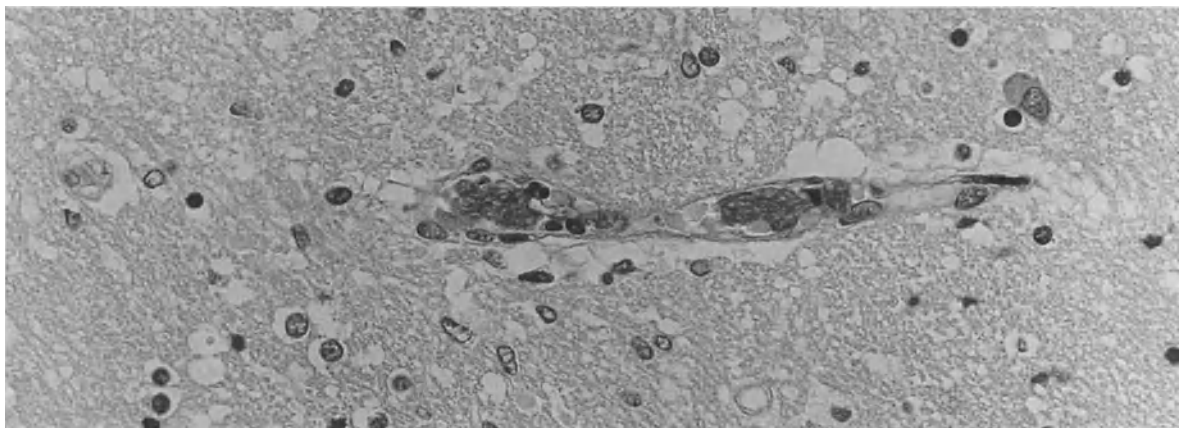


b

one of our cases of disseminated *P. carinii* infection *P. carinii* was shown immunohistochemically within the smallest blood vessels of the CNS without invasion of the cerebral parenchyma. A circumscribed perivascular edema in the microscopic dimension was an indication of this phenomenon (Fig. 3.52).

Nocardiosis

Nocardia belongs to the bacteria such as the actinomycetes, but nocardiosis is often classified as a mycosis (Joshi and Hamory 1991; Marin-Casanova et al. 1991). Our only case of nocardiosis did not show CNS involvement.

■ Tuberculosis

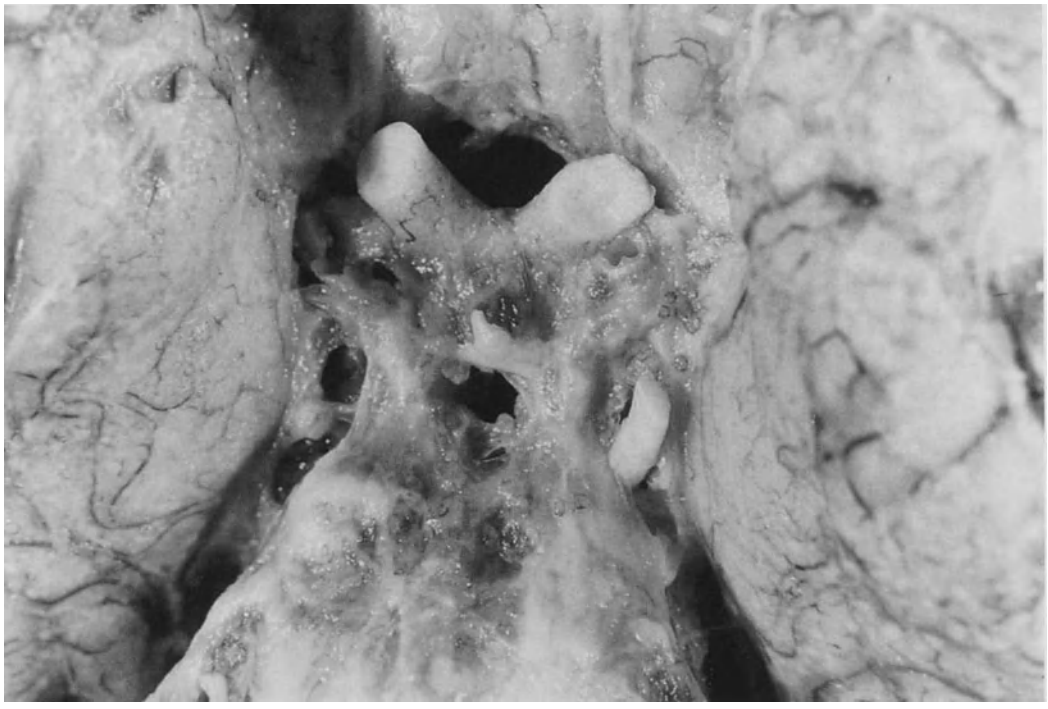
General clinical experience tells us that tuberculosis is not a very frequent complication in AIDS, and it is not classed as one of the opportunistic infections in the true sense (Joachim 1989; Füeßl 1991). Nonetheless, there are geographic variations, with frequent occurrences of pulmonary tuberculosis in AIDS patients in endemic areas (Emskötter 1991 b). It is assumed very generally that the risk of contracting tuberculosis is 100 times greater for AIDS patients than for the normal population (Füeßl 1991). The incidence of tuberculosis in AIDS patients is in accord with the high prevalence of histoplasmosis and coccidioidomycosis in AIDS patients in the relevant endemic areas (Joachim 1989). Nevertheless, *Mycobacterium tuberculosis* is not a typical opportunistic bacillus in AIDS (Sotrel 1989). An extensive study, however, showed that among Haitian immigrants to Florida there was a prevalence of tuberculosis of 650/100000 compared with only 11/100000 among the general population in the United States; the same study also showed tuberculosis in 27 out of 45 immigrants who had contracted AIDS (Joachim 1989).

Characteristic of tuberculosis in AIDS patients are the frequent extrapulmonary manifestations, found in 72 % of cases (Joachim 1989). Also stricking is the observation that active tuberculosis occurs mainly in AIDS patients with a history of intravenous drug abuse, and less so in homosexuals (Vinters and Anders 1990). Among the ten cases of a tuberculosis of the CNS in AIDS and AIDS-related complex reported by Bishburg et al. (1986) nine had a history of intravenous drug abuse; among the 15 AIDS patients with tuberculous infection in the series of Pons et al. (1988) there were also nine with a history of drug abuse. In the two observations of tuberculous meningoencephalitis in our series (a 39-year-old man and a 31-year-old man), long-standing heroin abuse was also noted.

The tuberculous infection of the brain and the meninges (Figs. 3.53, 3.54) occurs via hematogenous dissemination. There develops an acute to subacute basilar meningitis (Emskötter 1991 b). The hematogenous origin and the predominantly basilar spread of tuberculous meningitis in the region of the pons, optic nerve, and chiasma were also documented in the older literature (Scheidegger 1958). The basilar cisterns contain a fibrinous and gelatinous exudate. In accordance with the cases of tuberculous dissemination in earlier years, tuberculous meningitis is also the most important manifestation of tuberculosis in the CNS in AIDS patients (Harriman 1984). The direct spread of the infection to the cortical brain tissue leads to meningoencephalitis (Gosztonyi 1989).

In addition to edema, the impressive microscopic findings also show dense inflammatory cell infiltration with histiocytic and lymphocytic cells, which are diffusely disseminated or often arranged around blood vessels, and which in places also form nodular infiltrates. The nodular foci, which are even discernible macroscopically, only rarely contain a few epithelioid cells, but they tend to form central necroses. In these, one can find varying amounts of acid-proof bacilli. Polynuclear giant cells are not normally evident. In places the external cortical layers are included with cellular infiltrates and necroses; perivascular cell infiltrates in the cerebral cortex lead to the picture of perivenous encephalitis. The larger meningeal vessels are also often included in the inflammatory process with fibrinoid necrosis and cellular infiltration (Scheidegger 1958), or they exhibit a reactive endarteritis obliterans (Kirkpatrick 1991).

Further morphological manifestations exhibited in the cases that we have studied were a distinct focal or diffuse ventriculitis with focal loss of the ventricular ependyma and a plexus involvement accompanied by necroses and inflammatory infiltrates (Fig. 3.55). In our autopsy cases we observed no larger intracerebral tuberculous foci (so-called tuberculomas).



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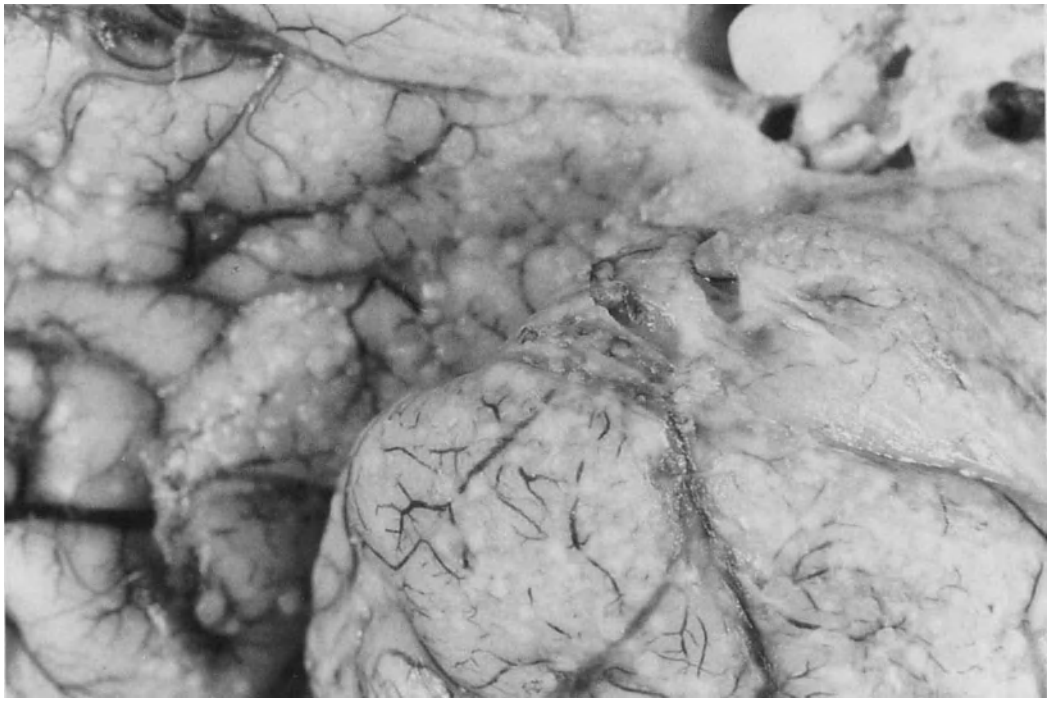
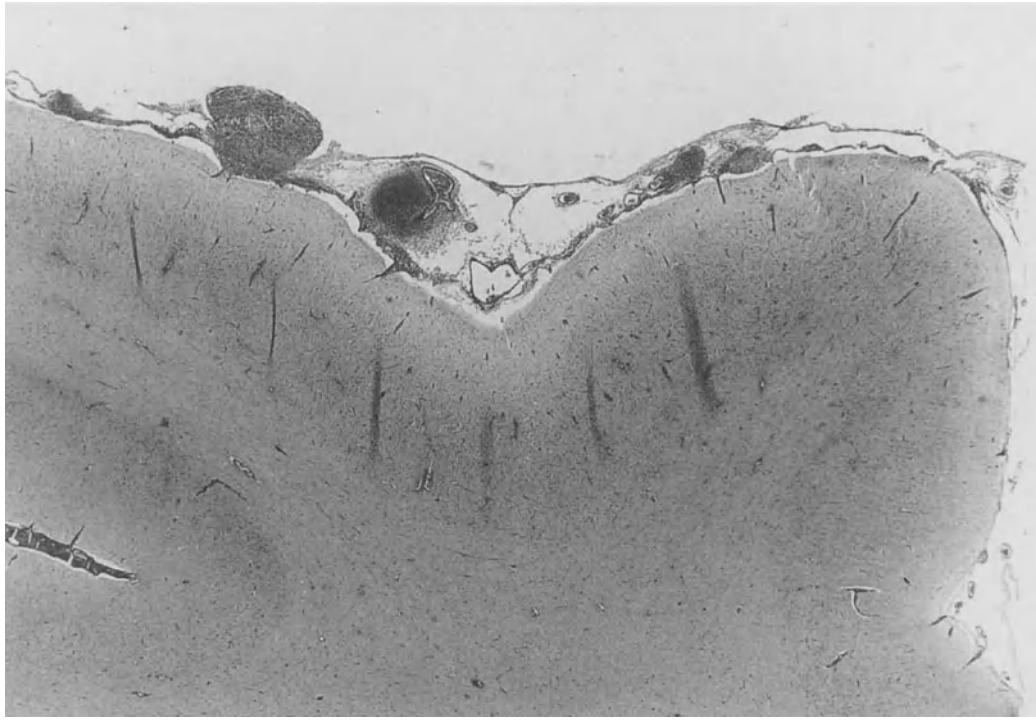


b

Fig. 3.53 a, b. Tuberculous meningitis in AIDS. **a** Richly fibrinous inflammatory exudate at the base of the brain. **b** Numerous "miliary" tubercles, clearly visible macroscopically in the only slightly opaque meninges at the base of the frontal lobe of the right cerebral hemisphere



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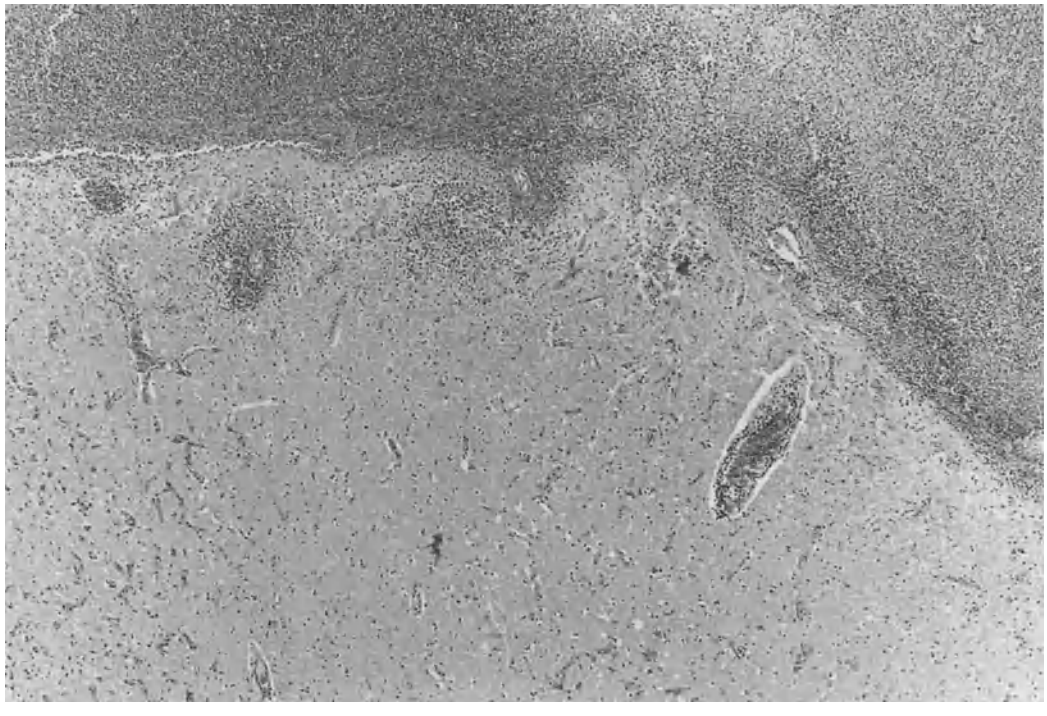

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Fig. 3.54a,b. Tuberculous meningitis in AIDS. **a** Nodular, partially perivascular necroses and cell infiltrates in the leptomeninges at the base of the frontal lobe (same case as Fig. 3.53b). H&E, ×2. **b** A larger tuberculous necrosis of the leptomeninges spreading to the surface cortical substance with perivascular cell infiltrates. H&E, ×4

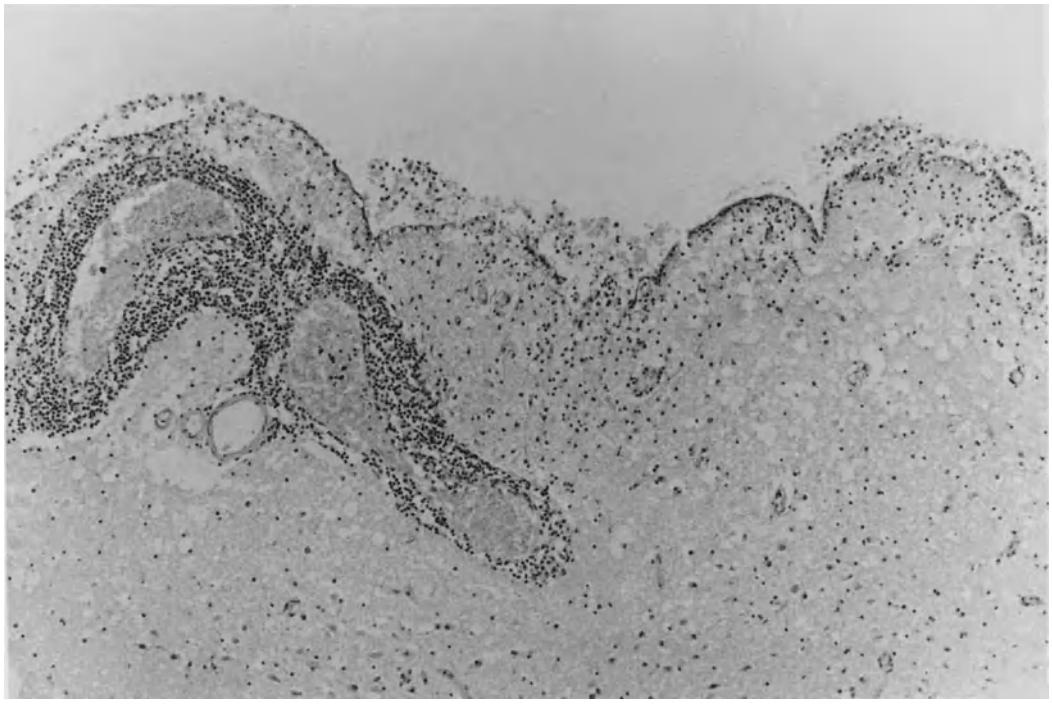


Fig. 3.55. Tuberculous ventriculitis. Perivenous lymphohistiocytic infiltrate, focal defects of the ventricular ependyma, and loose cell infiltrates and fibrin deposits; no epitheloid cell granulomas. H&E, ×10

■ Malignant Lymphomas of the CNS

Introduction

The occurrence of malignant tumors in the course of immunodeficiency syndromes has been known for a long time and was described in the era before the AIDS epidemic became apparent, which can be dated around 1981 (L'Age-Stehr and Helm 1991). A comprehensive survey of the literature on immunodeficiency disorders with malignant tumors (e.g., infantile X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, ataxia-telangiectasia, etc.) was compiled by Gatti and Good (1971) and recently reviewed by Schaefer (1991). In the same year there was also a report about brain tumors in recipients of kidney transplants (Schneck and Penn 1971). The cases reported comprised six primary brain tumors described as reticulum cell sarcomas (microgliomas) and two unclassified lymphomas. A series of 22 cases of primary malignant lymphomas of the CNS reported in 1984 by Helle et al. included no AIDS patients but noted seven patients (32%) with immunosuppression.

The first lymphomas of the Burkitt type in homosexual men were reported in 1982 (Ziegler et al. 1982). In the four cases described, tumor manifestations were found in various organs; at least three showed involvement of the CNS. The first definite cases of primary malignant lymphomas of the CNS in AIDS without manifestation in other organs were described in 1983 (Snider et al. 1983b). Primary lymphomas of the CNS were formerly regarded as generally very rare (Gonzalez Gonzalez and Schuster-Uitterhoeve 1983; Kernohan and Uihlein 1962) and made up only about 1%–2% of the intracranial tumors (Rosenblum et al. 1988; Xerri et al. 1990).

Nonetheless, malignant lymphomas of the brain were described in the literature as early as the 1940s and 1950s (Gerhartz 1951; Zülch 1951). The term malignant lymphoma was also used in reports on brain tumors during those years (Henschen 1955), although numerous other terms were common especially in Europe to describe corresponding cytological-histological findings: reticuloendothelial sarcoma (Zülch 1951), adventitial sarcoma (Xerri et al. 1990), malignant angioendotheliomatosis (Fulling and Gersell 1983; Woodman et al. 1986), reticulum cell sarcoma,

microglioma, and malignant reticuloendotheliosis (Sheibani et al. 1986). In the extensive and detailed presentation by Bailey (1929) there are case reports on analogous brain tumors termed perithelial or perivascular sarcoma.

The very good histological illustrations show the well-known angiocentric growth and vascular wall infiltration. The nomenclature of tumors and the involvement of the CNS have been discussed using a large amount of case material according to clinical, histological, and sometimes autopsy findings (John and Nabarro 1955). Especially the entity called in the past neoplastic angioendotheliomatosis (Fulling and Gersell 1983; Wick et al. 1981) was a very controversal subject, but it is now evident that malignant angioendotheliomatosis is an angiotropic large-cell lymphoma (Dozic et al. 1990; Sheibani et al. 1986; Wrotnowski et al. 1985). The lymphoid nature of the tumor cell growth was confirmed in histologically and cytologically analyzed cases (Ansel et al. 1982; Bhawan et al. 1985). Apart from exact cytological-histological descriptions, the older literature, using varying nomenclature, also contains reflections on the histogenetic derivation of lymphoreticular brain tumors (Fried 1926; Yuile 1938).

The broader range of findings obtained today as a result of the epidemiological situation confirm the earlier morphological representations and complete them with methodologically newer data; in principle, however, the tumor entities discussed here were known to the earlier authors (Snider et al. 1983b).

Incidence

Malignant lymphomas of the CNS as primary manifestation or as involvement in systemic disorders are rare findings (John and Nabarro 1955; Murphy et al. 1989; J. Simon et al. 1987; M. Simon et al. 1991; Xerri et al. 1990; Zülch 1951). The literature puts the incidence at around 1 % of brain tumors (Rosenblum et al. 1988; Xerri et al. 1990). Other authors' reported incidence rates diverge only slightly (Gerhartz 1951; Henschen 1955). More recent studies show an increase in the incidence of primary malignant lymphomas of the brain (Hochberg and Miller 1988). These cases are linked principally with immunosuppression, and in many cases the therapeutic immunosuppression seems to be a fundamental pathogenetic factor (Kay 1989; Murphy et al. 1989; Sotrel 1989). Feiden et al. (1989) found among 230 stereotactically examined brain tumors a total of 34 (!) malignant lymphomas (14.7 %); in their report the authors make no mention of the question of immune status. Another report on 54 cases of primary malignant lymphomas of the brain contains only one AIDS patients (Feiden et al. 1990). Gonzalez Gonzalez and Schuster-Uitterhoeve (1983) reported 15 cases of malignant lymphomas (6 %) out of an extensive series of 250 primary brain tumors; they also made no mention of immune status.

Full details of the epidemiology of the non-Hodgkin's lymphoma of the CNS (CNS NHL) are presented by Hochberg and Miller (1988). According to this, there has been a slow increase in the incidence since 1960; however, in the 5 years between 1980 and 1984 there was a tripling. EBY et al. (1988) also reported a tripling in the incidence rate of primary malignant lymphomas of the CNS in the period from 1973 to 1984. It is important to establish, however, that neither the AIDS epidemic nor other forms of immunosuppression by themselves explain the increase in incidence (Hochberg and Miller 1988; De Angelis et al. 1992). The incidence of primary malignant lymphoma of the CNS is increasing in both patients with AIDS and immunocompetent ones (Diamond et al. 1990). The trend of an increase in incidence can evidently also be seen independently of AIDS (Eby et al. 1988).

In the revised Center for Disease Control definition of 1987, primary malignant lymphomas of the brain in patients aged under 60 years were included in the AIDS-defining disorders (Goedert and Blattner 1988). However, in a criticism of this definition of AIDS in connection with CNS NHL, Feiden and Backmund (1991) pointed to the problematic aspects and noted that in the stereotactically obtained biopsy material which they studied (29 men and 25 women, aged 20–85 years) there was only one AIDS patient. They conclude that AIDS must not be diagnosed solely from evidence of CNS NHL in patients under 60 years of age; instead, the diagnosis should if possible rely on an HIV laboratory test or the determination of CD4-positive T-helper cells in the blood. Nonetheless, according to the details in the literature, around 3 %–6 % of AIDS patients develop primary malignant lymphoma of the CNS (Sotrel 1989; Vinters and Anders 1990; Chimelli et al. 1992); (6,6% d'Arminio Monforte et al. 1992). Meeker et al. (1991) report an incidence of between 1 % and 5 %. It is assumed that with better and more effective therapy of opportunistic infections and a longer survival time malignant lymphomas will become more frequent in AIDS patients (Meeker et al. 1991). While the risk in the general population contracting a lymphoma of the

CNS is very slight (0.0001 %), in immunosuppressed patients the risk increases to 0.2 % and in AIDS patients to 1.5 % (Levy and Bredesen 1988). In an extensive study involving 60 cases of AIDS-associated lymphoma (Levine et al. 1991) there were 11 cases (~ 18 %) with primary cerebral lymphoma, while 49 patients had a systemic disorder (Levine et al. 1991); in a further study, in which 39 HIV-positive patients with primary neurological symptoms were examined, 11 had a primary CNS-NHL (= 28 %) (Cornford et al. 1992).

NHL is the most frequent tumor of the CNS in AIDS patients; on the other hand, reports on the spread of Kaposi's sarcoma to the CNS are very rare (Dal Canto 1989; Gorin et al. 1985). In our own study of 180 autopsies of deceased AIDS patients there were 17 cases with malignant lymphomas of the CNS (9.4 %). In 13 cases the CNS was the only localization, and in 4 the CNS manifestation was a partial feature of a systemic disorder. It is noticeable that both our own experience and data in the literature show that the extranodal manifestations of malignant lymphomas predominate in AIDS (approximately 75 %) (Joachim 1991; Meeker et al. 1991). The literature also contains reports on malignant lymphomas of the brain in pediatric AIDS cases (Aricò et al. 1991; Keohane et al. 1991; Burns 1992).

Pathogenesis

Formal Pathogenesis

The ideas commonly held today about the formal pathogenesis of cerebral lymphomas were also discussed in the older literature (Kernohan and Uihlein 1962). As early as 1926 Fried in a case report pointed to the adventitial cells of the perivascular space (Virchow-Robin space). In another case report on a primary reticulosarcoma the author likewise regarded the adventitial cells, which he classified as histiocytes, as the cells of origin (Yuile 1938). The reported findings led to the conclusion that the microglia were of "histiocytic nature." The connections between microglia and neoplastic processes of the malignant lymphoma type were also discussed by Kernohan and Uihlein (1962). The authors describe the strong proliferation of microglia cells, the enlargement of the cells, which was visible in the Hortega's silver staining method but not in routine stainings, the formation of cell groups and nodules as the beginning of a focal tumor growth, and the transformation of microglia into round cells through loss of the cell processes. In a detailed study (Burstein et al.1963), the authors report clearly the anatomical proportions of the perivascular space and the leptomeninges and the stock of cells in this area.

Our findings in cases of malignant lymphomas of the CNS in AIDS fully confirm those of Kernohan and Uihlein (1962). The "activation" of the microglia cells with enlargement of the single cells and generally plump processes can be represented easily in lectin histochemical preparations with mistletoe lectin I (ML I). The predominantly perivascular growth around small arteries and veins or around arterioles and venules, which can occur together with nodular tumor infiltrates or alone, was also noted in the older literature (Kernohan and Uihlein 1962). The findings from our preparations accord with reports in the literature in suggesting the perivascular origin of intracerebral lymphomas. Even with varying nomenclature, especially in the older literature, the frequently illustrated findings are convincing and are in accord with the understanding of an adventitial neoplasia as derived from our preparations.

The perivascular macrophages, so-called pericytes, and the various forms of microglia, which also appear greatly proliferated and activated in HIV encephalitis preparations, cannot be definitively distinguished with present methods and preparations with ML I (Artigas et al. 1991 c; Franz et al. 1991).

Causal Pathogenesis

Permanent stimulation of the lymphoreticular cell system caused by antigens evidently plays an important role in the causal pathogenesis (Norenberg and Bruce-Gregorios 1991). In transplant recipients antigen stimulation should lead to a continuous proliferation of immunoblasts, with a possible neoplastic transformation. Microscopic findings on the gastrointestinal tract (Otto et al. 1981) can also be linked to persistent antigen exposure. Furthermore, regarding the pathogenesis of lymphomas of the brain, it has been suggested that immunosuppressive medications (azathioprine, cyclophosphamide) cannot pass the blood-brain barrier and affect mainly the B-cell system outside the CNS (Kay 1989). Thus proliferation of B-cells in the CNS remains uncontrolled and is not subject to general immunosuppression. In addition to the blood-brain barrier, the lack of lymph vessels in the brain is also regarded as an important factor in the origin and growth of brain tumors because these anatomical peculiarities also give the CNS a special

immunological position and prevent immunological surveillance of tumor growth (Burnet 1967). The occurrence of malignant lymphomas of the CNS with therapeutic immunosuppression accords with these pathogenetic ideas (Davensport et al. 1991; Kay 1989; Lipsmeyer 1972; Murphy et al. 1989; Sotrel 1989).

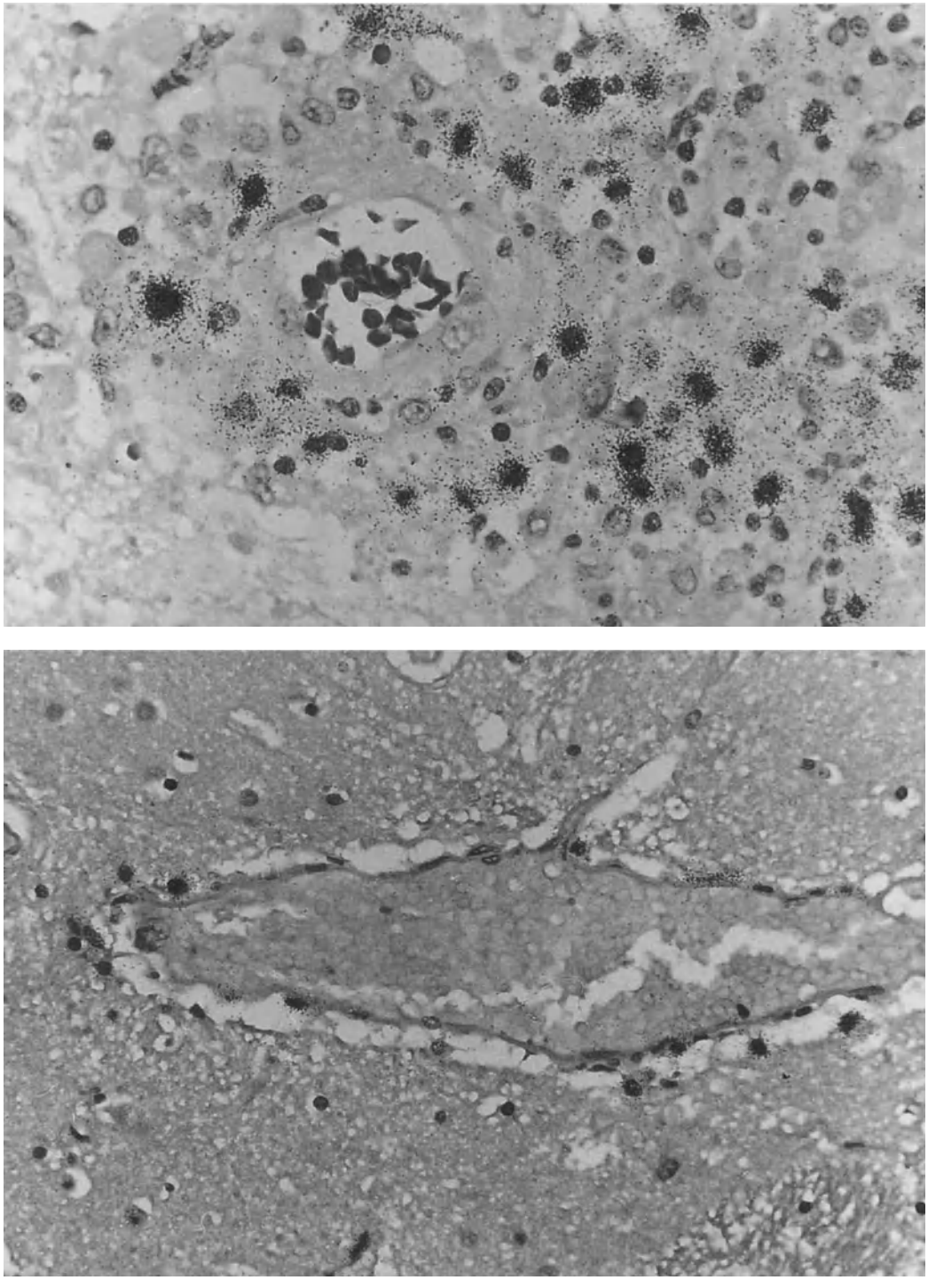
These discussions lead to the question of possible preneoplastic findings on the lymphoreticular tissue. The microscopic diagnosis is regarded as difficult and in the biopsy material as perhaps impossible (Otto et al. 1981). However, in organs with richly developed lymphatic tissue (e.g., gastrointestinal tract) transitional forms between hyperplasia and neoplasia are found (Otto et al. 1981; Wolf and Spjut 1981). The so-called progressive lymphoreticular hyperplasia is reported as an intermediate stage followed by manifest lymphomas in the small intestine after a period of months or years (Otto et al. 1981). Similar findings with hyperplasia of the lymphatic tissue and conversion into sarcoma were described in the small intestine with idiopathic steatorrhea as early as 1968 (Whitehead 1968). The polyclonal polymorphic B-cell lymphoproliferative disorder – characterized by polyclonal and polymorphous B-cells without cellular atypia, necrosis, or mitotic activity and with predominantly extranodal and particularly pulmonary localization is also regarded as intermediary proliferation between benign and malignant forms (V. V. Joshi et al. 1987). Microscopically, the fatal B-cell lymphoproliferative syndrome in allogeneic marrow graft recipients also exhibits polymorphous infiltration in the lymph nodes, with lymphoblasts, plasmacytoid cells, and giant cells of the Reed-Sternberg type (M. Simon et al. 1991). The literature also discusses the question of whether the entity known as lymphomatoid granulomatosis should be regarded as a reactive process and as preneoplastic (Sordillo et al. 1982; Vinters and Anders 1990).

The mixed-cell infiltrate with lymphocytes, histiocytes, plasma cells, plasmocytoid lymphocytes, and scattered atypical mononuclear cells shows, as in malignant lymphomas, a tendency to spread angiocentrically. The process probably begins as a polyclonal infiltrate and turns into a clonal overproduction of B-cells and lymphoma (Vinters and Anders 1990). The development of malignant lymphoma in a patient with lymphomatoid granulomatosis of the lung and long-standing Sjögren's syndrome was described by Capron et al. (1985). In their material from 15 cases with malignant lymphomas of the CNS, Morgello et al. (1990) frequently found an accompanying polyclonal mixed-cell infiltrate with B- and T-lymphocytes, plasma cells, and lymphoplasmacytoid cells. However, lymphomatoid granulomatosis is today regarded as a T-cell proliferation or a peripheral T-cell lymphoma (Kerslake et al. 1991).

There is extensive literature on the connection between EBV and malignant lymphoma (Fig. 3.56); (Editorial 1991; MacMahon et al. 1991; Hoffken 1992; MacMahon et al. 1992; Morgello 1992; Herbst et al. 1993). The first reports on the relationship between EBV and malignant lymphomas of the CNS or lymphomatoid granulomatosis were those of Veltri et al. (1982) and Hochberg et al. (1983). Extensive studies with high frequencies of Hodgkin's disease and Ki1 large cell anaplastic lymphomas (Anagnostopoulos et al. 1989), immunoblastic lymphomas, and lymphomas of the Burkitt type (Hamilton-Dutoit et al. 1991) also exhibit EBV involvement. In their series, Hamilton-Dutoit et al. (1991) found two main groups of AIDS-associated lymphomas: highly malignant lymphomas with abundant immunoblasts, which were 65% EBV positive, and lymphomas of the Burkitt type, which were 20% EVB positive. The EBV is thought to be involved in approximately 50% of AIDS-associated lymphomas (G. Niedobitek and Herbst 1991). The pathogenetic significance of EBV is also stressed by other researchers (Ambinder and MacMahon 1992; D'Amore et al. 1991; De Angelis et al. 1992; Bashir and Purtilo 1991; Bashir et al. 1989; Baumgartner et al. 1989; Borisch-Chappuis et al. 1990; Broder 1991; Hochberg and Miller 1988; Knowles et al. 1989; Nakhleh et al. 1991; Pedneault et al. 1992; Ruiz Marcellan et al. 1991; So et al. 1986; Vital et al. 1992).

Of our 17 cases of malignant lymphomas of the CNS, 10 were examined by in situ hybridization to detect EBV (carried out at the Institute of Pathology, Klinikum Steglitz, Freie University of Berlin Director: Prof. Dr. H. Stein). Of these one was negative and nine exhibited a definitely positive reaction (see Table 3.14). In perivascular infiltrates, the positive reaction generally affected large lymphoid tumor cells, whereas added small lymphoid cells were negative and must be regarded as reactive cells. On the other hand, single cells in the Virchow-Robin space and in the neuropil were strongly reactive and were thus identified as lymphoid tumor cells.

Also particularly interesting in this connection is the detection of EBV in four cases of fatally progressing B-cell lymphoproliferative syndrome after allogeneic bone marrow transplantation (M. Simon et al. 1991). Largely unclear are the relationships between the origin of a lymphoma in the context of AIDS and possible infection with the recently discovered human



a

b

Fig. 3.56 a, b. Cerebral lymphoma in AIDS. **a** Detection of EBV by in situ hybridization. (Patient no. 6, Table 3.14) ×60. **b** Several EBV-infected cells in a perivascular space of the white matter. In situ hybridization, ×40

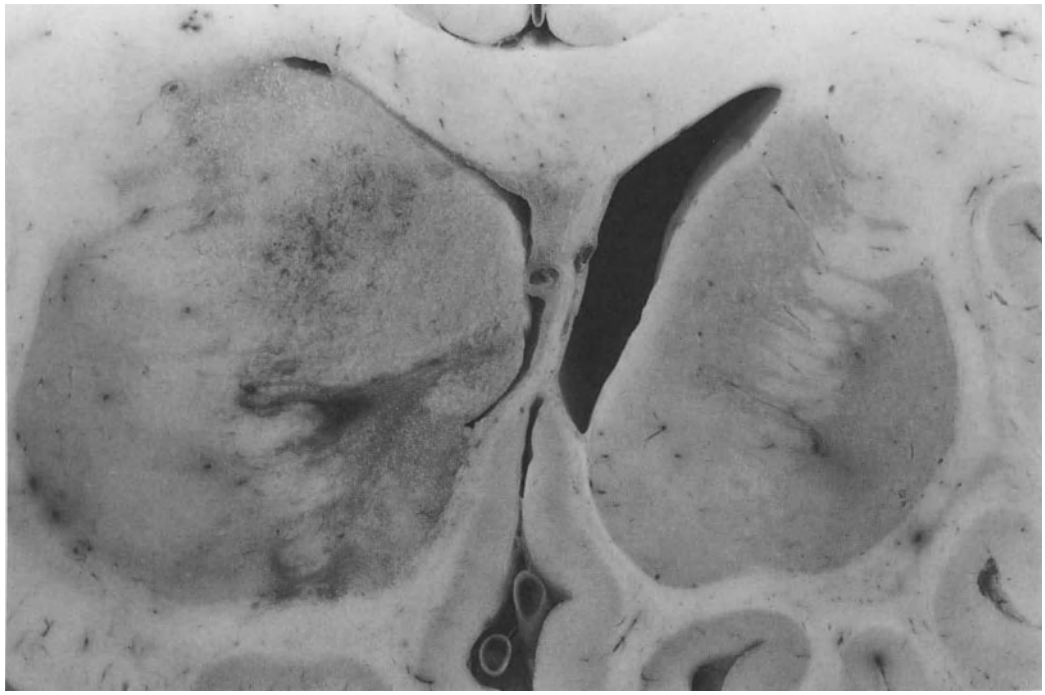


Fig. 3.57. Cerebral lymphoma in AIDS. Macroscopic findings: ill-defined tumor infiltrate in the area of the head of the caudate nucleus, internal capsule, and putamen with finely granular section and compression of the left lateral ventricle; circumscribed infiltration also in the pellucid septum. (Patient no. 10, Table 3.14)

B-lymphotropic virus, which is morphologically close to the herpesviruses and converts human B-lymphocytes into large mono- and binuclear cells with intranuclear and plasma inclusion (Salahuddin et al. 1986).

Some reports in the literature concern the activation of the c-*myc* oncogene in malignant lymphomas (Höfler 1988, 1990; Mitani et al. 1988; Subar et al. 1988). Among 16 cases of AIDS-associated lymphomas in 12 tumors Subar et al. (1988) found a c-*myc* gene rearrangement, while EBV sequences or proteins were detectable in only six tumors. A comprehensive study confirmed c-*myc* mRNA overexpression particularly in lymphomas with a high degree of malignancy, as are predominant in AIDS (Höfler 1988).

At present there is no evidence of a direct connection between HIV and malignant B-cell proliferation. The possible relationships, however, are discussed in the literature (Beissner et al. 1987; Nakhleh et al. 1989).

Pathology

Macroscopic Findings

In accordance with our own experience, the macroscopic findings in the literature are described as varyingly large, soft, gray-red tumor infiltrates with generally ill-defined margins (Fig. 3.57). In AIDS patients these are more frequently multi-central than usual (Vinters and Anders 1990) and often tend to necrosis (Di Carlo et al. 1986; Morgello et al. 1990; Sotrel 1989). It seems that primary CNS NHL are present as macroscopically visible tumor masses, whereas secondary infiltrates in systemic disorders or main tumor localizations in other organs are often not visible macroscopically and produce only more or less discrete angiocentric findings. The tendency of the secondary infiltrate to spread into leptomeninges, cranial nerves, and spinal roots is also stressed (Sotrel 1989). However, in the course of primary NHL of the CNS leptomeningeal involvement may occur (Freeman et al. 1986). A primary CNS NHL in a child (not an AIDS case) without intracranial tumor masses was reported by G. R. Jones et al. (1985). Here the diagnosis could be made only by liquor cytology. The cytologic examination of the cerebro-spinal fluid appears to be sensitive in the diagnosis of lymphoma and cryptococcal meningitis (Alappattu et al. 1987). A case was also

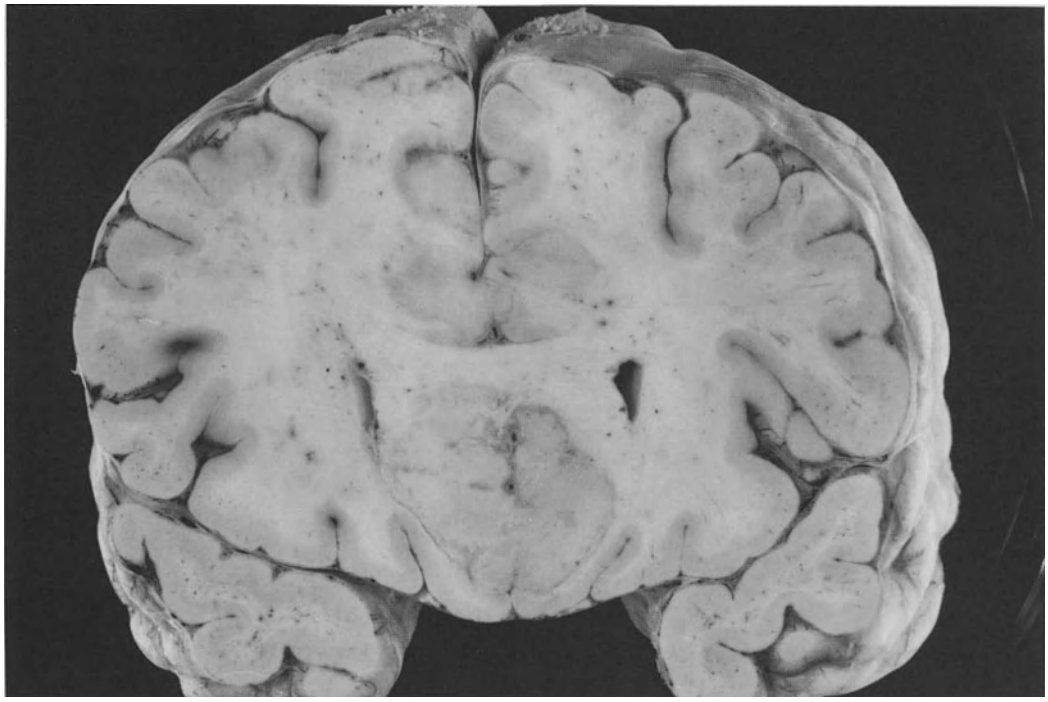
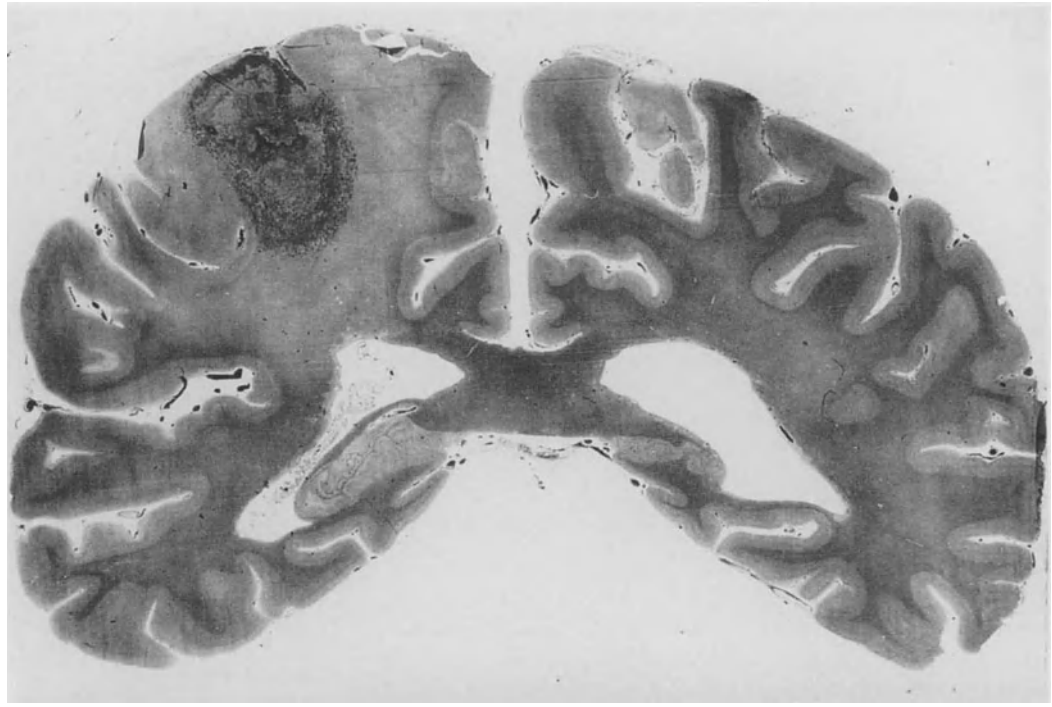


Fig. 3.58. Cerebral lymphoma in AIDS. Multicentric lymphoma with tumor infiltrates of varying size in the gyrus rectus, bilateral; in the gyrus cinguli, bilateral; and in the superior frontal gyrus, right. Small circumscribed tumor infiltration also in the adjacent part of the corpus callosum. (Patient no. 16, Table 3.14)

Fig. 3.59. Cerebral lymphoma in AIDS. Large tumor infiltrate in the mesencephalon with extension from the lamina tecti to the substantia nigra; distinct distension of the mesencephalon; aqueduct of the midbrain discernible in the middle of the infiltrate. (Patient no. 14, Table 3.14)



a

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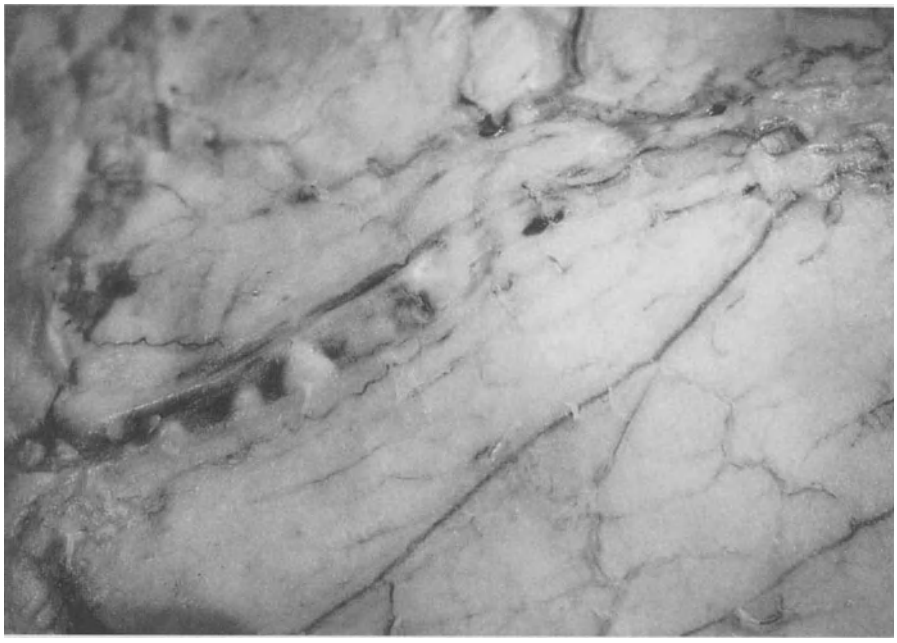
Fig. 3.60 a, b. Cerebral lymphoma in AIDS. **a** Large solitary tumor infiltrate in the cortex and subcortical cerebral white matter of the parietal lobe of the right cerebral hemisphere. Distinct perifocal edema. Double-hemisphere whole mount; H&E. **b** Lymphoma infiltration of the leptomeninges over the nodular tumor focus. (Patient no. 1, Table 3.14) H&E, ×4



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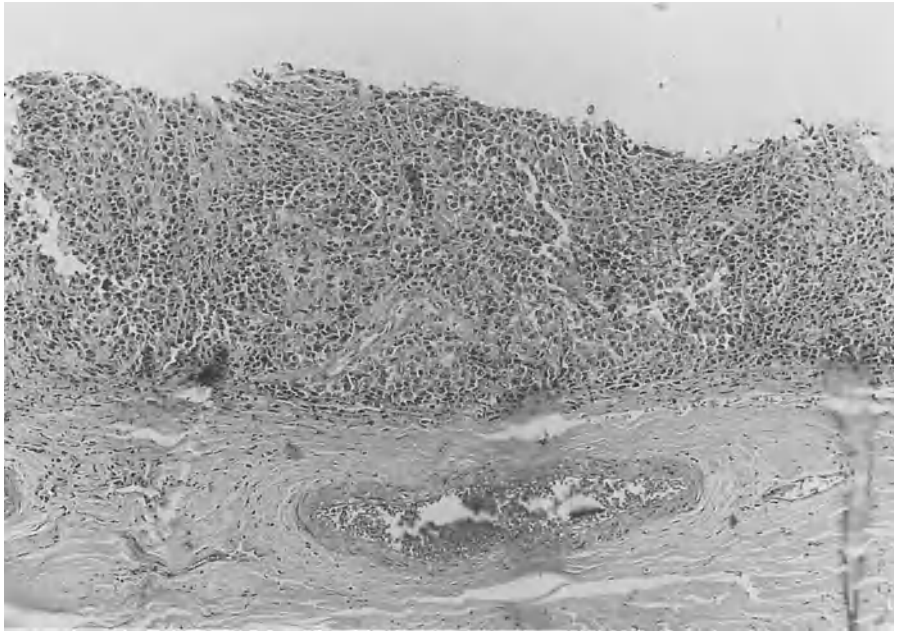


b

reported in the large series of John and Nabarro on malignant lymphomas of the CNS (1955) in which the tumor infiltrates were detectable only microscopically.

Tumor infiltrates can occur in all sections of the CNS, but sites of predilection include the deep cerebral gray matter, periventricular white matter, corpus callosum, and cerebellar vermis (Vinters and Anders 1990; Figs. 3.58–3.60). Solitary or multicentric in-

Fig. 3.61 a, b. Cerebral lymphoma in AIDS. **a** Micronodular lymphoma infiltrate of the dura mater along one branch of the middle meningeal artery. **b** Lymphoma infiltrate of the dura mater over the cross-section of an arterial branch. (Patient no. 12, Table 3.14) H&E, ×4

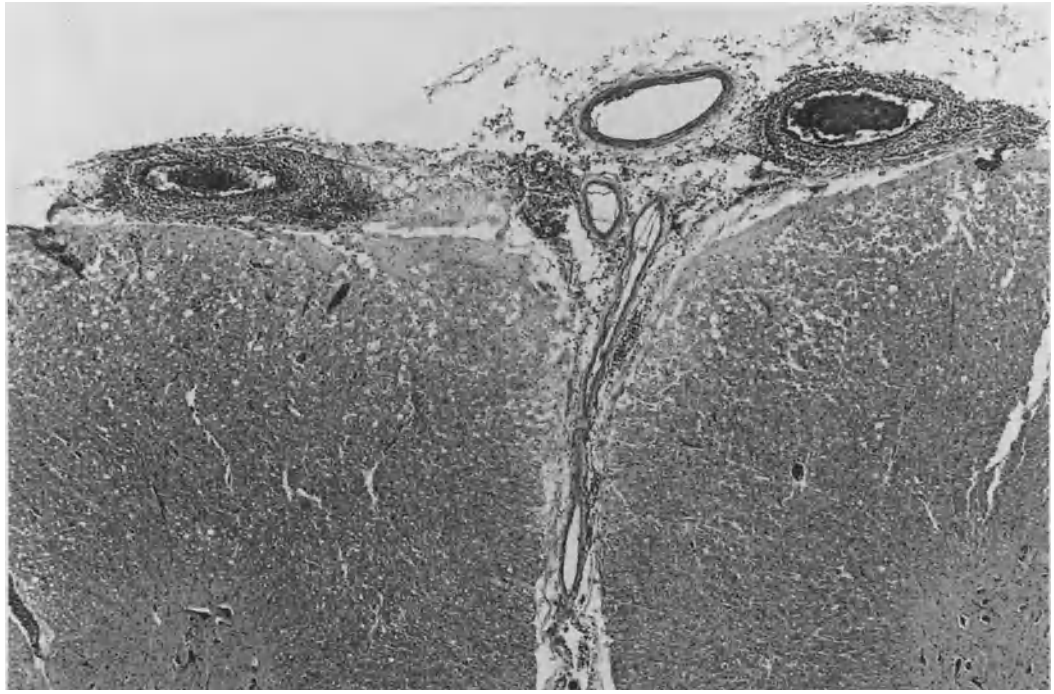


Fig. 3.62. Perivascular lymphoma infiltration in the pia mater of the spinal cord in a case of multicentric lymphoma of the brain. (Patient no. 16, Table 3.14) H&E, ×4

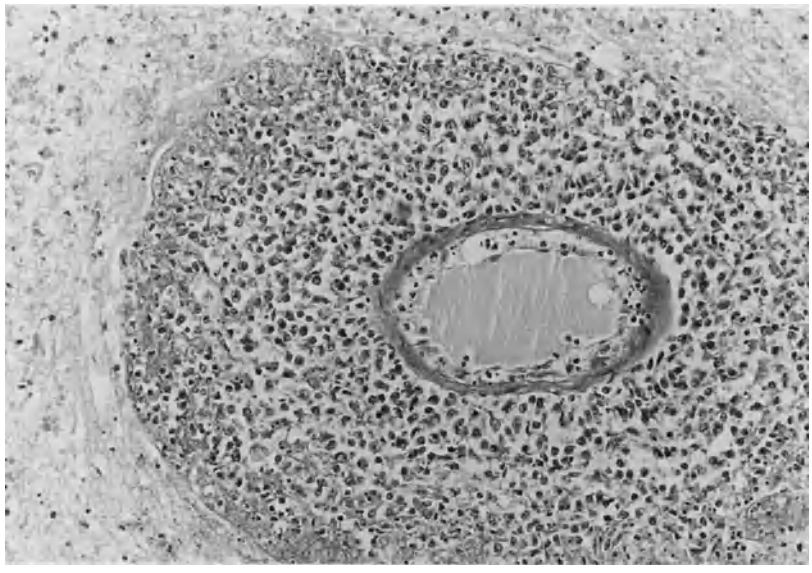
tracranial tumor infiltrates are more frequently found supratentorially (Jellinger and Paulus 1992; Merkel and Hansmann 1986; Riverola et al. 1991). The series of Hochberg and Miller (1988) included in addition to AIDS patients 56 cases of supratentorial and 21 of infratentorial localization. These authors described four manifestations as typical: solitary or multiple nodules, diffuse meningeal or periventricular infiltrates, uveal or vitreous deposits (uveitis/vitreitis), and intradural spinal masses. The localization of CNS NHL in AIDS corresponds to that of primary malignant lymphomas in other groups of patients in whom there is no known connection with an immunodeficiency syndrome (Helle et al. 1984). Other authors also report the supratentorial localization to be the more frequent (Davenport et al. 1991; Kawakami et al. 1985; Letendre et al. 1982; O'Neill et al. 1989).

A single observation in our own series revealed involvement of the dura mater with micronodular infiltration of the outer layer in a large cell anaplastic lymphoma of the lung (Fig. 3.61). The nodular infiltrates (1–3 mm in diameter) were located along the arterial ramifications and represented the only intracranial manifestation.

According to the literature available to us, malignant lymphoma of the spinal cord is rare, in non-AIDS patients (Hautzer et al. 1983; Mitsumoto et al. 1980) and in AIDS patients (Herbst et al. 1993). Leger et al. (1992) reported on a progressive polyradiculopathy in an AIDS patient, the cause of which was recognized autoptically as an infiltration of the leptomeninges, the lumbal cord and the anterior and posterior roots with a B-cell immunoblastic lymphoma. Two cases in our series showed perivascular lymphoma infiltration in the pia mater of the spinal cord and in the white matter of the anterior and posterior horns (Fig. 3.62). The invasion of the meninges by malignant lymphomas of the brain, in general, is confirmed by neuropathology (Berkefeld et al.; Da Paz, Kolmel 1992).

Microscopic Findings

The reported microscopic findings of AIDS-associated lymphomas of the CNS have generally been made on autopsy specimens (Levine 1988; Vinters and Anders 1990), but some were also from stereotactic tumor biopsies (Feiden and Backmund 1991; Feiden et al. 1989, 1990; Goldstein et al. 1990) or open surgery of the brain (Bergmann and Edel 1991; Nakamine et al.



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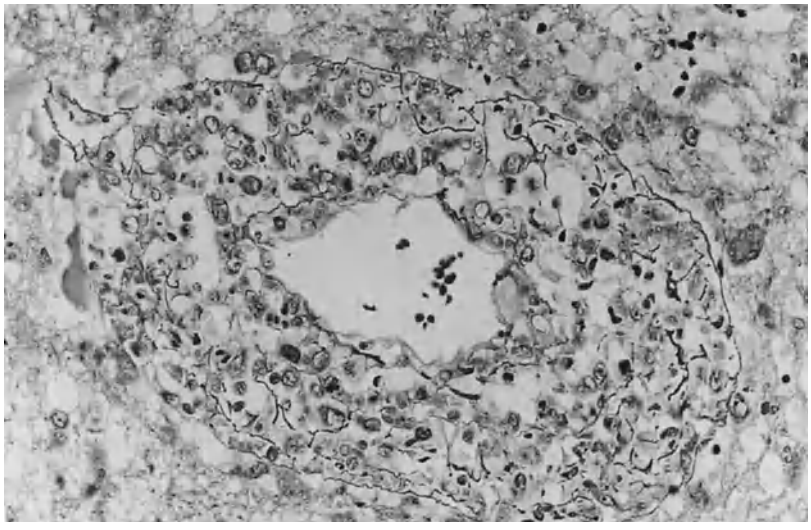

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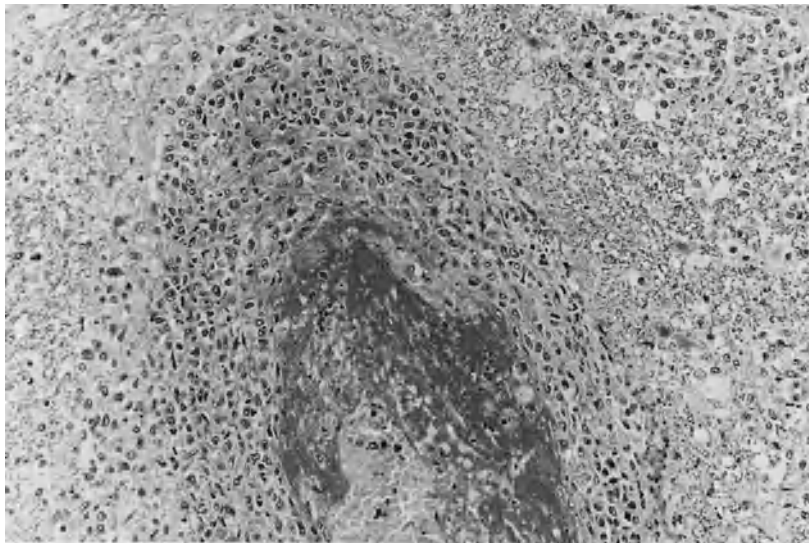

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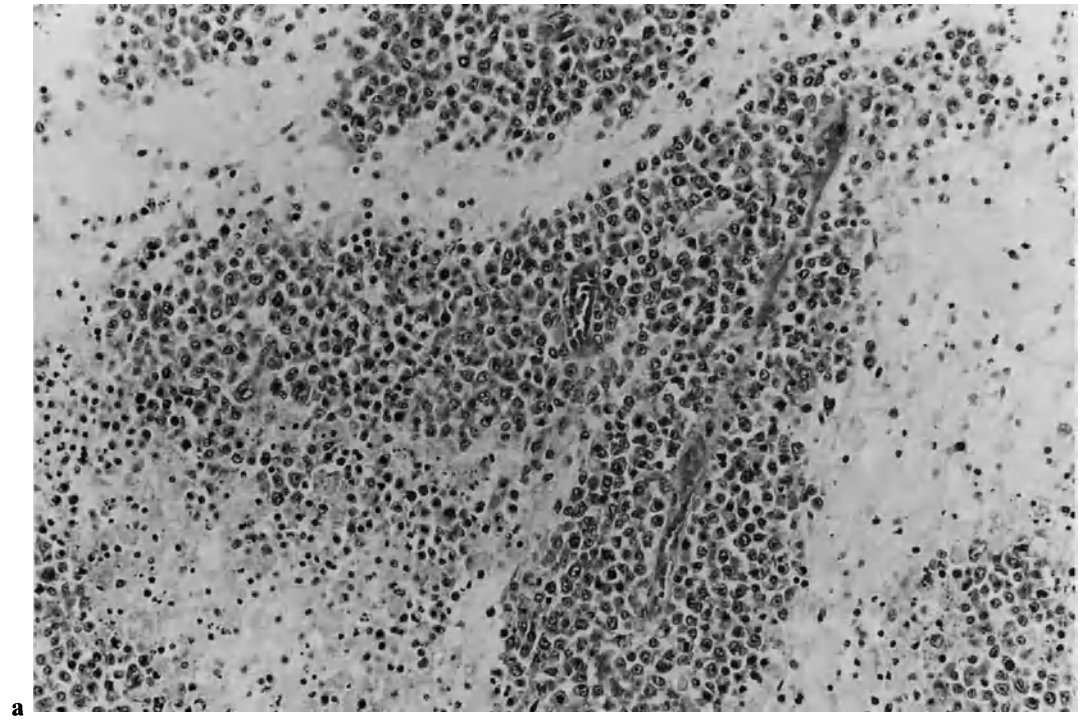

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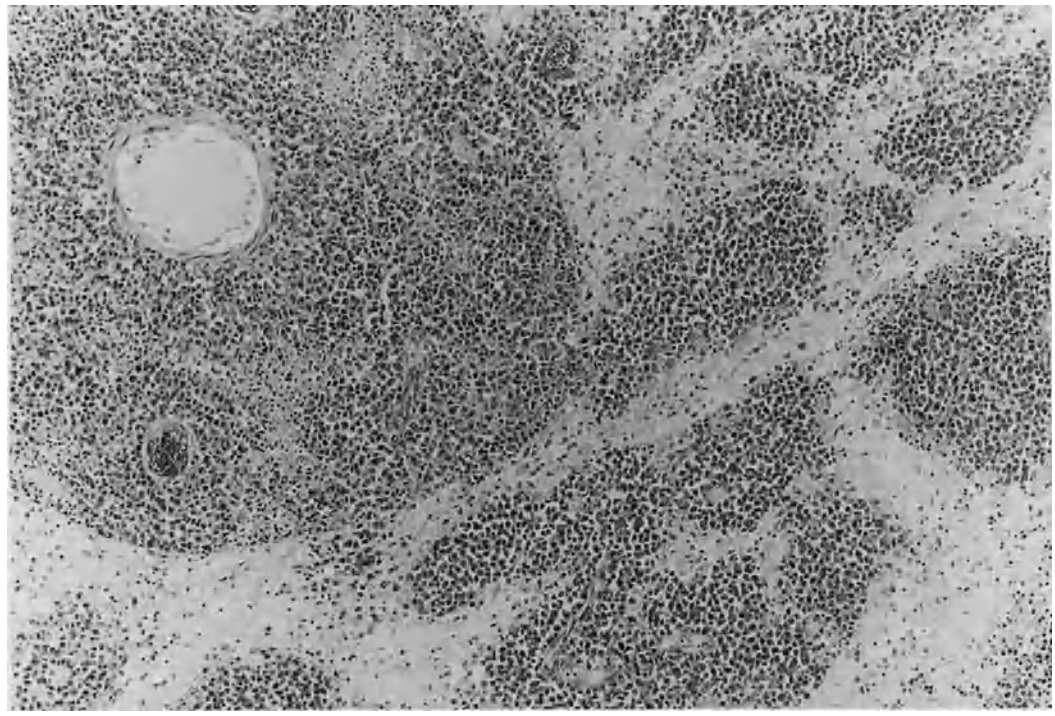


b

◀ **Fig. 3.63 a–c.** Malignant non-Hodgkin's lymphoma of the brain with angiocentric growth. (Patient no. 1, Table 3.14). **a** H&E, ×20. **b** Vascular wall infiltrate with splitting up of the fiber systems. Gomori silver stain, ×40. **c** Small blood vessel with lymphoma infiltration of the vascular wall and blockage of the lumen through fibrinous thrombosis. Glycol methacrylate; H&E, ×20

Fig. 3.64 a, b. Malignant non-Hodgkin's lymphoma of the brain with angiocentric growth. (Patient no. 3, Table 3.14). **a** Wide mantlelike infiltrate around blood vessels. Giemsa stain, ×40. **b** Wide mantlelike infiltrate around smaller blood vessels with confluence to larger complexes. Giemsa stain, ×20

1989). Although extensive tumor masses may dominate the morphological picture both macroscopically and microscopically, the fundamental growth pattern of cerebral lymphoma consists in an angiocentric dissemination (Murphy et al. 1989; Sotrel 1989; Vinters and Anders 1990; Fig. 3.63, 3.64), in the course of which a perivascular growth can be observed, generally in addition to a vascular wall infiltration (Snider et al. 1983 b; So et al. 1986; Wrotnowski et al. 1985).

When only weakly enlarged, the perivascular infiltrates can sometimes hardly be distinguished from inflammatory infiltrates (Sotrel 1989). The characteristic microscopic pattern led to the term neoplastic angioendotheliosis (Kitagawa et al. 1985; Mori et al. 1985). The perivascular growth accompanying small blood vessels in the periphery of nodular tumor infiltration often leads to underestimation of the tumor size (Murphy et al. 1989). The angiocentric growth has been illustrated and described in detail in extensive representations in the older literature (Bailey 1929; Gerhartz 1951; Kernohan and Uihlein 1962; Zülch 1951). We have seen the perivascular growth pattern in all our cases and regard it as especially typical of CNS NHL.

In silver-staining preparations, vascular wall infiltration appears clearly with splitting of the fiber system. Sometimes there is restriction and clotting of the lumen. Necroses occurring in the tumor infiltrates as a result of clotting can also be regarded as typical.

AIDS-associated lymphomas of the CNS tend to necroses regardless of therapeutic measures (Di Carlo et al. 1986; Feiden and Backmund 1991). Bleeding in the area of tumor infiltrates from NHL of the CNS is also understandable and is to be expected (Feiden and Backmund 1991).

The two systems for cytological classification of malignant lymphomas are the Kiel Classification (Lennert and Feller 1990) and the Working Formulation for Clinical Usage of the National Cancer Institute (1982). The prognostically relevant Kiel Classification has also been shown to be useful in the cytological classification of CNS NHL (Allegranza et al. 1984; Murphy et al. 1989; Paulus et al. 1992; J. Simon et al. 1987), although especially in AIDS these lymphomas often exhibit particularly pronounced pleomorphism and varying cellular composition (Morgello et al. 1990).

The vast majority of CNS NHL in AIDS are B-cell lymphomas (Egerter and Beckstead 1988; Formenti et al. 1989; Garson et al. 1988; Gill et al. 1985; McGrath et al. 1991; Hamilton-Dutoit et al. 1991; Meeker et al. 1991; Morgello et al. 1989; Paulus et al. 1992; So et al. 1986; Xerri et al. 1990; Zimmer et al. 1992) and are associated with a high degree of malignancy (Hochberg and Miller 1988; Murphy et al. 1989; Vinters and Anders 1990; Fig. 3.65). Immunohistochemical classification of CNS NHL in the era before recognition of AIDS showed a cytological conformability to lymphomas outside of the CNS (Taylor et al. 1978). There are only few cases of T-cell lymphomas noted in the literature (Gold et al. 1990). Ghali et al. (1990) reported an HIV-positive patient with a T-lymphoproliferative disorder (no CNS involvement) which was characterized basically by large granular lymphocytes (natural killer cells); immunohistochemically, however, only CD2 was expressed (Ghali et al. 1990). A pulmonary T-cell lymphoma in AIDS was described by Nasr et al. (1988), and a T-lymphoblastic lymphoma in an AIDS patient with infiltration of the lymph nodes and bone marrow and evidence of tumor cells in the cerebrospinal fluid was reported by Presant et al. (1987). Among the 24 cases of malignant brain lymphomas reported by Murphy et al. (1989) (apparently without AIDS cases) there were no T lymphomas, but there was one case of "T-cell-rich B-cell lymphoma" corresponding to the description by Ramsay et al. (1988).

Although the vast majority of CNS NHL are B-cell lymphomas, T-cell lymphomas do not seem to be as extraordinary as was once thought (Morgello et al. 1989). These authors reported eight patients with primary or secondary T-cell lymphomas of the CNS, but in the report there was no mention of an HIV infection.

Among ten cases of primary CNS NHL in the series of Bogdahn et al. (1986) there were two T-cell lymphomas (no mention of HIV infection). With a lack of a corresponding marker expression, in four cases of AIDS-associated CNS NHL there was mention of non-B-, non-T-lymphomas (Hamilton-Dutoit et al. 1991; Joachim et al. 1985). In our study material, the lymphomas with manifestation in the CNS observed in AIDS patients were mainly B-cell lymphomas. Only one case of a large cell anaplastic lymphoma lacked marker expression. One other case (number 2 in Table 3.14) was classified as Hodgkin's disease. Judging by their biological behavior, the CNS NHL of the AIDS patients are quite predominantly highly malignant tumors (McGrath et al. 1991; Joachim et al. 1985; Levine 1988; Mitrou 1991; Sotrel 1989; Vinters and Anders 1990). Clinically primary central nervous system lymphoma in AIDS patients presents a more aggressive variant than in non-AIDS patients (Diamond et al. 1990). However, there are also reports of lymphomas in AIDS patients with a low degree of malignancy (Schlote et al. 1987). Our own cases must be

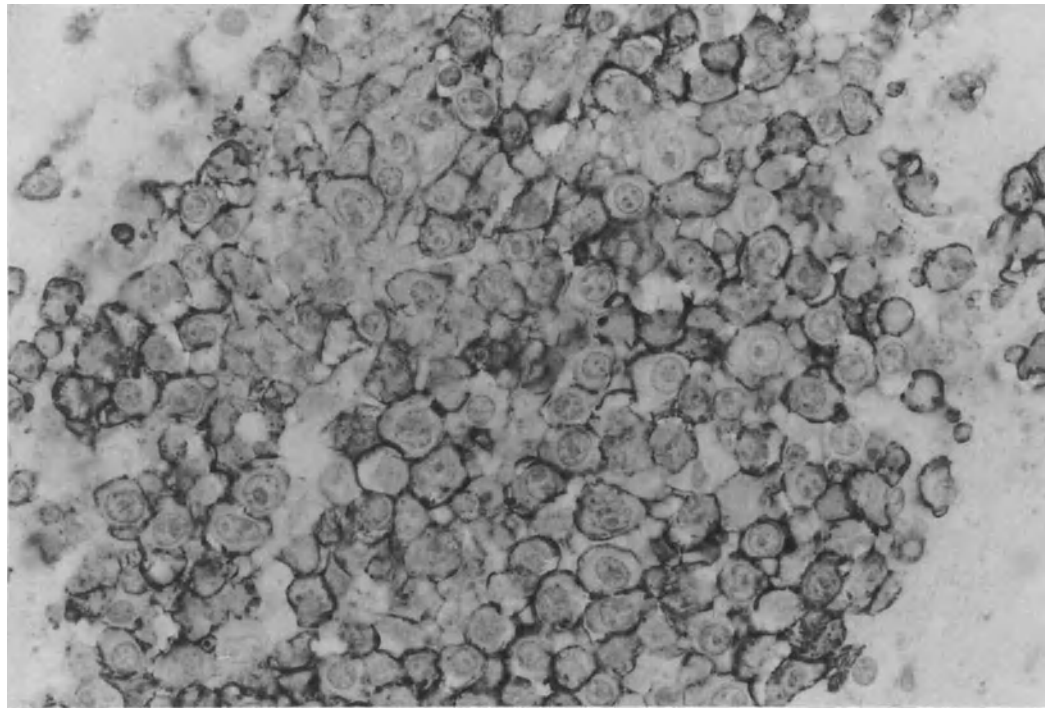


Fig. 3.65. Malignant non-Hodgkin's lymphoma of the brain. Highly malignant B-cell lymphoma (immunoblastic). B-cell marker, CD20, DAKO L26; ×60

termed highly malignant; they generally exhibited a high mitosis rate, and only two cases with a low mitosis rate were classified as being of low malignancy.

For the cytological classification of the CNS NHL, the Kiel Classification has been used with success (Allegranza et al. 1984; Bergmann and Edel 1991; Bogdahn et al. 1986). In reports on large numbers of CNS NHL cases in AIDS, however, the Working Formulation (1982) has generally been used (Di Carlo et al. 1986; Formenti et al. 1989; Gill et al. 1985; Morgello et al. 1990; So et al. 1986; Ziegler et al. 1982). The most frequent forms of CNS NHL in AIDS are immunoblastic lymphomas (Egerter and Beckstead 1988; Formenti et al. 1989; Gill et al. 1985; Rosenblum et al. 1988; So et al. 1986), small noncleaved cell lymphomas (Formenti et al. 1989; Rosenblum et al. 1988; So et al. 1986), diffuse histiocytic lymphoma (Snider et al. 1983b), large cell lymphoma (some mixed with lymphoplasmacytoid infiltrates) (Morgello et al. 1990), large cell high-grade non-Hodgkin lymphoma, centroblastic lymphoma, multicentric immunoblastoma (Iglesias-Rozas et al. 1991), centroblastic polymorphous, and centroblastic-centrocytic (Bergmann and Edel 1991; Merkel and Hansmann 1986). Cytologically, however, all cell types in the Working Formulation (National Cancer Institute 1982) are encountered in CNS NHL (Xerri et al. 1990). Nonetheless, the literature refers to the pleomorphic cytological picture of cerebral lymphomas, which makes classification according to the "Updated Kiel Classification" very difficult and a division of the highly malignant B-cell lymphomas of the brain into small-cell and large-cell forms seems adequate (Paulus et al. 1992). The literature repeatedly stresses the tendency of CNS NHL to mixed pleomorphic infiltration of malignant tumor cells, also with mature lymphocytes and macrophages (Sotrel 1989). The majority of cases exhibit at least accompanying mixed polyclonal infiltrates of B- and T-lymphocytes, plasma cells, and lymphoplasmacytoid cells (Di Carlo et al. 1986; Morgello et al. 1990). The description of our own cases follows the Kiel Classification (Table 3.14).

Table 3.14. Malignant lymphomas of the CNS: case descriptions

No.	Age (years)	Sex	Macroscopic findings and location	Manifestation in other organs	Classification	EBV (ISH)	LMP (CS 1–4)
1	47	M	Solitary nodular mass (about 30 mm in diameter): right parietal lobe, cortex and subcortical white matter	–	B-cell lymphoma; high-grade malignancy (centroblastic, pleomorphic); admixture of immunoblasts (5 %), macrophages (10 %), few centrocytic elements, and few T-cells	+	+
2	61	M	Pons, origin of n. trigeminus	Liver, spleen, lymph nodes, kidney	Lympho-granulomatosis (Hodgkin's disease)	+	+++
3	27	M	Three nodular masses (20–30 mm in diameter): putamen, n. caudatus, thalamus, white mater of the left insula, pons	–	B-cell lymphoma; high-grade malignancy (immunoblastic)	+	+
4	45	M	NV (pons)	–	B-cell lymphoma; intermediate to high-grade malignancy (centroblastic--centrocytic/ centroblastic	+	+
5	43	M	Nodular masses: cerebellum (about 50 mm in diameter) n. amygdalae left (15 mm in diameter) n. caudatus right (5 mm in diameter)	–	B-cell lymphoma; low-grade malignancy (lymphoplasmacytoid immunocytoma, pleomorphic subtype)	NP	+
6	33	M	NV	Systemic disease, lung, lymph nodes	B-cell lymphoma; low-grade malignancy (centroblastic--centrocytic); admixture of lymphocytes, macrophages and plasmocytoid elements, T-cells about 10 %	+	+
7	42	M	Large nodular mass with extension in the frontal, parietal, and occipital lobes and in the basal ganglia of the left hemisphere	–	B-cell lymphoma; high-grade malignancy (centroblastic, pleomorphic); admixture of T-cells (10 %), KP1-positive macrophages (5 %), centrocytoid elements and few immunoblasts	NP	++
8	45	M	NV	–	B-cell lymphoma; high-grade malignancy (centroblastic); admixture of few T-cells (2 %), centrocytoid and plasmacytoid elements	+	+

Table 3.14. Continued

No.	Age (years)	Sex	Macroscopic findings and location	Manifestation in other organs	Classification	EBV (ISH)	LMP (CS 1–4)
9	37	M	NV (plexus choroideus, paraventicular white matter, cerebellum, tractus opticus left)	–	B-cell lymphoma; low-grade malignancy (lymphoplasmacytoid immunocytoma); admixture of T-cells (10%), and few KP1-positive macrophages, plasmacytes (20%)	+	+
10	43	M	Nodular masses (about 30 mm in diameter): n. caudatus left, s. nigra, pons, diffuse infiltration of the leptomeninx	–	B-cell lymphoma; high-grade malignancy (centroblastic)	+	+
11	25	M	NV (putamen, n. caudatus, capsula interna, s. nigra white mater of the cerebellum)	–	B-cell lymphoma; high-grade malignancy (centroblastic)	+	0
12	43	M	Micronodular infiltration of the dura mater	Systemic disease	large cell anaplastic lymphoma; high-grade malignancy (no further classification)	NP	+
13	31	M	NV (paraventricular white matter)	Lung	B-cell lymphoma; high-grade malignancy (centroblastic, pleomorphic)	NP	NP
14	36	M	Solitary nodular mass (25 mm in diameter): mesencephalon	–	B-cell lymphoma; high-grade malignancy (centroblastic)	NP	+
15	51	M	Nodular mass (about 40 mm in diameter): caput n. caudati, capsula interna, corpus callosum, centrum semiovale, fornices	–	B-cell lymphoma; high-grade malignancy (centroblastic, pleomorphic); admixture of few T-cells (2%) and KP1-positive macrophages	0	++
16	44	M	Four nodular masses: gyri recti, on either side (40:40:35 mm) gyrus cinguli, on either side (20:15 and 10:10 mm) gyrus frontalis superior right (10:10 mm)	–	No classification (autolytic changes; immunoblastic?)	NP	++
17	34	M	nodular mass (20 mm in diameter): n. caudatus, c. interna, putamen, left	–	B-cell lymphoma; high-grade malignancy (centroblastic, pleomorphic)	NP	++

ISH, In situ hybridization; LMP, latent membrane proteins; NV, not visible; NP, not performed.

■ Spongiform and Vacuolar Changes of the CNS Tissue

Introduction

Sponginess, spongiosity, vacuolar changes, vacuolation, spongy degeneration, and spongiform-dystrophic syndrome are all names frequently used to describe unspecific damage of the brain tissue secondary to hypoxia, opportunistic infection, edema, etc. The indiscriminate use of these terms has led to some confusion. The various terms commonly found in the literature to refer to a light-microscopically discernible spongiform loosening of the gray or white matter, with vacuoles that are of varying size and usually optically empty, have been the subject of critical discussion (Peiffer 1984). Here, disregarding the unclear etiopathogenetic aspects, classical neuropathology also describes such syndromes as Creutzfeldt-Jakob disease and Canavan's disease (Becker and Yates 1991).

In view of the findings made from our material, we differentiate between:

- Spongiform encephalopathy
- Spongiform leukoencephalopathy
- Vacuolar leukoencephalopathy
- Spongiform and vacuolar changes of the substantia nigra
- Wernicke's encephalopathy

Since myelin damage (myelinolysis) is involved at least partially in the changes described, we include processes with more extensive findings and demyelinations in this section:

- Multifocal pontine leukoencephalopathy
- Central pontine myelinolysis
- Multiple sclerosis-like leukoencephalopathy

The CNS presents, in HIV infection, a variety of vacuolar and spongiform changes that are morphologically very well defined: vacuolar myelopathy, vacuolar leukoencephalopathy (VL), spongiform encephalopathy, and spongiform leukoencephalopathy. The morphology each of these changes is very constant, and it seems that they belong to some specific conditions, although the etiology and pathogenesis are actually not known and are presumably nonuniform.

Spongiform Encephalopathy

Spongiform encephalopathy (strictly speaking, polioencephalopathy) pathologically identical to changes found in Creutzfeldt-Jakob disease has been described in a 28-year-old patient with AIDS (Schwenk et al. 1987b); this case very probably represents a rare coincidence of HIV infection with Creutzfeld-Jakob disease in a young person. At the time of publication of this case we began to look for similar changes in our material, and we found spongiform-like changes in five AIDS patients with dementia (Artigas et al. 1989b, 1990c). The changes appear in the first three layers of the cerebral cortex, and in the nucleus caudatus and thalamus (Fig. 3.66) in the vicinity of the ventricle surface. They are accompanied by slight astrocytosis and focal loss of neurons. These "spongiform" changes are not AIDS specific and have been described in a variety of degenerative brain diseases (Artigas et al. 1989), in alcohol encephalopathy, and in experimental thiamine deficiency (Schochet and Nelson 1991). The localization of the changes in the vicinity of the cerebrospinal fluid (CSF) may indicate that they are produced by toxic substances present in the CSF. In the study of our material we have frequently found similar changes, in varying degrees of intensity, in patients with and without dementia (63 out of 180 cases in our series).

Similar findings have been described in a 25-year-old man clinically with HIV encephalopathy, with prominent cortical atrophy and neuronal loss (Gray et al. 1991a). Goldwater et al. (1985) described fibrillar material bearing structures resembling scrapie-associated fibrils on electron microscopy in the hippocampus of a patient with AIDS encephalopathy and spongiform changes. The structures illustrated by these authors are very probably remnants of hyperplastic astrocytes with large amounts of fibrillary glial proteins. We ourselves have observed such structures in the spinal cord in a case of vacuolar myelopathy with strong astrocytosis.

Interesting enough in this regard, molecular biological studies have shown stem loops in HIV and prion protein (causal agent of Creutzfeldt-Jakob disease) mRNAs (Wills and Hughes 1990), as well as an accumulation of transcripts coding for prion protein in astrocytes in HIV infection (Müller et al., 1992).

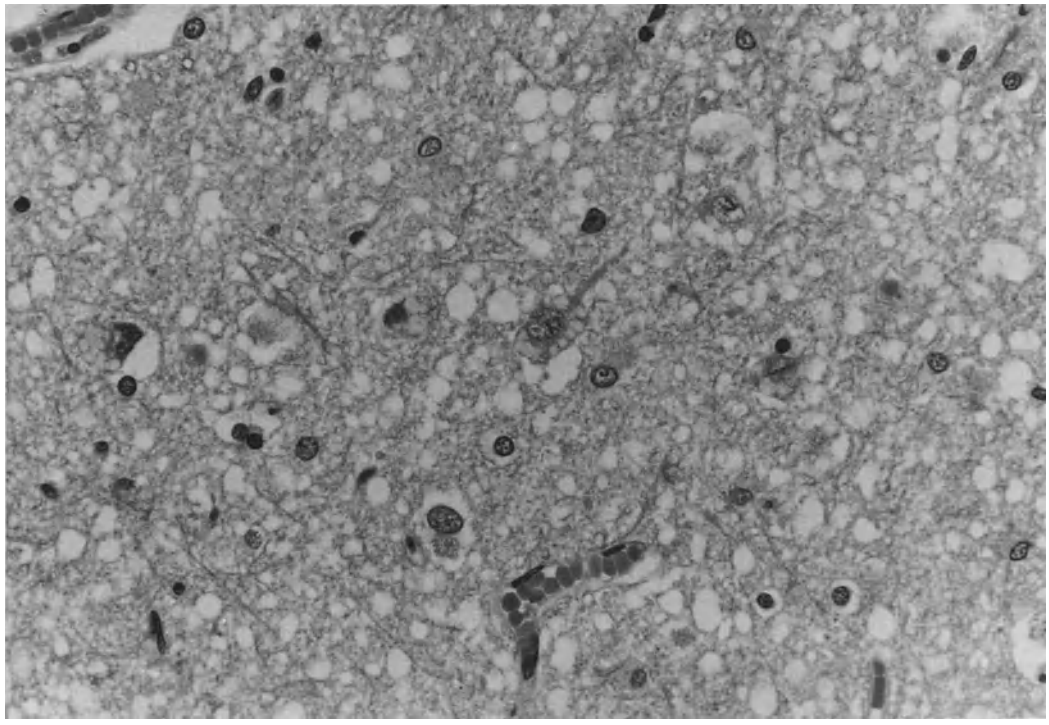


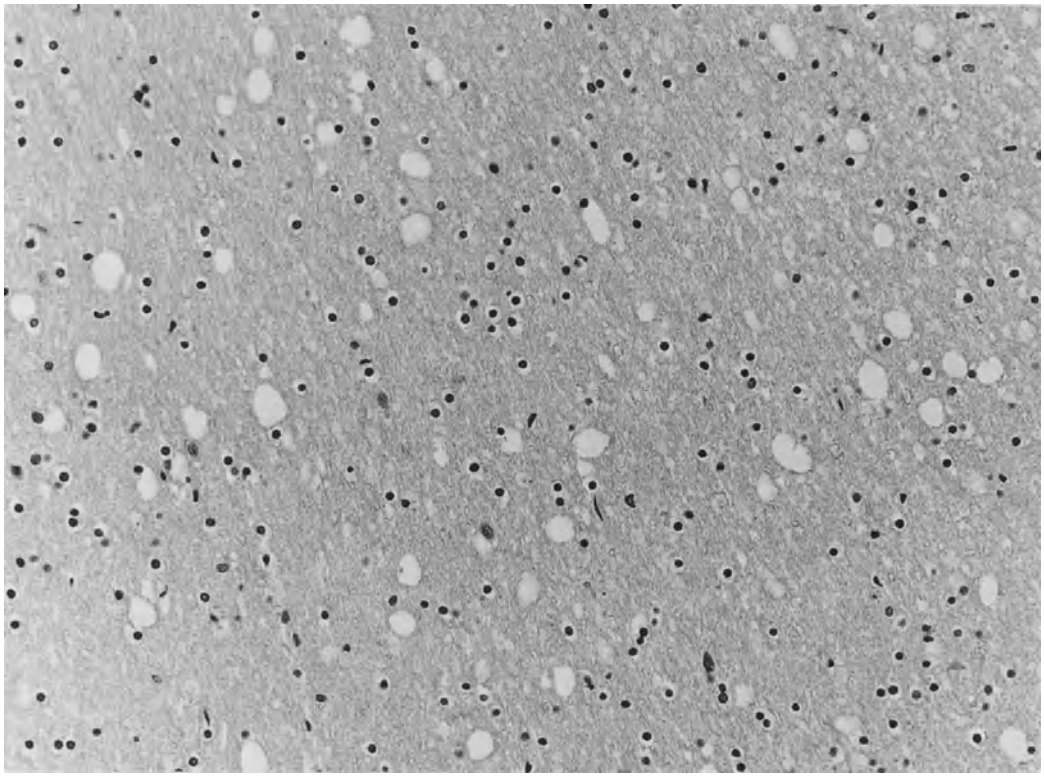
Fig. 3.66. Spongiform encephalopathy (polioencephalopathy). Typical spongiform pattern of the neuropil in thalamus. Note the capillary at the bottom of the picture without surrounding shrinking artifacts. Glycol methacrylate; H&E, ×20

Spongiform Leukoencephalopathy

Navia et al. (1986) described "vacuolation of the white matter consisting of scattered single vacuoles involving the centrum semiovale, internal capsule, brainstem, and cerebellum." These authors found such changes in 51% of their cases. We have seen similar changes as "circumscribed areas of a delicate spongiosity and randomly dispersed vacuoles" in the white matter of cases with spongiform encephalopathy, although we earlier misnamed this condition as "vacuolar leukoencephalopathy" (Artigas et al. 1989b, Fig. 3.67a). This condition, spongiform leukoencephalopathy, has been not included in the neuropathological consensus about HIV infection in CNS (Budka et al. 1991). However, it is very frequent, 44% in our material, and it is morphologically well characterized. It consists of rounded vacuoles 10–50 μm in diameter in the white matter of the brain, brain stem, and cerebellum, and in rare cases even in the spinal cord. The vacuoles are smaller than those from VL, and characteristically they never contain axons or macrophages. Occasionally, cytoplasmic remnants or altered cellular nuclei, probably of oligodendroglial cells, are seen within the vacuoles. There is no tissue reaction of any kind to be seen. In severe cases the vacuoles increase in size and tend to coalesce. We performed immunocytochemical studies with antibodies against HIV and common opportunistic viruses with negative results.

Vacuolar Leukoencephalopathy

VL is characterized by numerous elliptic, oval or rounded vacuoles in the white matter of the cerebrum or brain stem and in the internal capsule (de la Monte et al. 1986). The cavities are larger than those of spongiform leukoencephalopathy and frequently contain axon remnants and/or one or two macrophages (Fig. 3.67b). They probably originate as a process of myelinolysis of thick myelin sheaths that envelop thick axons of long tracts. The etiology of this myelinolysis, and of the similar myelinolysis of vacuolar myelopathy, is unknown. In our experience we



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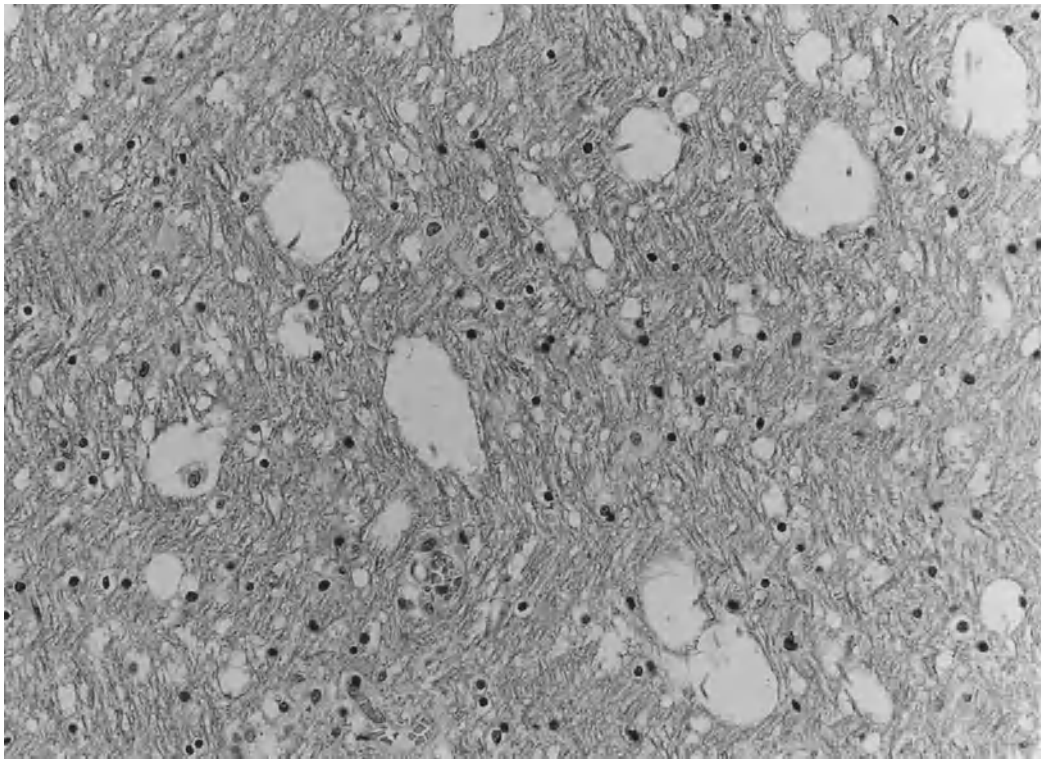

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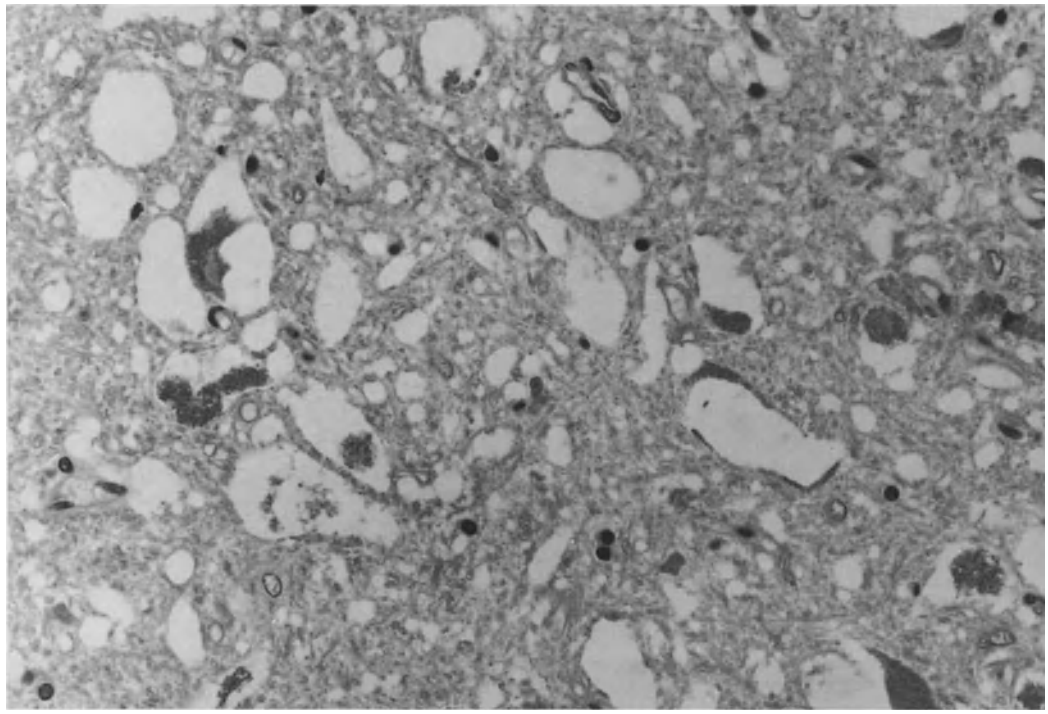


◀ **Fig. 3.67 a, b.** Illustration of the differences between the two entities of "spongiform" and "vacuolar" leukoencephalopathy (with identical magnification); differences in size, contour, and content. **a** Spongiform leukoencephalopathy. Numerous small round-oval, optically empty vacuoles with sharp borders within the white matter of the centrum semiovale. H&E, × 10. **b** Vacuolar leukoencephalopathy. Numerous larger vacuolar cavities with irregular borders, sometimes containing macrophages or axon remnants; internal capsule. H&E, × 10

Fig. 3.68. Spongiform and vacuolar changes of the substantia nigra. Small spongiform lesions in the neuropil and larger vacuolar cavities with cell remnants, mainly melanin granula; these larger cavities result apparently from cell swelling and necrosis. Glycol methacrylate; H&E, × 40

found VL within long tracts of the cerebrum and pons as well as in the centrum semiovale. We usually found VL in cases with HIV leukoencephalopathy and severe vacuolar myelopathy. In other cases it appears isolated in the tracts of the internal capsule. VL has been repeatedly described in AIDS patients (Horoupian et al. 1984; Rhodes 1987; Rhodes et al. 1989). A case with severe changes has been reported as multifocal vacuolar leukoencephalopathy by Schmidbauer et al. (1990b).

Spongiform and Vacuolar Changes in the Substantia Nigra

Some AIDS patients present with parkinsonism (Nath et al. 1987; Enzensberger 1989) or parkinson-like symptoms. An undue susceptibility of some patients with AIDS to drug-induced parkinsonism has also been reported (Edelstein and Knight 1987). We, for the first time, reported morphological changes of the substantia nigra in AIDS patients (Artigas et al. 1989c). In 16 out of 60 examined cases we found depigmentation of the substantia nigra, vacuolization of the neurons, neuron loss, and sponginess of the neuropil (Fig. 3.68). "Depigmentation," however, cannot be considered as a pathological change in young persons, who form the majority of patients in our series. Melanization of neurons in the substantia nigra is a physiological aging-related process (Hirano 1983, 1991). Current studies on our material show that the pigmentation of the substantia nigra macroscopically

and histologically correlates with the age of the patients. Therefore, the morphological symptom of "depigmentation" of the substantia nigra should be evaluated with great caution and criticism.

Furthermore, we observed vacuolization of the neurons with cell loss in a majority of cases and sometimes a fine spongiosity of the neuropil in the substantia nigra. The spongiosity is well delimited to this nucleus, the surrounding structures appearing as normal. In addition to a finely spongiform loosening of the neuropil, there was in some cases a coarse, irregular vacuolation with remnants of melanin granules as a result of cell swelling with ensuing cytolysis. Nerve cells also often showed nuclear swelling and karyolysis. However, the neuron depopulation that we have described has since been confirmed. Recently, a morphometric study of the substantia nigra in AIDS patients showed atrophy of neuronal bodies and a significant reduction in the number of neurons (lower than 25%; $p<0.01$) as compared to age-matched control persons (Reyes et al. 1991).

The significance and etiology of these changes remain obscure. In ultrastructural and immunocytochemical studies we have not found any opportunistic causal agent. Surprisingly, these changes, which we observed frequently in the first few years (in about 35% of all cases), have appeared only very rarely in more recent years.

Wernicke's Encephalopathy

Wernicke's encephalopathy has been reported in a small number of AIDS patients with and without a history of ethanol abuse (Burns et al. 1991; Foresti and Confaloneri 1987; Schwenk et al. 1990). It was described in one instance as a temporary complication of treatment with zidovudine (Davtyan and Vinters 1987). In five cases of our series we found morphological changes compatible with Wernicke's encephalopathy. In four there were perivascular hemorrhages in the periventricular tissue of the third ventricle and/or in the periaqueductal region, in one of the cases associated with sudden death. In one other case we found infiltration of macrophages and multinucleated cells containing p24 antigen in both corpora mammilaria. However, in none of these six cases was the clinical diagnosis of Wernicke's encephalopathy made.

Multifocal Pontine Leukoencephalopathy

Small, asymmetric foci of necrosis within the basis pontis, consisting of foci of vacuolation with loss of myelin and macrophage infiltration, have been observed in patients with AIDS (Vinters et al. 1987; De Girolami et al. 1992). These lesions may also show axonal injury with numerous axonal swellings as well as calcifications. They are very similar to the multifocal pontine lesions described by Breuer et al. (1978) in patients who received systemic and/or intrathecal chemotherapy and CNS radiation for brain tumors. We have observed such lesions in a few of our cases. Vinters et al. (1987) noted a predilection of these lesions for the pontocerebellar tracts of the basis pontis.

In some respects, the conclusions drawn from our observations deviate from the information in the literature. The distribution of the foci is irregular, we did not observe any calcification, and the macrophage infiltration is conspicuous in the immunohistochemical preparations. The etiology of this condition is unknown.

Central Pontine Myelinolysis

Central pontine myelinolysis has also been identified in a small number of cases of AIDS (Vinters and Anders 1990; Burns et al. 1991). We observed similar lesions in two cases of our autopsy series. The myelinolytic lesions were rather diffuse, without sharp limits, and affected almost all of the pons (Fig. 3.69). The histological findings, however, correspond largely to the original description given in the literature (Adams et al. 1959; Norenberg and Bruce-Gregorios 1991).

Multiple Sclerosis-like Leukoencephalopathy

Multiple sclerosis-like leukoencephalopathy has been described in ten patients, two of them with fulminating outcome (Berger et al. 1989b, 1992, Gray et al. 1991b). Clinical, radiological and pathological findings are indistinguishable from classical multiple sclerosis.

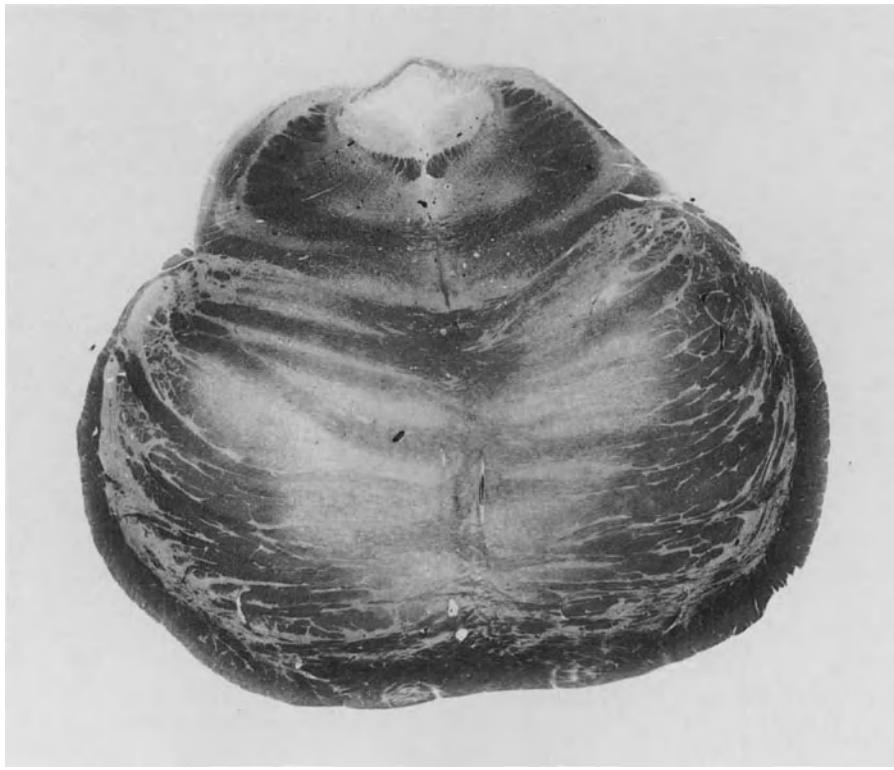


Fig. 3.69. Central pontine myelinolysis. Large irregular demyelination areas in the central part of the pons. Celloidin; myelin stain

■ Vascular Lesions and Intracranial Hemorrhages

Vascular changes and their consequences are relatively rare in our autopsy material. Intracranial hemorrhages in the form of parenchymal hemorrhages of the brain and spinal cord or epidural, subdural, or subarachnoid lesions are reported in the relevant literature (Mizusawa et al. 1988; Berger et al. 1990; De Girolami et al. 1992), but general experience shows them to be of minor importance numerically. Very few of the findings hitherto reported can be regarded as AIDS specific. In principle, embolic vascular occlusions and their consequences must be expected (De Girolami and Smith 1992). In particular, with cachectic patients in the final phase, an abacterial (marantic) endocarditis with embolic attacks in the context of a consumption coagulopathy must be included in diagnostic considerations (Vinters and Anders 1990).

Thrombotic endocarditis, usually right-sided and asymptomatic, is often first noted at autopsy (Anderson and Virmani 1990). Systemic thromboembolic disease with multiple cerebral infarcts, however, was seen only in three AIDS cases. A further cause of intracranial hemorrhages in AIDS patients concerns the defective coagulations in hemophilia (Esiri et al. 1989; Lantos et al. 1989), a syndrome that is not represented in our study material. On the other hand, our autopsy and biopsy study material frequently shows bone marrow damage with megakaryocytic dysplasia, which has often been the subject of comparative histological and cytological studies (Thiele et al. 1991; Kaloutsi et al. 1991). This damage, especially in the final phase of a pathological process, can be accompanied by a tendency to hemorrhage. Nevertheless, potentially fatal hemorrhages are hardly ever observed with the thrombocytopenic purpura frequently registered in AIDS patients, the pathogenesis of which is unclear (O'Hara 1989).

In the relevant literature there are descriptions of inflammatory vascular wall lesions in the region of the CNS and the meninges (Scaravilli et al. 1989 b; Vinters and Anders 1990); individual cases with granulomatous angiitis (Yankner et al. 1986) and necrotizing vas-

culitis (Vinters et al.1988) have also been mentioned. Inflammatory-necrotizing vascular wall changes were found in our series in only two cases of tuberculous meningoencephalitis, here, however, without larger hemorrhages. Characterized as noninflammatory, proliferative vascular wall changes in small-caliber vessels have been described by Smith et al. (1990) and De Girolami et al. (1992) in a case of HIV-1 leukoencephalopathy (see also Cho et al. 1987).

More or less pronounced findings on capillaries, arterioles, and venules with endothelial swelling and nuclear atypia are, however, frequently observed in the white matter. If we disregard more extensive hemorrhages as a consequence of tumor infiltrates (malignant lymphomas), in our autopsy material of 180 cases there were only four cases with relevant findings (2.2 %): one case with a subarachnoid hemorrhage of unexplained origin, a relatively large subdural hematoma in thrombocytopenia, a brain infarct in the territory of the cerebral posterior artery in a patient with toxoplasmosis, and one case with proliferative changes in smaller vessels with numerous smaller hemorrhages in the cerebral cortex.

■ Pathology of the Spinal Cord

Spinal cord disease is common in patients with HIV infection. All processes that affect the brain may also appear in the spinal cord, although with a lower frequency. In our series the spinal cord was examined in 100 cases. The most frequent pathological entity of the spinal cord among AIDS patients was vacuolar myelopathy (VM; Table 3.15).

Table 3.15. Morphological changes in the spinal cord of 100 patients with AIDS

Vacuolar myelopathy	48
Mild changes	20
Moderate changes	18
Severe changes	10
HIV myelitis	6
Toxoplasmic myelitis	2
CMV myelitis	6
Lymphoma	2
Cryptococcosis	1
Gracile tract degeneration	1
Hyaline globules	3
Severe myelopathy of unknown origin	1
Cases without pathological changes	39

In a few cases there were more than one diagnosis in the same patient.

Vacuolar Myelopathy

First reported in 1985 (Goldstick et al. 1985; Petito et al. 1985), VM ist a spinal cord disease found almost exclusively in adult patients with AIDS; only three cases have been reported within the pediatric population (Dickson et al. 1989; Sharer et al. 1990). Gross examination of the spinal cord shows no changes except in cases with particularly severe myelopathy; in these cases symmetric white-grayish discoloration within the posterior columns of the cervical cord may be present (Artigas et al. 1990 e).

Microscopic examination of the spinal cord shows vacuolar changes of the posterior and lateral tracts as well as, to a lesser degree, the anterior pyramidal tracts along with the presence of foamy macrophages (Petito et al. 1985; Singh et al. 1986; de la Monte et al. 1987; Sharer et al. 1986 b; Eilbott et al. 1989; Grafe and Wiley 1989; Maier et al. 1989; Rhodes et al. 1989; Bergmann et al. 1992). The vacuolation is not, however, confined to specific white matter tracts. The myelopathy typically involves the cervical and thoracic cord, the lumbal segment only being affected in a few cases (Artigas et al. 1990 d, e). The elementary lesion is the formation of numerous intramyelinic vacuoles mostly within the inner lamellae of the myelin sheaths (Petito et al. 1985). As the primary vacuoles gain in length, along the axon traject, the myelin sheath becomes detached from the axolemma, and the vacuoles appear between the axon and the myelin sheath (Artigas et al. 1990 e). Cytoplasmic vacuolization of large macrophages and small intraaxonal vacuoles may contribute to the histological picture of white matter spongiosity and vacuolation (Artigas et al. 1990 d).

The changes vary from mild to severe (Petito et al. 1985; Rosenblum et al. 1989; Artigas et al. 1990 e; De Girolami et al. 1991). Mild changes are characterized by the presence of no more than 20–30 vacuoles per transverse section of the spinal cord, some of them containing macrophages. Moderate changes are defined by numerous nonconfluent vacuoles, as well as by discrete invasion of phagocytic cells. In severe cases, there appear large areas of vacuolar changes composed of numerous confluent vacuoles and conspicuous infiltration of macrophages and microglial cells (Artigas et al. 1990 e; Figs. 3.70, 3.71).

Our previous studies showed that the vacuoles, in a three-dimensional reconstruction, consisted of fusiform cavities, 30–180 μm in maximal diameter and 200–500 μm in length. They are characteristically delimited by a thin sheath of distended myelin. Most of these cavities, which otherwise are optically empty,

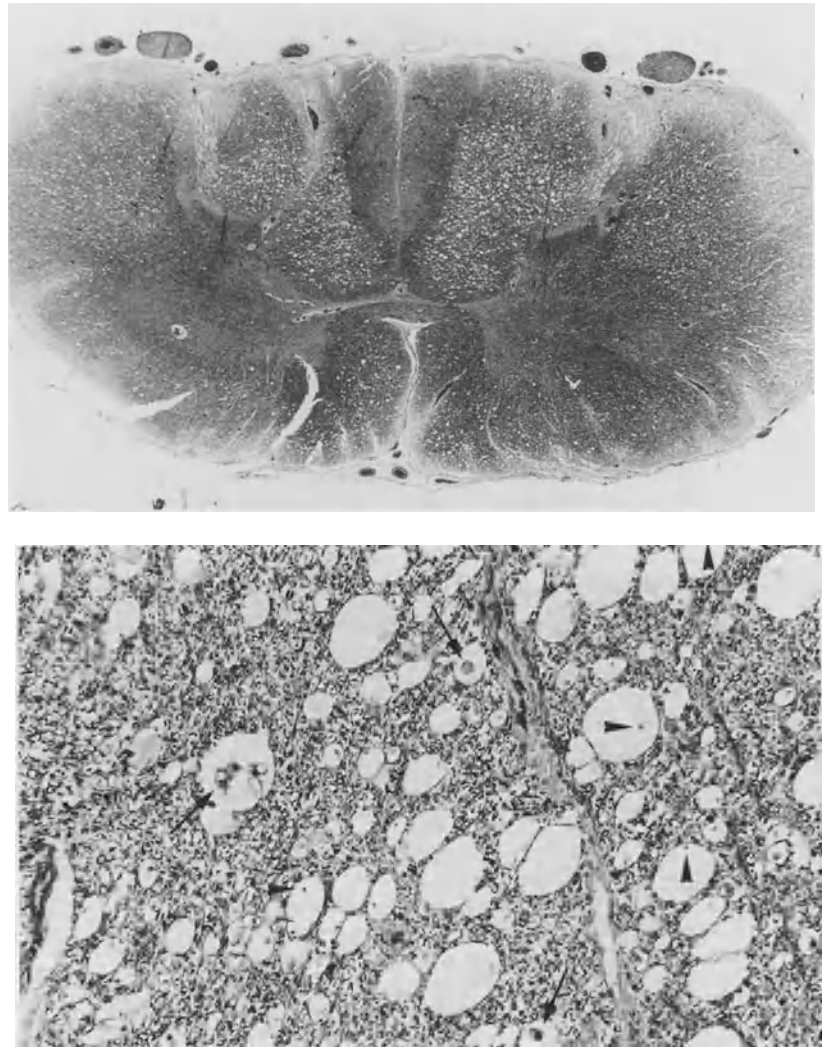
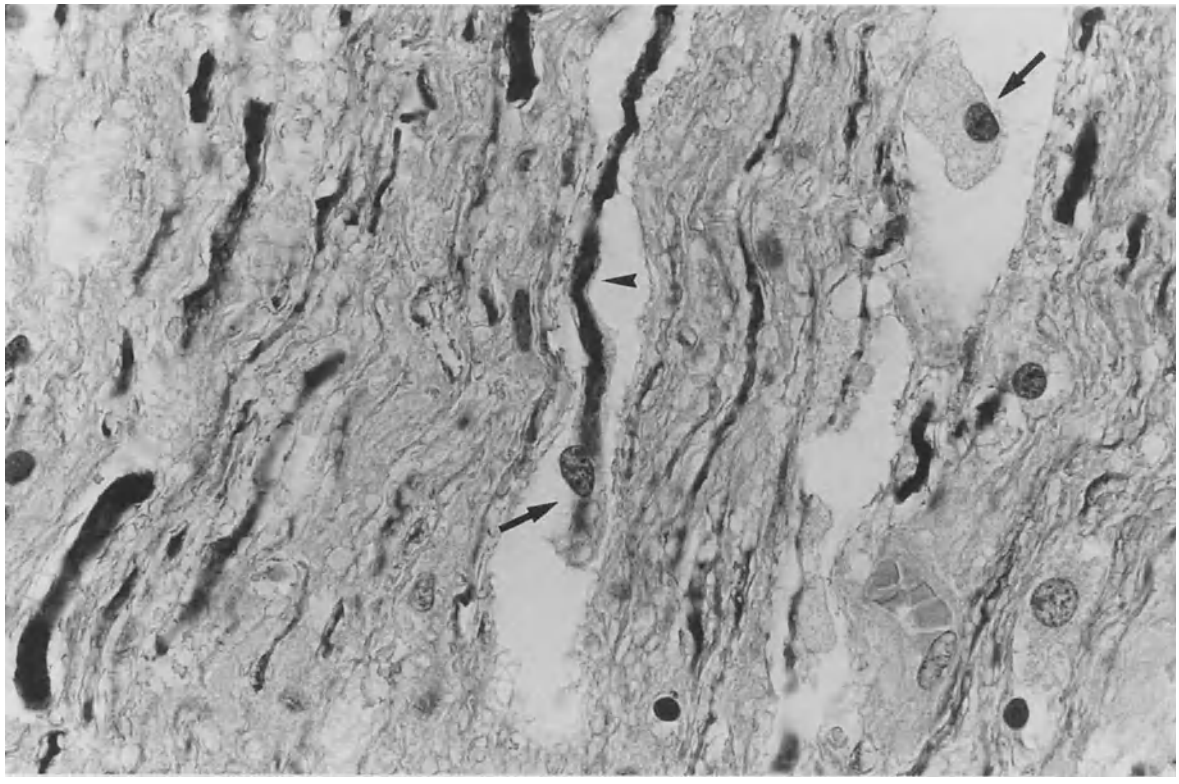


Fig. 3.70 a, b. **a** Cross-section through the cervical spinal cord. Vacuolar changes severely affect the posterior columns (Burdach) and to a lesser degree the lateral pyramidal tracts. The anterior pyramidal tracts display minimal change. Myelin stain, × 4. **b** Cross-section of the posterior columns showing numerous vacuoles. A few vacuoles contain macrophages (→) or axon remnants (▶). Glycol methacrylate; H&E, × 20

still contain an axon cylinder or remnants of them. Frequently, the vacuoles, despite their size, are partially or completely occupied by macrophages. These cells are in close contact with disrupted axons which may also be seen within the cytoplasm of the macrophages (Fig. 3.72). The myelin sheaths and the residual tissue between the vacuoles appear extremely attenuated, sometimes even leading to coalescence.

The process is accompanied by infiltration of macrophages and activated microglial cells in the white matter of the spinal cord, always more marked in areas of vacuolar changes. The intensity of the macrophage infiltration, which in both hematoxylin-eosin and periodic acid – Schiff staining seems to be discrete, may be reliably judged only in immunocytochemic studies using macrophage markers (CD68) or the lectins RCA-1 and ML I (Artigas et al. 1991 c). A surprising feature is that the macrophage infiltration is usually not perivascularly related but is widely spread in the area of cross-section of the spinal cord. Leptomeningeal spaces are devoid of phagocytic cells. Macrophages containing myelin debris are present only in areas of severe tissue disruption in cases of severe myelopathy. Here, the myelin sheaths are already destroyed, the cord tissue appears wasted, and only the blood vessels are well preserved. In these cases perivascularly located macrophages are present. They contain myelin debris and droplets staining positively



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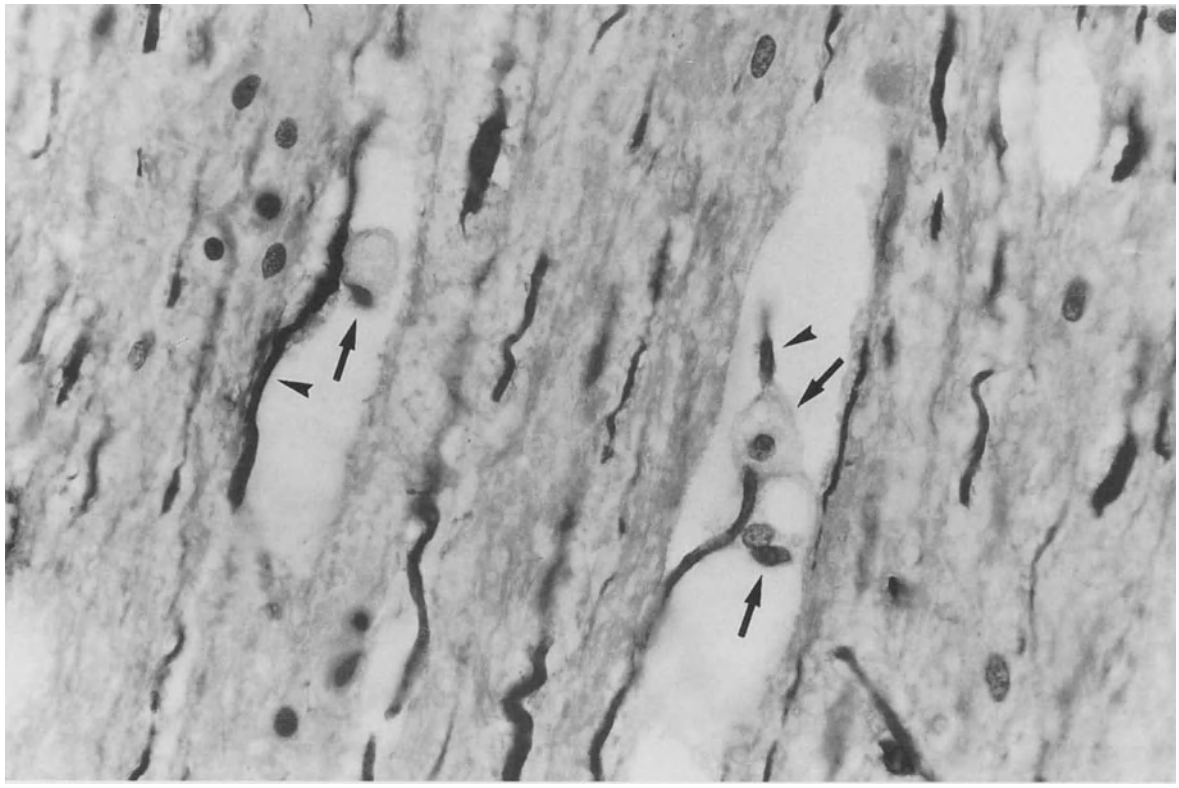

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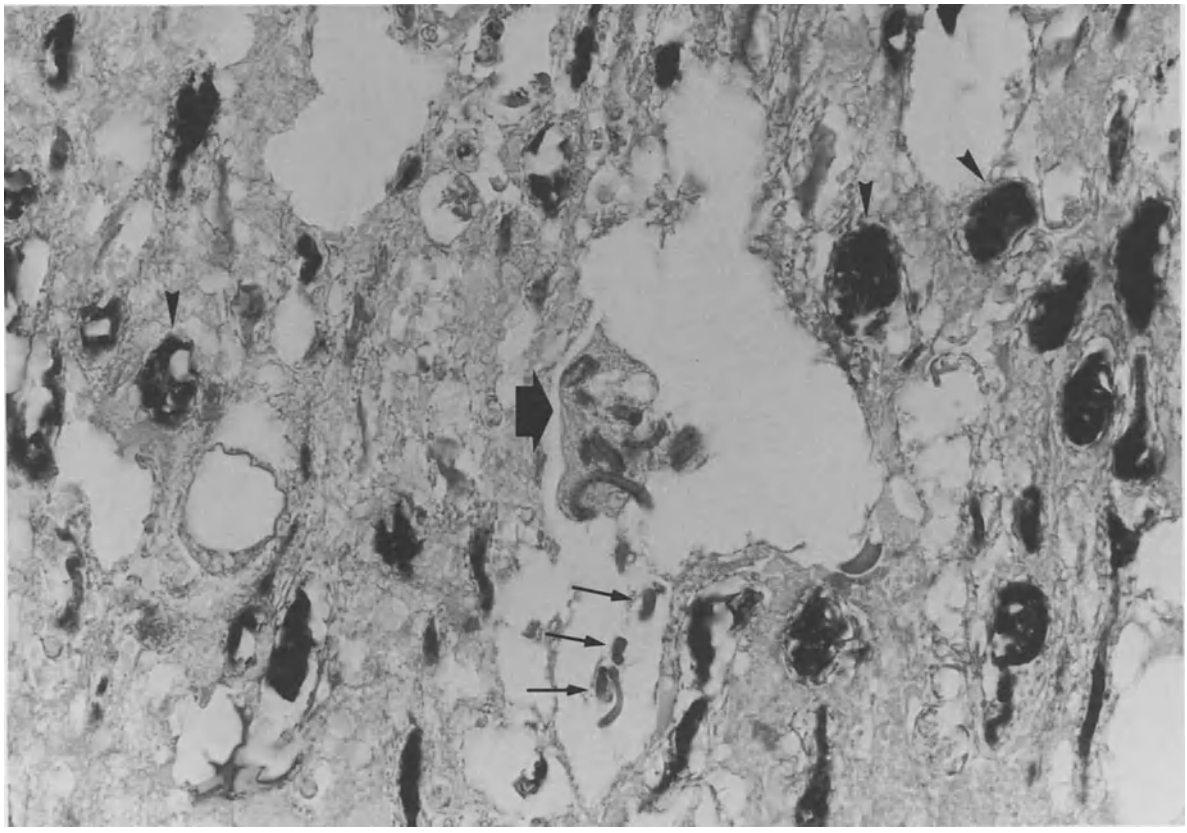

◀ **Fig. 3.71 a, b.** **a** Longitudinal section through the posterior columns showing elongated vacuoles containing an axon (▶) and macrophage (→). Thoracic cord, neurofilament; APAAP, ×60. **b** Longitudinal section through the posterior columns (same patient). Elongated vacuoles containing phagocytes with foamy cytoplasm (→) in direct contact to axon fragments (▶). Thoracic cord, neurofilament; APAAP, ×60

Fig. 3.72. Large macrophage within a vacuole phagocytosing an axon. Fragments of the axon are visible in the cytoplasm of the macrophage (↑); other axon remnants (→) are free at the bottom of the vacuole. Numerous axon swellings (▶). Neurofilament; ×50

for Sudan black B but not for oil red (Artigas et al. 1990 d, e). Axonal swellings may also be seen within the vacuoles. They appear in large numbers in the periphery of the spinal cord. Furthermore, the spinal cord shows an intensive astrogliosis in the white matter, which is much more strongly marked in the periphery. Numerous reactive astrocytes are also present in the gray matter (Artigas et al. 1990 e). Ultrastructural studies confirmed light-microscopic observations (Petito et al. 1985; Maier et al. 1989; Artigas et al. 1990 e).

The etiology and pathogenesis of VM remain obscure. It seems unlikely that it is due to direct damage of the HIV or to secondary infections. The first reports of VM emphasized the close similarity of this conditions to subacute combined degeneration of vitamin B_{12} deficiency (Petito et al. 1985). However, appropriate serum assays (Price et al. 1988 b; Rhodes et al. 1989) and the localization of the changes (Pant et al. 1968; de la Monte et al. 1987; Artigas et al. 1990 e) discarded this possibility. A striking association has been repeatedly identified between CMV infection of the brain and/or other organs and VM (Rhodes et al. 1989; Artigas et al. 1990 d, e; Burns et al. 1991). However, CMV infection is very frequent in HIV-infected persons. Grafe and Wiley (1989) and we ourself never found CMV antigen in areas of VM. Changes similar to VM have been reported in a patient with systemic lupus erythematosus (Johnson and Richardson 1968) and in 12 immunocompromised persons without AIDS (Kamin and Petito 1988).

Attempts have been made to correlate the pathological changes of VM with the presence of HIV. However, the results of numerous studies using virus isolation (Ho et al. 1985; Levy et al. 1985 b; de la Monte et al. 1987), in situ hybridization (Eilbott et al. 1989), and immunocytochemic techniques (Maier et al. 1989;

Gabuzda et al. 1986; Grafe and Wiley 1989; Rhodes et al. 1989; Vazeux et al. 1987; Artigas et al. 1990d,e; Bergmann et al. 1993) presented contradictory conclusions. Using immunocytochemic methods, Rosenblum et al. (1989) showed that the presence of the HIV in the spinal cord correlates with an inflammatory myelitis but not with VM.

There are important differences in the frequency of VM in autopsy series: 2%–3% in Switzerland (Lang et al. 1989), 11% in Boston (de la Monte et al. 1987), 21% in Dallas (Burns et al. 1991), 30% in New York (Petito et al. 1986), and 48% in our series (Artigas et al. 1990e). The high rate of VM in our series could be attributed to geographic differences reflecting variations in nutritive and metabolic situations (Budka 1991a). Other factors may be the intensive sampling of the spinal cords at autopsy, the use of macrophage markers in the diagnosis, and the careful study of numerous preparations, paying attention even to minimal changes.

In the literature, as well as in our experience, there is some support for a direct correlation between the severity of myelopathy and the presence of HIV encephalitis and HIV leukoencephalopathy (Price et al. 1988b; Artigas et al. 1990e; Bergmann et al. 1993). However, the myelopathy can certainly occur alone. In our material, HIV encephalitis and HIV leukoencephalopathy were found in seven and three cases, respectively, out of nine cases with severe VM. Clinical studies show that 60% of patients with VM show associated AIDS dementia (Maleßa 1991).

Human T-Lymphotropic Virus Type I-Associated Myelopathy

Recent reports have linked the development of myelopathies, which clinically were formerly known as tropical spastic paraparesis, to the human T-lymphotropic virus type I (HTLV-I; Grimaldi et al. 1988; Minato et al. 1988; Osame et al. 1987). The morphological changes consist of inflammation and sponginess but not of vacuolar changes (Robertson and Cruickshank 1972). Vacuolar changes more similar to VM have been reported in only one case of HTLV-I related myelopathy (Akizuki et al. 1989). Pathological examination of three cases showing coinfection with HIV and HTLV-I revealed atrophy of the spinal cord with meningeal thickening, axonal loss and demyelination of the lateral and anterior columns, but no evidence of vacuolar changes (Brew et al. 1989; Rosenblum et al. 1992).

HIV Myelitis

HIV myelitis represents the spinal cord equivalent of HIV encephalitis (Fig. 3.73). For a long time the morphological changes of this entity were not correctly separated from VM; thus HIV myelitis was recognized relatively late as an isolated condition. Multinucleated cells and HIV antigen have been observed in the spinal cord both with VM (Gray et al. 1988; Maier et al. 1989; Rosenblum et al. 1989) and without VM (Grafe and Wiley 1989; Rhodes et al. 1989; Sharer et al. 1990). Rosenblum et al. (1989) demonstrated that the presence of the HIV in the spinal cord correlates with inflammatory myelitis. Consequently, Geny et al. (1991) reported a case of HIV myelitis with typical infiltration of macrophages and multinucleated cells in the gray and white matter of the spinal cord, whereas the brain was not affected. Although HIV myelitis can occur alone, it frequently appears associated with VM, and its recognition may be not easy. In a large series it has been reported with a frequency of 8% (Hénin et al. 1992). In our material we found six cases.

Myelopathies Caused by Viruses of the Herpes Group

Herpes simplex I and II can produce myelitis with the virus spreading centrally from the genitalia along the sacral nerves. A case of thoracic myelitis by herpes simplex II virus (Britton et al. 1985) and a cervical myelitis caused by coinfection of herpes simplex II virus and CMV have been described in AIDS patients (Tucker et al. 1985). Herpes zoster virus myeloradiculitis has been reported in a few AIDS patients (Thornton et al. 1989; Dix and Bredesen 1988; Burns et al. 1991). McArthur (1987) found a liquefactive necrosis of the thoracic cord in an AIDS patient who developed a thoracic myelopathy several months after herpes zoster affection of a thoracic dermatome. However, in the histological examination there was no evidence of herpes zoster or of vasculitic changes. CMV necrotizing myelopathy has been described in HIV infection (Moskowitz et al. 1984c; Tucker et al. 1985; Morgello et al. 1987; Dix and Bredesen 1988; Vinters et al. 1989; Grafe and Wiley 1989; Bélec et al. 1990; Chimelli et al. 1990; Hénin et al. 1992; Burns et al. 1991). It may also be the initial manifestation of AIDS (Mahieux et al. 1989). We found CMV myelitis in six cases of our series. In a further case, in which the spinal cord was not totally removed, therefore not in-

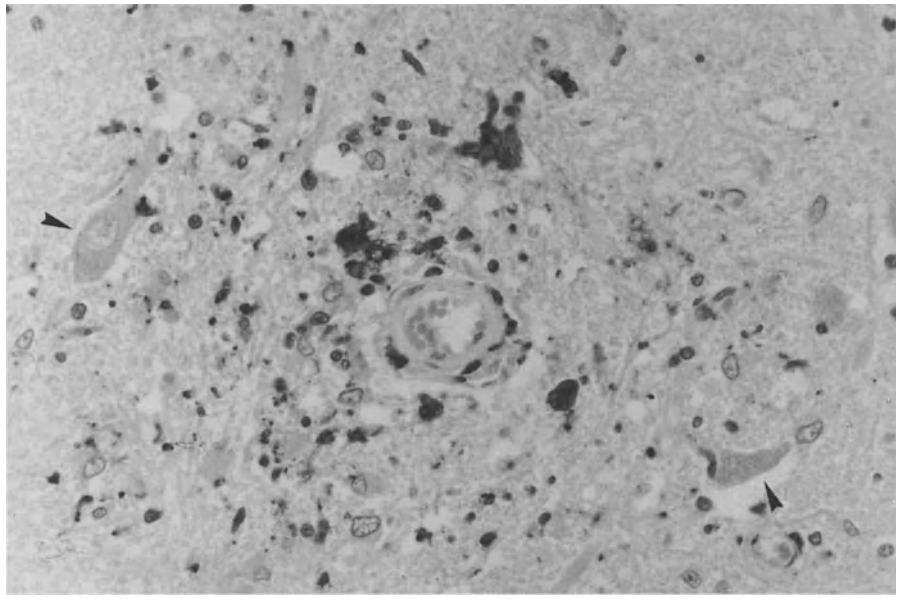

Fig. 3.73. HIV myelitis. Loosely arranged macrophages in the surroundings of a small blood vessel in the gray matter of the spinal cord. Two neurons (▶) are to be seen. Thoracic cord; KP-1, APAAP, ×40

cluded in Table 3.15, we observed CMV myelitis in the upper part of the cervical cord. The morphological findings are characterized by patchy subpial necroses with macrophages and cytomegalic cells, glial nodules, isolated inclusion-bearing cells, and diffuse microglia proliferation.

Necrotizing Toxoplasmic Myelitis

Necrotizing myelitis by infection with *T. gondii* has been repeatedly described (Navia et al. 1986; Mehren et al. 1988; Herskovitz et al. 1989; Nag and Jackson 1989; Emskötter 1991 a; Burns et al. 1991). We found this condition in two cases with severe toxoplasmic ventriculoencephalitis.

Progressive Multifocal Leukoencephalopathy

Affection of the spinal cord in progressive multifocal leukoencephalopathy (PML) is very rare (Richardson 1961). In an AIDS series Hénin et al. (1992) described one and Kuchelmeister et al. (1993) two cases of PML with spinal cord involvement. We examined the spinal cord of six patients with cerebral PML, with negative results. Burns et al. (1991) also reported normal findings of the spinal cords in two patients with PML.

Lymphoma

Malignant lymphomas rarely affect the spinal cord. Hénin et al. (1992) found such affection in four cases, while our own material contained only two cases with lymphoma infiltration of the spinal cord; all cases, our own and those from the literature, were B-cell lymphomas and were associated with cerebral and/or systemic manifestations.

Cryptococcosis

Crytococcosis affecting the spinal cord has been reported in a few cases (five cases in the series of Hénin et al. 1992). In our material it was found in only one case.

Syphilitic Myelopathy

Two cases of syphilitic myelopathy with postmortem confirmation have been reported in AIDS patients (Berger et al. 1989).

Changes of Unknown Origin and Unknown Nosological Significance

1. A degeneration of the gracile tract has been described in four AIDS patients. There was a striking loss of axons and myelin sheaths confined to this tract, most prominent in the upper thoracic or cervical cord (Rance et al. 1988). We found a similar degeneration in only one case of our series.
2. In the spinal cord of three Aids patients we observed the presence of extracellular hyaline globules (Fig. 3.74). In a case with VM this material partially filled the typical vacuoles of VM, or it formed large chains in the white matter visible in longitudinal sections. This substance showed positive staining with a zidovudine antibody in immunocytochemical studies (Artigas et al. 1991 a, b). We observed similar hyaline globules, but not chains, in the white matter of the brain in nine AIDS patients. The nosological significance of these findings is obscure.
3. In addition, we observed one case with VM associated with a severe myelopathy of unknown etiology.

Case Report. A 44-year-old man was known to be HIV positive since March 1989. By the end of that year the patient showed progressive disturbances in gait. In January 1990 he showed spastic paraplegia with a complete spinal cord syndrome at level T3. The patient was cachectic, and his condition steadily worsened. He died on 14 April 1991 with septic shock. Postmortem examination of the CNS showed a strong atrophy of the spinal cord more marked at the upper thoracic and cervical levels. Histological examination disclosed a severe vacuolar myelopathy at the cervical, thoracic, and lumbal levels. Furthermore, there was a massive infiltration of the white matter by macrophages which showed a fine and very regular vacuolation of the cytoplasm. Thick concentric layers of similar macrophages were seen around the walls of numerous blood vessels (Fig. 3.75). In the upper thoracic part of the spinal cord, in only one spinal cord segment, we found a fine cytoplasmic vacuolation of almost all neurons of the gray matter, sometimes with remnants of the Nissl bodies between the walls of the vacuoles (Fig. 3.76). The cellular membrane was not disrupted. To our knowledge these changes had not been reported in AIDS patients.

Fig. 3.74 a, b. **a** Hyaline globules in the white matter of the spinal cord, showing a weak stain with PAS (▶). ×60. **b** Droplets of different sizes with positive zidovudine staining in an area with discrete sponginess of the white matter. Antizidovudine; ABC method, ×60 ▶

Fig. 3.75. Myelopathy of unknown etiology. Concentric layer of foamy macrophages around a small blood vessel in the upper thoracic part of the spinal cord. Glycol methacrylate; H&E, ×40 ▶

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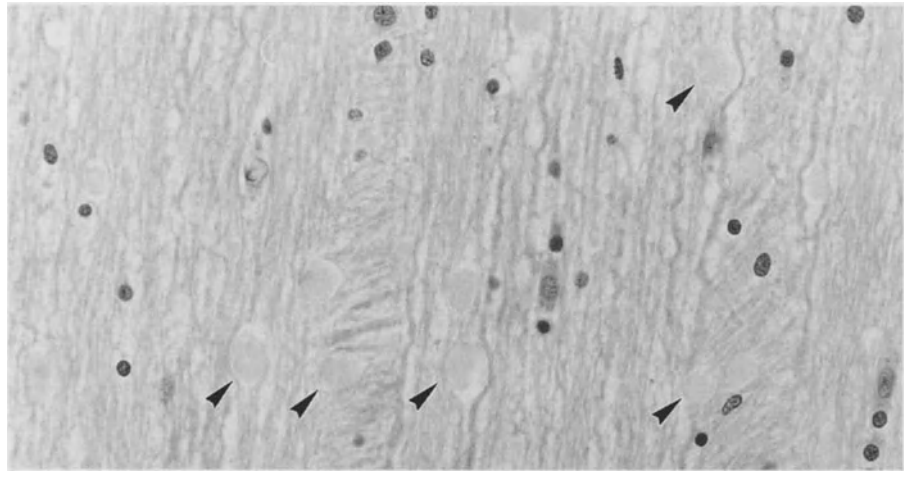

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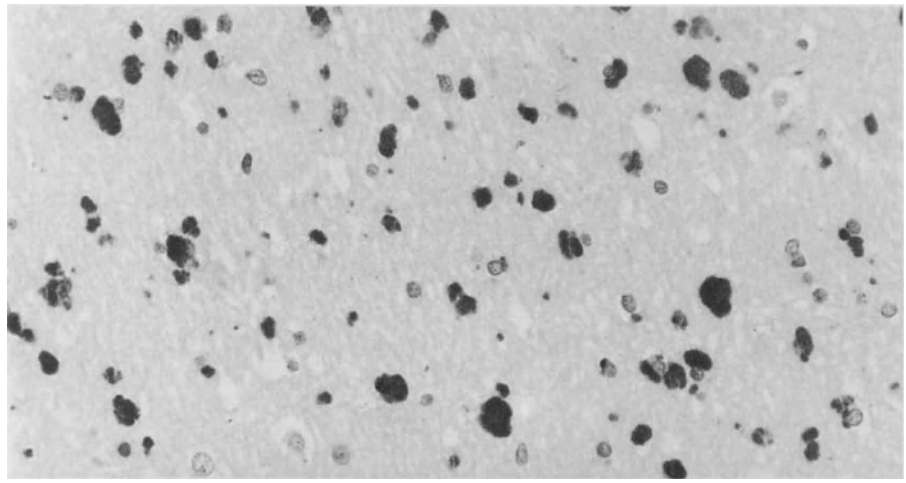

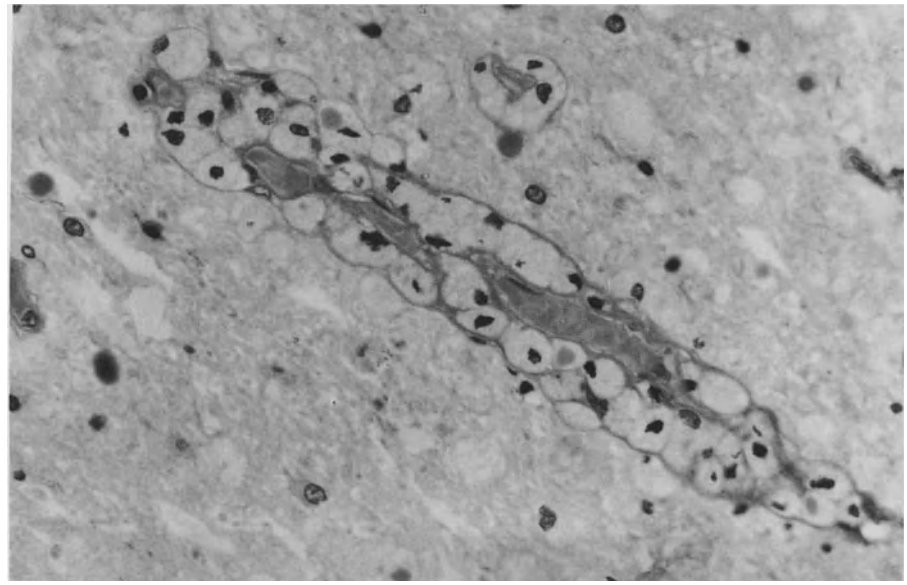

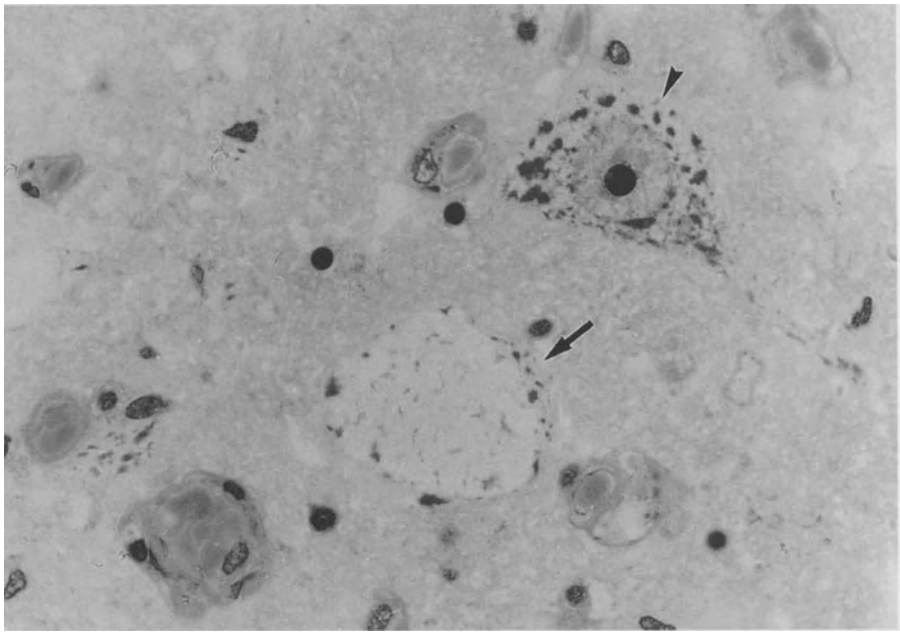

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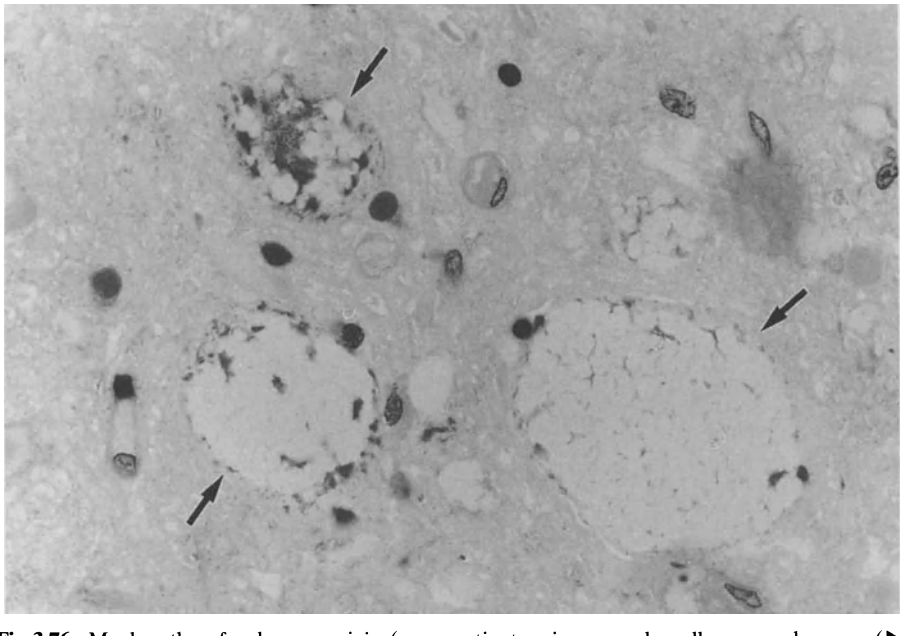

b

Fig. 3.76. Myelopathy of unknown origin (same patient as in Fig. 3.75). Neurons of the gray matter in the thoracic cord with conspicuous cell swelling and reduction of the Nissl bodies. A nearly well preserved neuron (▶) and consecutively increasing swelling of the cytoplasm (→). Glycol methacrylate; Bielschowsky-Plien cresyl violet technique, × 60

■ Pituitary Gland

We studied the hypophysis in 150 cases of our series. The gland was sectioned in the equatorial plane and both halves were embedded for histological examination. In the literature we found only two studies concerning morphological changes of the pituitary in patients with AIDS (Vinters and Anders 1990; Sano et al. 1989). In general we distinguish between: changes due to primary HIV infection, changes due to opportunistic infections, necroses of unknown origin, and atrophic changes.

Changes due to Primary HIV Infection

Typical multinucleated giant cells have been described in the neurohypophysis in two cases (Kato et al. 1987 b; Vinters and Anders 1990).

Changes due to Opportunistic Infections

Involvement of the pituitary is associated with generalized or cerebral infection by opportunistic organisms. Usually the inflammatory reaction of the adenohypophysis is minimal or absent, while the neurohypophysis shows more marked cellular reaction.

Pituitary involvement by infections with *T. gondii* has been reported in several instances (Gransden and Brown 1983; Sano et al. 1989; Vinters and Anders 1990). This is characterized by multiple necroses of variable size in the adenohypophysis (eight cases of our autopsy series). The necrotic foci are usually well demarcated, showing free tachyzoites in the periphery. Numerous adenohypophysial cells at the border of necrotic areas show tachyzoites within the cytoplasm. Bradycysts and tachyzoites are seen with conventional and immunocytochemical techniques. Tissue damage rarely reaches the range of 90 % which is required to produce hypopituitarism. Hence, only exceptionally is pituitary affection followed by clinical manifestation (Milligan et al., 1984).

Nuclear and cytoplasmic inclusions typical of CMV infection has been described in adenohypophysial and endothelial cells of the adenohypophysis (Vinters and Anders 1990; Sano et al. 1989). In the neurohypophysis, CMV infection is suggested by microglial nodules (Vinters and Anders 1990; Sano et al. 1989). We observed one case with a few cytomegalic adenohypophysial cells, and another case with multiple cytomegalovirus-related necroses in the adenohypophysis and with cytomegalic changes of pituicytes in the neurohypophysis.

Pituitary involvement in *Pneumocystis carinii* infection, characterized by multifocal necroses containing many *P. carinii* cysts located near blood vessels, has been reported in two cases (Sano et al. 1990; Telzak et al. 1990). In our study material there was one patient (a 41-year-old man) with recurring *P. carinii* pneumonia, immunohistochemical evidence of numerous microorganisms in the capillaries of the brain, and numerous parenchymatous organs, and in the hypophysis, although without the formation of necroses. Involvement of the pituitary gland in cryptococcal infection has been illustrated in one case (Vinters and Anders 1990) and affection of the neurohypophysis by *Blastomyces dermatitidis* has also been found in one case (Harding 1991). Another solitary case of our autopsy series showed necrosis of the adenohypophysis due to bacterial thrombotic occlusion of a parenchymal vessel.

Necroses of Unclear Etiology

Sometimes areas of necrobiosis and recent or old necrosis, without recognizable causal agents are found (Vinters and Anders 1990; Sano et al. 1989). In five cases we found such lesions. The frequency of these necroses in other series is higher than that anticipated in non-AIDS autopsy series (Vinters and Anders 1990). A severe terminal hypoxic state may cause necrotic changes in several cases.

Hyperplasia and Neoplasms of Specific Pituitary Cell Types

Adenomas, generally prolactinomas, and nodular hyperplasia of adenohypophysial cells have been reported in a few cases (Sano et al. 1989); however, its frequency was the same as in age matched control patients. We found a nodular hyperplasia of pituicytes, so-called Priesel's nodules, in a few cases. Morphological evaluation of functional cell types by means of immunocytochemical techniques using antibodies against seven adenohypophysial hormones showed no differences with material from control persons (Sano et al. 1989).

Atrophic Changes

We observed severe atrophy of the pituitary in three cases. The first case showed a severe CMV infection of the adenohypophysis and pars nervosa; the second patient had a history of syphilis; neuropathological examination showed a large, old infarct in the territory of the middle cerebral artery and a recent, necrotic encephalitis of unknown etiology; the last one was that of a 42-year-old man who showed a severe brain atrophy (brain weight 1150 g) with progressive multiple leukoencephalopathy.

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Chapter 4

Clinical Ophthalmology in AIDS

B. Girard, P. Le Hoang

Ocular disorders are frequently observed in patients with AIDS, involving 40%–94% of patients during the course of the disease (Holland et al. 1982, 1983; Freemann et al. 1984; Fujikawa 1988; Palestine et al. 1984; Schuman et al. 1987; Le Hoang et al. 1989a; Table 4.1). Ocular complications of AIDS can be subdivided according to their basic pathological process: vascular, infectious, neoplastic, or neuro-ophthalmological.

Table 4.1. Ocular manifestations found in patients with AIDS (70% of cases)

Retinal vascular noninfectious disorders	
Cotton-wool spots	40%
Retinal microangiopathy: microaneurysms, retinal hemorrhages, ischemic maculopathy	
Retinochoroidal infection	
Cytomegalovirus	20%
Toxoplasma gondii	4%
Herpes simplex	<1%
Peummocystis carinii	<1%
Candida albicans	<1%
Syphillis	<1%
Corneal and adnexal infection	1%
Cytomegalovirus	
Herpes simplex	
Herpes zoster	
Neoplasms	
Kaposi's sarcoma	3%
Oculo-orbital lymphoma	<1%
Neuro-ophthalmological signs	5%
Oculomotor palsies	
Visual field defects	
Papilledema	
Optic atrophy	

■ Retinal Microvascular Disorders

Cotton-Wool Spots

Cotton-wool spots (CWS) are the most frequently observed ophthalmoscopic sign (30%–53%) in patients with AIDS (Newsome et al. 1984). The lesion is not associated with a functional disturbance and is often discovered on routine general physical examination. CWS are neither specific nor pathognomonic. The funduscopic appearance of the lesion in AIDS patients is similar to that in non-AIDS patients with systemic diseases such as diabetes, hypertension, and acute disseminated lupus erythematous. CWS present

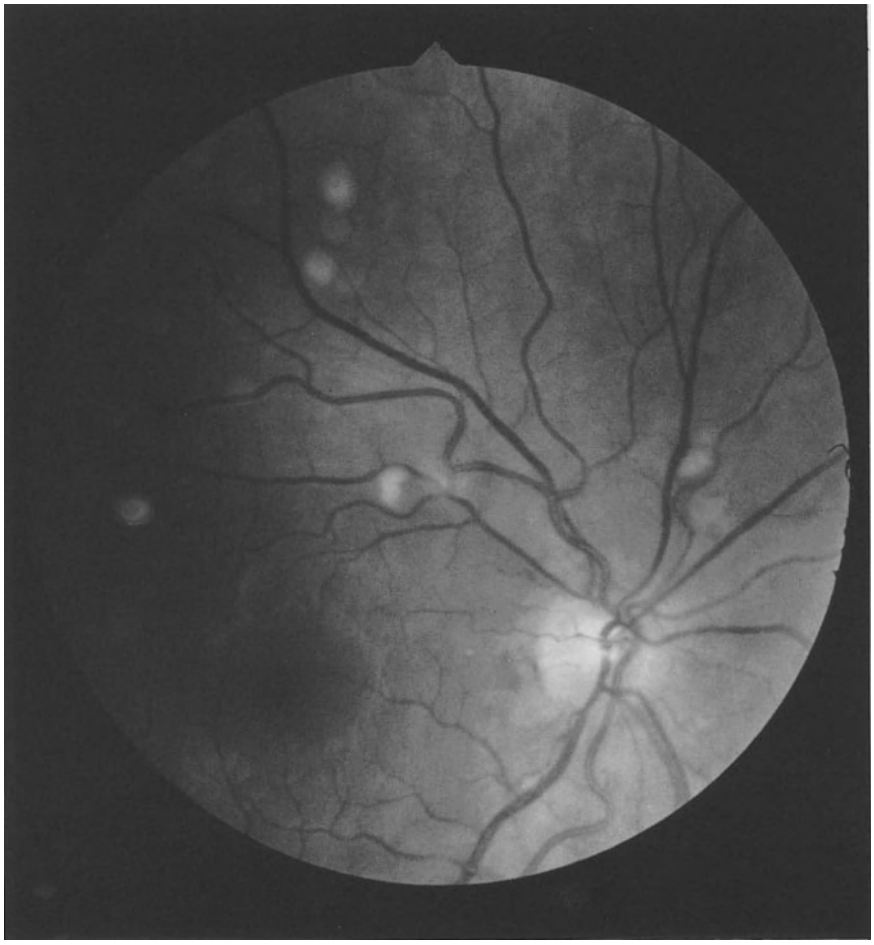

Fig. 4.1. Disseminated CWS in posterior pole

clinically as superficial, yellow-white retinal lesions with a fluffy or flocculent, poorly circumscribed appearance and partly masking retinal vessels (Fig. 4.1). They occur predominantly at the posterior pole, are often bilateral, and vary in number and size, sometimes reaching papillary diameter. CWS can regress spontaneously, and it is therefore imperative to follow the patient with sequential ophthalmoscopic examinations, especially, since the lesions may favor the development of cytomegalovirus (CMV) retinitis. This association is possibly due to the fact that CWS are invariably associated with an altered blood-retinal barrier (Pepose et al. 1983, 1985; Rodrigues et al. 1983). CWS should be distinguished on funduscopic examination from foci of early CMV chorioretinitis.

The clinical evolution of these two lesions is distinctive. Early viral retinitis characteristically gives rise to an expanding whitish retinal patch. CWS, on the other hand, often resolve spontaneously within 4–6 weeks, leaving no evidence of a residual scar. Nevertheless, on initial funduscopic examination it may be difficult to distinguish between the two lesions. The differential diagnosis, of course, determines the course of treatment. In addition to the clinical evolution of the two lesions, retinal fluorescein angiography is very helpful in distinguishing between them. CWS produce initial blockage, followed by a central hypofluorescence with occasionally faint hyperfluorescence in the marginal area during the late phase. The "halo" effect is thought to be due to an altered region of vascular permeability at the outer border of the ischemic zone. On the other hand, an early focus of CMV retinitis of comparable size to a CWS gives rise to a blockage of the choroidal fluorescence both in the early and late stages of the angiographic study.

From the pathogenetic standpoint, CWS are the result of localized axonal swelling in the nerve fiber layer due to a disturbance of anterograde and retro-

grade axoplasmic transport, thought to have an ischemic basis. The clinical appearance of CWS is not specific for AIDS. Identical lesions are observed with occlusion of retinal precapillary arterioles. Histopathological examination discloses cytoid bodies. The pathogenesis of CWS in AIDS patients is not understood. Although CWS can coexist with CMV retinitis, they do not seem to be caused by a direct effect of CMV itself, as indicated by the absence of viral antigens in the center of the lesions (Pepose et al. 1983). Mechanical occlusion of small vessels has been reported in association with the intravascular infectious agents *Aspergillus* (Pepose et al. 1985), *Pneumocystis carinii* (Kwok et al. 1982), and *Cryptococcus neoformans* (Pepose et al. 1983) in the retina adjacent ot the CWS. It has also been proposed that infection of vascular endothelial cells or neuroretinal cells by HIV-1 or CMV induces a microangiopathy which leads to CWS (Pomerantz et al. 1987). The presence of immunoglobulins within CWS may be the result of circulating immune complexes (Pepose et al. 1985).

CWS are now recognized as a severe prognostic sign in the course of AIDS, being associated with a 1-year mortality of 81 % (Holland et al. 1983) versus 44 % in the absence of CWS. They are most often observed in patients who have multiple infections and in those with Kaposi's sarcoma (Holland et al. 1983; Schuman and Friedman 1983; Palestine et al. 1984). Many patients with CWS have an associated *Pneumocystis carinii* pneumonia (Friedman 1984). The ophthalmological manifestations are linked to the degree of immunosuppression (Palestine et al. 1984; Khadem et al. 1984). The occurrence of CWS is correlated with a level of circulating T4 lymphocytes of 760/cm^3 and a ratio of T4/T8 lymphocytes of 0.39, whereas CMV retinitis is associated with a level of circulating T4 lymphocytes of 514/cm^3 and a ratio of T4/T8 lymphocytes of 0.21 (Le Hoang et al. 1989a; Brezin et al. 1990). CWS may precede infectious retinitis. Patients must be followed closely to monitor the possible occurrence of opportunistic retinal infections.

Ischemic Retinal Microangiopathy

Ischemic retinal microangiopathy is very frequent, being found in 89 %–100 % of cases of autopsy examination (Newsome et al. 1984; Pepose et al. 1985). Early microangiopathy is often clinically silent. Before the development of retinal hemorrhages or CWS only fluorescein angiography can detect the lesions. Retinal microangiopathy shows areas of retinal ischemia characterized by regions of hypofluorescence bordered by dilated capillaries. At a more advanced stage, ischemic retinal microangiopathy can be complicated by the development of microaneurysms (20 %), retinal hemorrhages (15 %–40 %), and CWS (23 %; Palestine et al. 1984). Rarely, an ischemic maculopathy (6 %) can result in severe visual loss (Pepose et al. 1985).

Retinal Vasculitis

There have been several descriptions of retinal vasculitis. This lesion is especially reported in African children with the AIDS-related complex, but it can also occur in adult patients with AIDS (Kestelyn et al. 1985b). It presents as perivasculitis, often peripheral and involving veins and may leave a pigmented scar along the vessels. These fluffy perivascular lesions differ from the well-circumscribed patchy vascular sheathing seen next to active or treated CMV retinitis. They may be diffuse and extend from the periphery of the retina to the posterior pole. The etiology of this vasculitis is unknown but can be attribued to viral infection of the perivascular retina due to a CMV viremia superimposed on a retinal microvasculopathy (Le Hoang et al. 1989a).

■ Infectious Retinitis and Chorioretinitis

The most serious ocular manifestations of AIDS are due to opportunistic infections of the eye. These often lead to blindness. Numerous agents have been incriminated. The most frequently documented infectious agents are: cytomegalovirus, *Pneumocystis carinii, Toxoplasma gondii,* herpes simplex, and *Candida albicans.* Necrotizing CMV retinitis is by far the most common ocular infection in patients with AIDS; other infectious agents are rare.

Ocular involvement is often associated with systemic CMV infection. The eye may be the initial site of CMV infection; therefore all patients presenting with CMV retinitis should be studied carefully for evidence of disseminated infection.

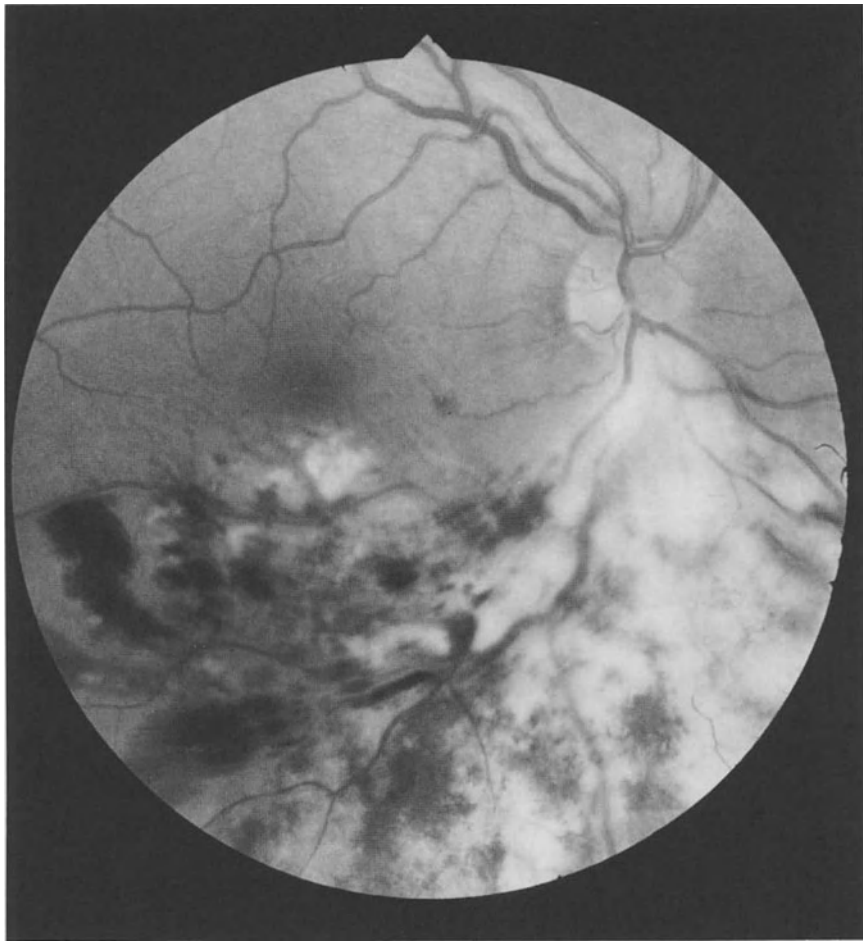

Fig. 4.2. CMV retinitis. Severe ischemic and hemorrhagic necrosis involving temporal and inferior retina

CMV Retinitis

CMV retinitis is the most frequent opportunistic infection, occurring in 14%–46% of cases (Holland et al. 1983; Palestine et al. 1984; Jabs et al. 1989; Le Hoang et al. 1989). It can be discovered at the time of initial general physical examination. CMV retinitis may be multifocal, bilateral at the outset (25%), or secondary (20%).

The early lesion appears as a small yellow-white patch, often angiocentric, with relatively sharp borders. It extends by centrifugal spread, and the advancing edge of viral proliferation results from the coalescence of multiple foci at the periphery of the main lesion. There is often a sharp line of demarcation between the affected and the normal retina. Concomitant vascular involvement gives rise to hemorrhages. CMV necrotizing retinitis is especially distinctive because of its hemorrhagic appearance. The destroyed atrophic retina leaves a pigmented scar. The typical funduscopic appearance is that of a series of concentric layers, having at the periphery a ring of punctate foci of retinitis, toward the center a wider band of viral proliferation, and a core of destroyed retina undergoing atrophy. At the center of the lesion the vasculature has the appearance of whitish ropy strands. There is very little inflammation of the vitreous. The ophthalmoscopic picture is therefore very characteristic (Fig. 4.2). In 15% of patients with retinitis and 1.8% of those with AIDS, CMV retinitis is the first clinical manifestation of AIDS (Henderly et al. 1987a; Sison et al. 1991). Many patients with CMV retinitis go on to develop of retinal detachment because of multiple sites of retinal dehiscence caused by multifocal retinal necrosis (Palestine et al. 1984; Freeman et al. 1987;

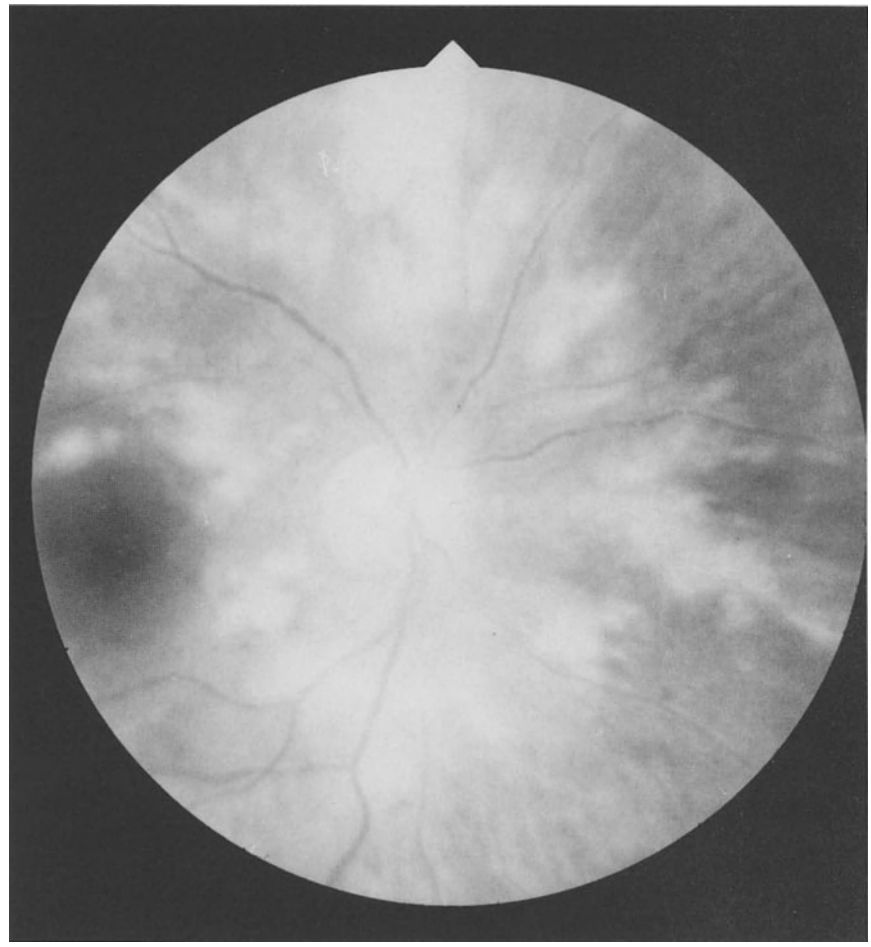

Fig. 4.3. CMV retinitis before treatment

Dugel et al. 1991). The prognosis for functional recovery is guarded, even with surgery (vitrectomy, silicone oil).

In patients with AIDS, CMV retinitis should be distinguished clinically from other causes of infectious retinitis and from CWS. In general, the clinical picture of CMV retinitis is very characteristic, but it may at times be confusing especially in the early stages of the disease. Another confounding variable is the occurrence of coinfection with other agents. Retinal angiography and laboratory studies are often helpful ancillary studies. Chorioretinal biopsy is rarely indicated.

Fluorescein retinal angiography of CMV retinitis lesions shows early blockage followed by a central area of hyperfluorescence, with late staining from the center to the periphery of the lesion. The advancing edge of viral proliferation is hypofluorescent; thus the zone of late hyperfluorescence is smaller than the lesion seen on funduscopic examination.

There are two sites of localization of CMV infection that are especially severe from the clinical standpoint. Extension to the fovea leads to irreversible loss of central vision. Involvement of the papilla is extremely serious as it leads to destruction of the optic nerve fibers and may result in vascular occlusion. It appears as a swelling of the optic disc and is accompanied by hemorrhages, especially if associated with adjacent retinal lesions. Viral involvement of the papilla can also simulate the picture of a central retinal vein occlusion from which it must be differentiated. In the early studies, CMV retinitis was said to lead invariably to a poor prognosis and death of the patient within 6–8 weeks (Holland et al. 1983). With the advent of therapy for CMV retinitis the prognosis has considerably improved (Holland et al. 1990; Gross et al. 1990).

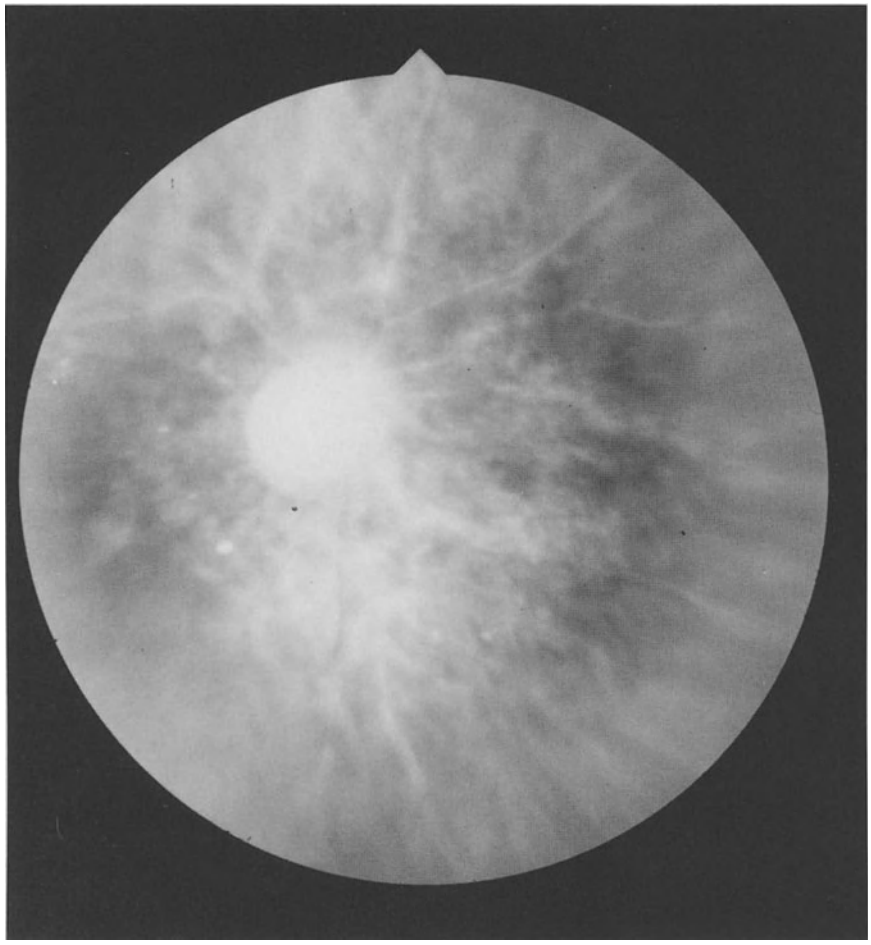

Fig. 4.4. Treated CMV retinitis. Note peripupillary scar after 1 month of treatment with foscarnet (same patient as Fig. 4.3)

Furthermore, the length of survival has progressively increased to an average of 5 months between 1984 and 1987 (Holland et al. 1990) and to 8 months in 1990 (Gross et al. 1990). Recently, Holland et al. (1990) reported a survival of more than 24 months.

Two active virostatic drugs against CMV are now available: ganciclovir or (dihydroxy propoxymethlye guanine; Laskin et al. 1987; Mar et al. 1983) and trisodium phosphonoformate (foscarnet; Öberg 1983; Ringden et al. 1985). Both ganciclovir and foscarnet are effective modes of treatment (Collaborative DHGP Treatment Study Group 1986; Holland et al. 1987; Jabs et al. 1987; Palestine et al. 1986; Le Hoang et al. 1986). In our series treatment with these drugs has resulted in a remission rate of CMV retinitis of 88%, with complete resolution of the necrosis in 74%. The whitish zones of necrosis gave way to a focal scarring (Figs. 4.3, 4.4). Nevertheless, these drugs do not allow complete eradication of the virus since they are merely virostatic; in addition, the picture is complicated by the persistent, severe immunodepression that is characteristic of patients with AIDS. Histopathological examination of the eyes of treated patients demonstrates the persistence of the virus the retina (D'Amico et al. 1986; Pepose et al. 1987; De Girolami et al. 1989), which explains the recurrence of acute disease following interruption of treatment. It is therefore essential to maintain a continuous treatment program, at lower doses.

Among our patients who received an intitial treatment following an acute attack but who were not maintained on the drug we have observed recurrence of retinitis in 100% of cases. This followed an average of 21 days after interruption of the intial treatment. In patients with maintenance treatment, the frequency of recurrence diminishes. It is also possible that the

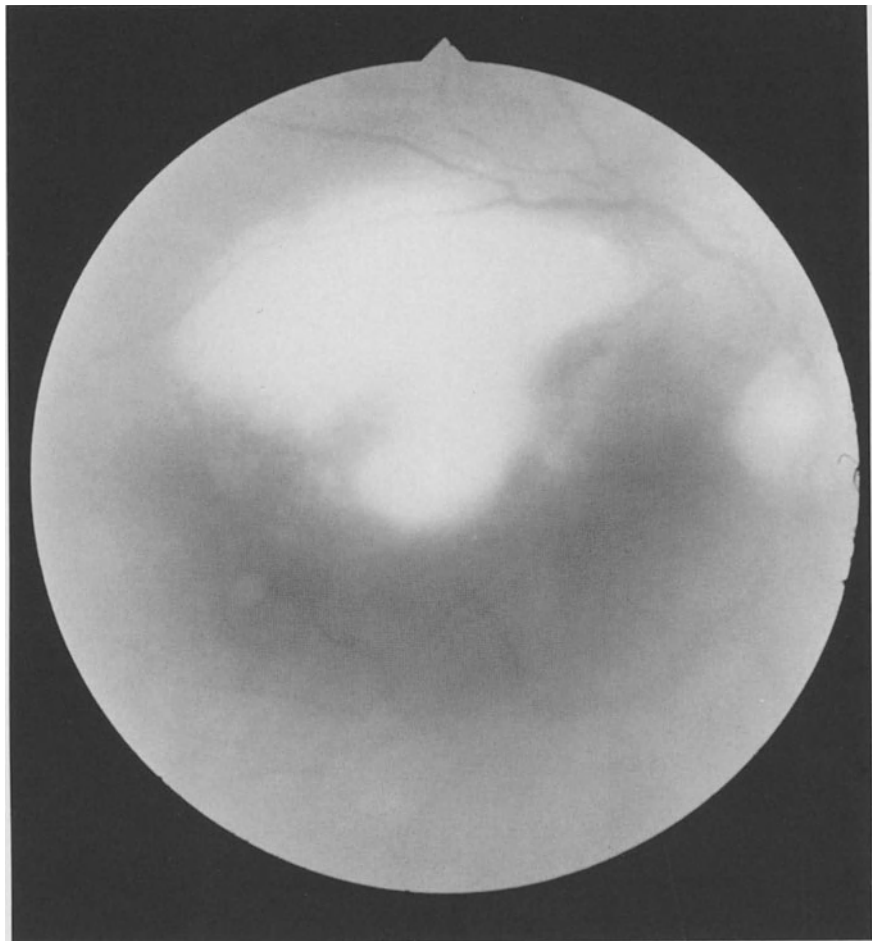

Fig. 4.5. Toxoplasmic choroidoretinitis. Extensive lesion involving the macula

type of drug used modifies the frequency of recurrences. After 6 months of maintenance treatment, recurrence of CMV retinitis was less frequent with foscarnet than with ganciclovir (Le Hoang et al. 1989 b). Recurrences that occur while on maintenance therapy are generally responsive to higher (initial dose) therapy. Cases of resistance to ganciclovir have also been reported (Erice et al. 1989).

Secondary side effects of virostatic agents can limit their use in these patients. Ganciclovir can induce bone marrow toxicity, which enhances the toxicity of zidovudine. Foscarnet can cause renal insufficiency; this can be reversed by stopping administration of the drug. It appears to begin as functional renal insufficiency which progresses to destructive lesions in the kidney (Deray et al. 1989). Foscarnet seems to be a viable therapeutic alternative in the treatment of CMV retinitis especially when the use of other drugs like zidovudine have led to bone marrow depression. Ganciclovir can be injected directly into the vitreous (200 μg) to avoid systemic absorption of the drug. The intravitreous injections are initially given twice a week, followed by treatment once a week as a maintenace dose (Henry et al. 1987; Ussery et al. 1988). This regimen leads to regression or stabilization of the retinitis. The topical route of administration does not, of course, deal with the problem of systemic CMV infection. Other methods of administration are presently under study, in particular intravitreal diffusion drugs (intraocular sustained-release devices), which seem effective for periods of 3–4 months (Sanborn et al. 1992).

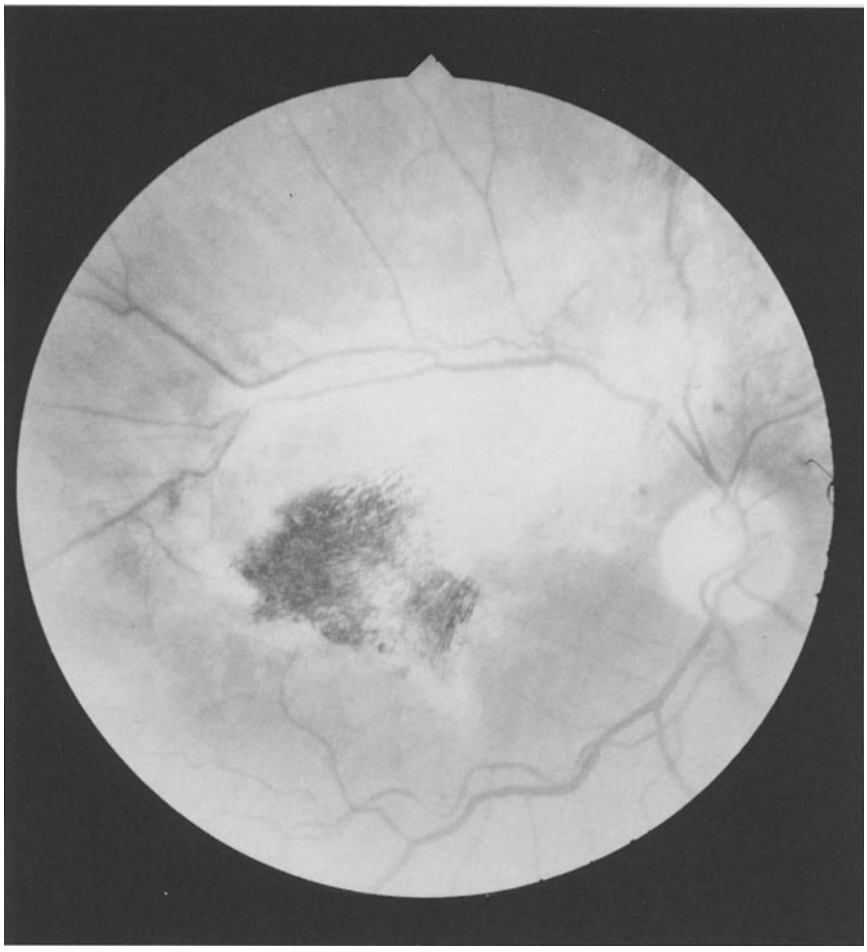

Fig. 4.6. Toxoplasmic choroidoretinitis after 4 months of treatment. The scarred lesion is stable (same patient as Fig. 4.5)

Toxoplasmosis

In dinstinction to cerebral toxoplasmosis, ocular toxoplasmosis is rarely observed in AIDS patients. The incidence is between 2%–4%, although it has been increasing steadily in recent years (Schuman and Friedman 1983; Friedman 1984; Hénin et al. 1987; Le Hoang et al. 1989; De Girolami et al. 1989). The combination of ocular and cerebral toxoplasmosis is observed in around 4% of cases. In spite of its extreme rarity ocular toxoplasmosis can sometimes be the first manifestation of AIDS (Weiss et al. 1986), and in our experience it amounts to as many as two cases per thousand (Le Hoang et al. 1989a). The toxoplasmic lesions observed in patients with AIDS are often multiple. The inflammatory retinal-choroidal focus is yellowish white on funduscopic examination, the borders of the lesion are indistinct, and the lesion itself is slightly elevated and generally nonhemorrhagic. The toxoplasmic retinal necrosis is often accompanied by a significant amount of inflammation, especially in the anterior segment (numerous retrocorneal precipitates, cellular Tyndall phenomenon of the aqueous humor, posterior synechiae) and significant vitreous involvement (Fig. 4.5). The angiographic appearance demonstrates, after the initial blockage effect, a peripheral hyperfluorescence which extends to the center. The zone of hyperfluorescence in the late phase is more extensive than the lesion seen on funduscopic examination, thereby often excluding the possibility of a CMV retinitis. The level of specific antibodies in the aqueous humor is sometimes helpful in rendering a diagnosis, but this may be of little help in patients with AIDS. A specific therapeutic trial is also of diagnostic value.

The classic modality of treatment includes combination therapy with pyrimethamine and sulfadiazine. This treatment sometimes results in side effects, as pyrimethamine can induce neutropenia, and sulfadiazine can lead to allergic reactions. Patients who tolerate the drus should be maintained on them to avoid recurrence. The treated lesion goes on to cicatrization (Fig. 4.6).

In patients with AIDS it has been difficult to determine with certainty whether ocular toxoplasmosis is secondary to acquired or congenital disease. The absence of preexisting retinal scars suggests an acquired infection; on the other hand, there are many instances of reactivated, congenital toxoplasmosis not associated with foci of old scars.

Acute Retinal Necrosis

Acute retinal necrosis is rare in patients with AIDS, occurring once in 26 patients (3.8%), according to Freeman et al. (1986), and in 1% of cases in our experience with 939 patients (unpublished data). The process is that of a severe necrotizing of retinitis beginning at the periphery of the fundus and extending progressively with fingerlike extensions toward the posterior pole. The lesions are often accompanied by vitreous involvement, severe arteritis, and periphlebitis. Although initially described as a strictly unilateral lesion in immunocompetent individuals (Urayama et al. 1971), retinal necrosis can occur bilaterally, at the outset or over time, where it is referred to as bilateral acute retinal necrosis (Topilow et al. 1982). The necrosis leaves behind areas of retinal atrophy, which is the basis for retinal detachments that may occur later in the course of the disease (Culbertson et al. 1983).

The etiology of the disorder is still obscure. Numerous infectious agents have been proposed, supported by clinical serological or histopathological (light- and electron-microscopic) data. Herpesviruses have been the most commonly incriminated pathogenetic agents. Herpes simplex and especially herpes zoster (Culbertson et al. 1986; Freeman et al. 1986) are the most frequently detected viruses. According to Fujikawa (1988), the virus is present only at the beginning of the illness. Retinal biopsies studied at a later date show only retinal gliosis without evidence of virus particles. The pathogenetic role of the Epstein-Barr virus is difficult to establish. Rarely, *Toxoplasma gondii* has been held responsible for the lesions (Parke and Font 1986). Other pathogenetic mechanisms have also been proposed. Culbertson et al. (1983) proposed an immunological theory with precipitation of antigen-antibody complexes on the vascular wall akin to the Arthus phenomenon; Ando et al. (1983) suggested the possibility of an underlying a platelet dysfunction; Kestelyn et al. (1985 a) invoked the role of circulating immune complexes. Topilow et al. (1982) found similarities between the necrotizing vasculities of the syndrome of retinal necrosis and that observed in systemic disorders, in particular, those of disseminated lupus erythematosus. They consider the syndrome of acute retinal necrosis to be a noninfectious manifestation of AIDS.

Treatment of the syndrome of acute retinal necrosis is difficult, and the prognosis for functional recovery is poor. Treatment with intravenous acyclovir has been proposed at a daily dose of 1500 mg in three divided doses with close monitoring of serum creatinine (Blumenkranz et al. 1986; Culbertson et al. 1983; Palay et al. 1991). Acyclovir can also be injected into the vitreous, especially at the time of vitrectomy. Anticoagulants and corticosteriods at high doses have been proposed to counteract a postulated immune phenomenon (Ando et al. 1983). However, in patients with AIDS, administration of corticosteriods is not advisable. In the most severe forms, vitrectomy with injection of silicone oil and associated with a scleral indentation has prevented retinal detachment. Unfortunately, both medical and surgical treatments are disappointing.

Herpetic Retinitis

In distinction to mucocutaneous herpes, herpetic retinitis is a rare disorder in patients with AIDS (Pepose et al. 1984). It leads to retinal necrosis which has a yellow-white floccular appearance with sharp borders and sometimes ensheathes blood vessels and extends to the vitreous. Herpes simplex type I is present in the retinal layers and may also be seen within the endothelial cells. The diagnosis of herpetic retinitis is difficult to establish on clinical grounds alone, especially in patients with AIDS, where there may be numerous superimposed opportunistic infections that obscure the typical picture. CMV may reactivate a latent infection in vitro (Culberg-Poley et al. 1979). The appearance of strains of herpes simplex which are resistant to specific treatment is recognized in experimental studies in the mouse; this possibility is still theoretical in the clinical setting (Pepose et al. 1984). The diagnosis can be entertained in an appropriate clinical

context (herpetic mucocutaneous infection), in patients with the typical ophthalmoscopic appearance, and also taking into account the response to treatment (Fujikawa 1988).

Herpesvirus in partially sensitive to ganciclovir, although this drug is more effective against CMV. On the other hand, due to the lack of response to acyclovir the role of herpesvirus in this form of retinitis is not completely eliminated. In difficult cases retinal biopsy may be necessary to determine with certainty the pathogenetic agent and to select appropriate treatment. The specific treatment for herpes simplex retinitis is acyclovir, administered intravenously at 10 mg/kg three times a day in patients with normal renal function. The treatment is often disappointing (Margolis et al. 1991).

Ocular Candidiasis

Although mucocutaneous candidiasis is extremely frequent in patients with AIDS, intraocular infection by *Candida* is extremely rare (0.4% in our series). Both in our series and in the literature (Schuman and Friedman 1983) it seems to occur in intravenous drug abusers. A case of endophthalmitis caused by *Candida albicans* was described (Heinman 1987) in a bisexual man who was not known to be a drug addict, where the source of infection was presumed to be a urethral catheter.

Contamination of the choroidoretinal tissues is thought to occur by hematogenous disemmination from *Candida* sepsis. Patients with AIDS have only rarely been shown to have *Candida albicans* septicemia (Pepose et al. 1985). Choroidoretinal candidiasis is recognized ophthalmoscopically as multiple foci of creamy white or yellowish discoloration having poorly circumscribed borders, variable size, and frequent extension into the vitreous. The vitreous is the site of rounded, beady deposits that often float freely without attachment to the retina. Signs of uveitis eventually predominate, with the formation of posterior synechiae, sometimes with extensive involvement of the vitreous, which may obscure the typical choroidoretinal lesions. The diagnosis is difficult to confirm without positive blood culture. It should be suspected in drug addicts and in hospitalized patients (catheterized, etc.) who develop cutaneous/scalp candidiasis (with positive culture) and have the characteristic ocular lesion. A diagnostic and/or therapeutic vitrectomy may be considered. The discovery of candidal endophthalmitis in patients with AIDS must be followed by long-term systemic treatment. Amphotericin B administered intravitreously at 5 μg should be initiated at the end of vitrectomy (Elliott et al. 1979). Ketoconazole or 5-flucytosine can be given orally. The combination of these drugs with amphotericin is recommended to avoid the development of resistant strains.

Syphilitic Retinitis

Syphilis is not an opportunistic infection. It may be associated with retinal necrosis, where prognosis is better than in cases caused by some of the viral agents described above. It is difficult to reach a definitive diagnosis since the clinical aspects of syphilitic retinitis may be confusing. Syphilitic retinitis is rare; it presents ophthalmoscopically as a large whitish blotch without evidence of hemorrhage (Berry et al. 1987; Johns et al. 1987; Stoumbos and Klein 1987; Tramont 1987). Although differential diagnosis with CMV retinitis is generally clearcut from the ophthalmoscopic examination, it is sometimes difficult to rule out toxoplasmic or other types of infection. The diagnosis can be confirmed by specific serology, which often shows very high titers, and by the excellent clinical response to penicillin, which must be administered intravenously at very high doses – 20×10^6 IU per day for 3 weeks. Ocular involvement can sometimes be associated with clinical neurological signs and symptoms (Johns et al. 1987). The extreme gravity that complications of syphilis may have in immunosuppressed patients underlines the need to diagnose and treat the infection promptly.

Other Infectious Agents

Other infectious agents often recognized only at autopsy examination include: *Mycobacterium avium intracellulare* (Pepose et al. 1985), Pneumocystis carinii (Rao et al. 1989; Dugel et al. 1990) *Cryptococcus neoformans,* and *Histoplasma capsulatum* (Macher et al. 1985; Newman et al. 1983; Pepose et al. 1985). These rare intraocular infections are often associated with CMV retinitis.

■ Involvement of the Anterior Segment

Ophthalmic Zoster

Ophthalmic zoster can be the first manifestation of HIV infection in previously healthy young individuals (Cole et al. 1984; Sandor et al. 1986). Since ophthalmic zoster ordinarily affects older individuals, the occurrence of such a lesion in young patients suggests an early clinical manifestation of immunosuppression secondary to AIDS. Patients with AIDS have a high incidence of corneal (punctate, dendritic, or stromal keratitis complication) and uveal (iridocyclitis) disease (57 %–86 %). Treatment is based primarily on antiviral agents (vidarabine, acyclovir) administered either systemically or topically. In spite of therapy, ocular lesions often become chronic and are frequently recurrent. Isolated zoster keratitis without cutaneous eruption may present with a dendritic aspect that can mimic herpes simplex infection (Engstrom and Holland 1988).

Other Forms of Keratitis

Herpes simplex keratitis and fungal keratitis due to *Candida albicans* (Santos et al. 1986) or *Candida parapsilosis* (Parrish et al. 1987) are observed in AIDS patients. Keratis may also be secondary to a syndrome of ocular keratoconjunctivitis sicca (3 % of patients in our series; Khadem et al. 1984); this syndrome can be aggravated by drug treatment. Keratoconjunctivitis secondary to CMV has also been described in this context (England et al. 1982).

■ Neoplasms

Kaposi's Sarcoma

Kaposi's sarcoma is found especially in homosexual patients with AIDS (45 %) and is encountered less often in drug addicts or heterosexuals with the disease (4 %) (Friedman-Kien 1978). It appears as dark purple nodules or plaques on the skin. In patients with AIDS, the lesions are disseminated. At the onset, Kaposi's sarcoma can involve the mucosa (oral, digestive, or genital). Examples have also been described of visceral and lymph node involvement. Conjunctival or palpebral Kaposi's sarcoma is the third most common ocular lesion in patients with AIDS after CWS and CMV retinitis. In most series it is described in 0 %–10 % of cases (in our series 2.5 %). It may present in two different forms: as a small reddish nodule, a few millimeters in diameter, or a reddish, fleshy, sometimes pedunculated, and well-vascularized appearance. The lesion may be obscured by a subconjunctival hemorrhage. The differential diagnosis includes chalazion, foreign body granuloma, cavernous hemangioma, melanoma, and metastatic tumor. Kaposi's angiosarcoma is characterized by a proliferation of newly formed blood vessels within a stroma containing fusiform cells.

Kaposi's sarcoma has been associated with antigens of the HLA system: AW 19, DR 5, and recently DRW 53 (Brenner et al. 1982; Friedman-Kien 1978; Safai et al. 1985). Herpeslike viral particles have been described in tissue cultures of the tumor; there is also a concomitant elevation in anti-CMV antibody titers (Dicarlo et al. 1986). According to these authors an oncogenic effect on the virus is of possible etiological significance. In addition, a growth factor is elaborated by CD 4 cells infected by HIV-1 and HIV-2 that seems to have activity on the fusiform cells of Kaposi's sarcoma as well as on normal endothelial cells. Finally, the fusiform cells are capable of producing an endothelial growth factor. Theoretically, the tumor can grow by the release of growth factors secreted by CD 4-infected cells (Salahuddin et al. 1988).

Conjunctival Kaposi's sarcoma rarely requires surgical intervention. Chemotherapy (bleomycin) or immunotherapy (alpha-interferon) can be tried in disseminated Kaposi's sarcoma.

Non-Hodgkin's Orbital Lymphoma

An extremely high incidence of non-Hodgkin's lymphoma has been observed in patients with AIDS. The prognosis in these patients is extremely grave. The development of lymphoma in AIDS is due to an unchecked proliferation of monoclonal B-cells secondary to a defect in T-cell regulation or a transformation of the B-cells by a virus. B-cell transformation has been postulated to be due to infection by Epstein-Barr or other virus (Purtillo 1980). In Africa, where Kaposi's sarcoma and Burkitt's lymphoma are endemic, there is a strong association between CMV and Kaposi's sarcoma and between EBV and Burkitt's lymphoma (Giraldo et al. 1980).

Although cerebral lymphoma is often observed in patients with AIDS, ocular orbital lymphoma is quite

rare. The initial presentation can be confusing, as the ophthalmoscopic appearance can mimic that of uveitis (Lopez et al. 1991). The diagnosis is based on radiological examination, biopsy of the tumor, or analysis of the vitrectomy fluid, combined with histological and immunocytochemical examination. Chemotherapeutic regimens (chlorambucil, cyclophosphamide, vincristine) and radiotherapy are indicated to reduce tumor volume.

■ Neuro-ophthalmological Manifestations

Cerebral lesions found in patients with AIDS are responsible for the neuro-ophthalmological manifestations: oculomotor palsies, disturbances of conjugate eye movement, visual field defects, optic neuropathies, and visual hallucinations. These lesions are either secondary to a direct attack by HIV-1 on the nervous system or due to secondary involvement of the nervous system (aseptic meningitis, dementia, cerebral lymphoma, increased intracranial pressure, or opportunistic infection by bacteria, fungi, virus, or parasites). The incidence of neuro-ophthalmological manifestations in patients with AIDS is about 6%–8% (Le Hoang et al. 1989a; Mansour 1990; Jabs et al. 1989; Freeman et al. 1984; Palestine et al. 1984). The neurological manifestations in patients with AIDS approach 60%, and neuropathological evidence of CNS involvement reaches 90% in autopsy studies (Gabuzda et al. 1986; De Girolami et al. 1989; De Girolami et al. 1990).

Ocular motor palsies of III, IV, and VI nerves may be unilateral or bilateral. They are often secondary to an intracerebral infectious focus in the vicinity of the cranial nerve nucleus. Cerebral toxoplasmosis is the most frequently described etiological agent. There can also be extrinsic oculomotor palsies, intrinsic palsies (pupillary Bernard-Horner syndrome) and conjugate palsies (Snider et al. 1983; Antworth and Beck 1987; Berger et al. 1987; Freeman et al. 1984; Hamed et al. 1988). The clinical diagnosis of cerebral toxoplasmosis is sometimes difficult to establish. Radiological imaging studies may show a distinctive picture with contrast ring enhancement. Serology for toxoplasmosis may also be helpful, although it is not always positive in patients with AIDS. Improvement after specific treatment (clinical improvement or stabilization and radiological evidence of cicatrization of the lesions) strongly supports the diagnosis of toxoplasmosis. Nevertheless, histological examination may be necessary to confirm the diagnosis.

Herpetic involvement has been reported. A patient with cutaneous zoster who developed paralysis of the IV and V nerves improved after systemic treatment with acyclovir (Palestine et al. 1984; Mansour 1990).

Disturbances of ocular motility are sometimes early manifestations of cerebral lymphoma (Snider et al. 1983; Palestine et al. 1984; Mansour 1990). Increased intracranial pressure in the setting of cryptococcal meningitis associated with basal arachnoiditis can lead to involvement of cranial nerves (Freeman et al. 1984; Palestine et al. 1984). Tuberculous meningitis can also give rise to ocular motor palsies due to similar mechanisms (Le Hoang et al. 1989).

Optic nerve neuropathies include papilledema, papillitis, acute anterior ischemic optic neuropathies, and retrobulbar neuropathies. Papilledema is frequent (Mansour 1990) and may result from a cryptococcal meningitis, cerebral toxoplasmosis, or intracerebral lymphoma.

Papillitis can be the result of retinal infection with CMV extending along the nerve fiber layer. It responds to specific antiviral treatment. Secondary optic atrophy can occur after extensive scarring of the retina. Acute anterior ischemic optic atrophy may be associated with circulatory disturbances similar to arterial occlusion at the optic nerve head; it may also be associated clinically with papilledema (Mansour 1990).

Retrobulbar neuritis suggests neurosyphilis (Carter et al. 1987; Hamed et al. 1988; Zaidman 1986). The diagnosis is supported by positive serology (fluorescent treponemal antibody-absorption test 4+). Nevertheless, negative serological results of the CSF do not rule out the diagnosis, and a favorable response to treatment supports it (Hamed et al. 1988).

Visual field defects are related to involvement of the visual pathways. These may be secondary to intracerebral infections, cerebral lymphomas, progressive multifocal leukoencephalopathy, or to AIDS encephalitis (Snider et al. 1983). Homonymous hemianopsia was present in one third of patients with progressive multifocal leukoencephalopathy (Slavin et al. 1989). Among the 18 patients reported 12 had ophthalmological symptoms with progressive multifocal leukoencephalopathy (six had temporal homonymous hemianopsia and one inferior quadrantanopsia). Computed tomography (CT) showed evidence of hypodense lesions that did not enhance with contrast. These lesions were noted along the visual pathways. Magnetic resonance imaging (MRI) was able to demonstrate lesions that were missed by CT, and this is presently the neuroradiological examination of choice (Berger et al. 1987).

When it involves the optic pathways, cerebral toxoplasmosis can give rise to the field defects (Snider et al. 1983; Le Hoang et al. 1989; Girard et al. 1989). Visual hallucinations and cortical blindness (Hamed et al. 1988; Schuman et al. 1987) are rarely observed and can be associated with an infectious or neoplastic process in the occipital cortex. Neuro-ophthalmological examination in patients with AIDS can ascertain preclinical involvement of the nervous system by HIV. The discovery of an ocular motor or visual field defect in such patients should be followed by radiological study (CT or MRI). The radiological picture may suggest progressive multifocal leukoencephalopathy or cerebral toxoplasmosis. Neurosyphilis, tuberculous meningitis, and cryptococcal meningitis should also be excluded.

■ Conclusion

Ophthalmic manifestations of AIDS are nonspecific. Retinal involvement is frequent (66% of cases) and often subclinical (CWS, early viral retinitis), thus indicating systemic ophthalmological examination in these patients. CWS are associated with a less favorable prognosis. Opportunistic infections may involve the eye. CMV retinitis is the result of systemic dissemination and can occasionally be an early manifestation of AIDS. This is often associated with a poor prognosis. Funduscopic examination is a noninvasive and efficient clinical method to identify and follow an infectious process in these patients.

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Chapter 5

Ocular Pathology of AIDS

P. McKelvie, U. De Girolami, D. Hénin, and J.-J. Hauw

Over the past 10 years a number of studies from North America, Europe, and Africa have described in detail the range of clinical ophthalmological manifestations observed in patients with AIDS (Khadem et al. 1984; Palestine et al. 1984; Pepose et al. 1985; Mines and Kaplan 1986; Schuman et al. 1987; Fabricius et al. 1988; Holland and Kreiger 1988; Kreiger and Holland 1988; Martenet 1988; Nussenblatt 1988; Culbertson 1989; Jabs et al. 1989 b; Jensen and Klinken 1989; Le Hoang et al. 1989; Ward et al. 1989; Bienfang et al. 1990; Deschenes et al. 1990; Kestelyn 1990; Jabs 1992). Ophthalmic disorders are much less frequent in children with AIDS (Dennehy et al. 1989). It is now recognized that as many as 90% of adult patients with AIDS develop ocular lesions during the course of their disease, and there are many detailed accounts of the histopathology of the eye at postmortem examination. We have previously reported a series of cases from the R. Escourolle Laboratory at the Hôpital de La Salpêtrière that were carefully followed clinically and that received complete autopsy examinations including a study of the eyes (De Girolami et al. 1989 a, b). Subsequently we have studied over 80 cases; these form the basis of our experience reported here. The ophthalmological manifestations of AIDS can be subdivided into five general categories: retinal microvascular disorders, infectious diseases, diseases of the cornea and conjunctiva, neoplasms, and neuro-ophthalmological disorders.

■ Retinal Microvascular Disorders

Cotton-wool spots (CWS) are the most frequent ocular lesions in patients with AIDS, observed in 50%–90% of cases (Holland and Kreiger 1988; Nussenblatt 1988; Pivettiv-Pezzi et al.1988; Jabs et al. 1989 b; Bernauer and Daicker 1990). On funduscopic examination they appear as whitish, superficial, flocculent, retinal lesions ranging from one eighth to one half the papillary diameter. They occur most often on the temporal side of the posterior pole. The lesions may regress after 4–6 weeks and recur, leaving no evidence of a residual scar on funduscopic or angiographic study. CWS have long been recognized in systemic disorders associated with disturbances of the retinal microcirculation, such as hypertension, diabetes mellitus, systemic lupus erythematosus, leukemia, and Waldenström's macroglobulinemia (Ashton and Harry 1963; Brown et al. 1985). Histological studies (Ashton and Harry 1963; Pepose et al. 1985) have shown that CWS are foci of retinal thickening of the nerve

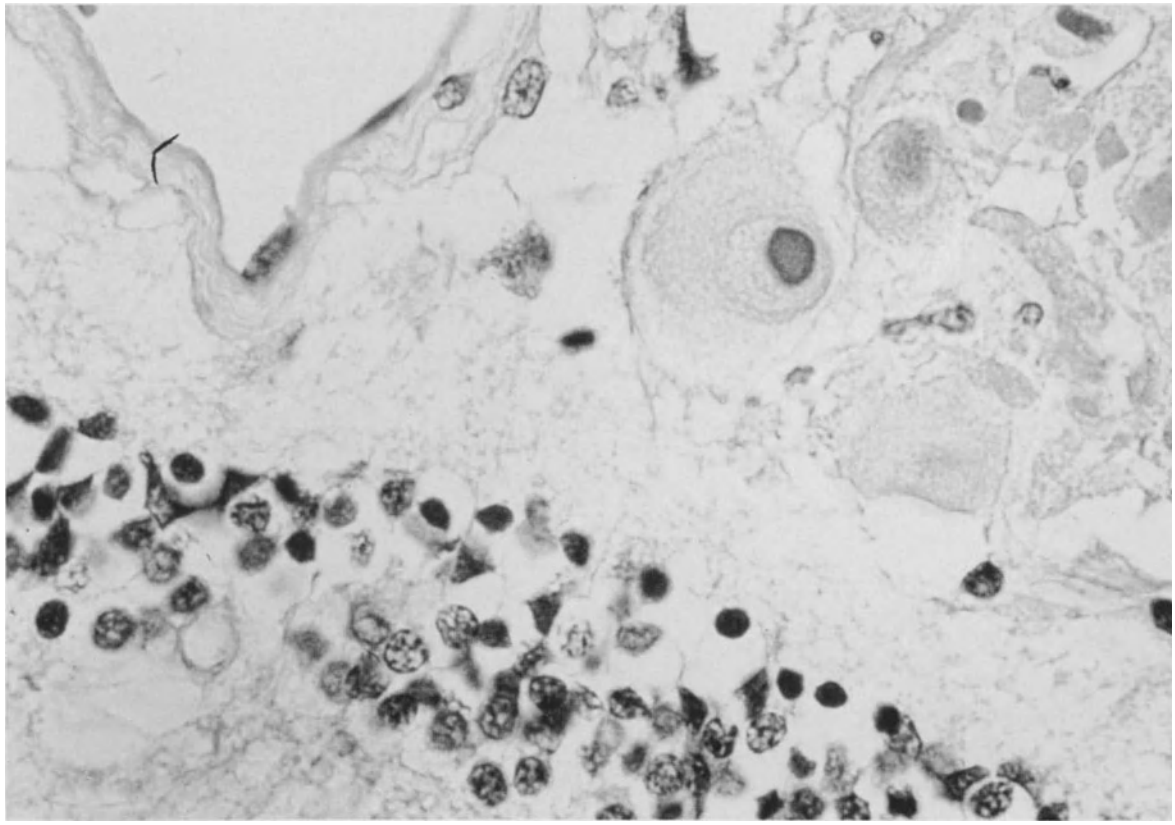

Fig. 5.1. Cotton-wool spots. Cross-section of retina showing nerve fiber layer at top. Note several cytoid bodies with dense eccentric cores. H&E, ×350

fiber containing "cytoid bodies," i.e., eosinophilic hyaline structures about 50 μm in average diameter with a poorly defined dense core (Fig. 5.1). The axonal nature of the lesion can be well demonstrated with silver impregnation techniques (Fig. 5.2). CWS have been produced experimentally with laser photocoagulation of retinal arterioles, and it is suggested that they are ischemically derived axonal swellings due to interruption of retrograde and/or anterograde axoplasmic transport (McLeod et al. 1977; Chihara 1983; Murata and Yoshimoto 1983).

McLeod (1981) reviewed the extensive literature and discussed the postulated mechanisms of the formation of CWS in AIDS. Histologically, CWS are identical in AIDS and non-AIDS cases. Hypothetical mechanisms of injury include infection of the vessel itself or perivascular cells by viruses (cytomegalovirus, CMV; HIV-1?), microthrombosis or embolization, and altered vascular permeability (Newsome et al. 1984). Their pathogenetic relationship to *Pneumocystis carinii* (Kwok et al. 1982) is in doubt. Calcification of cytoid bodies occurs rarely and may be related to alterations in the blood-retinal barrier (Tanenbaum et al. 1987). The demonstration of circu-

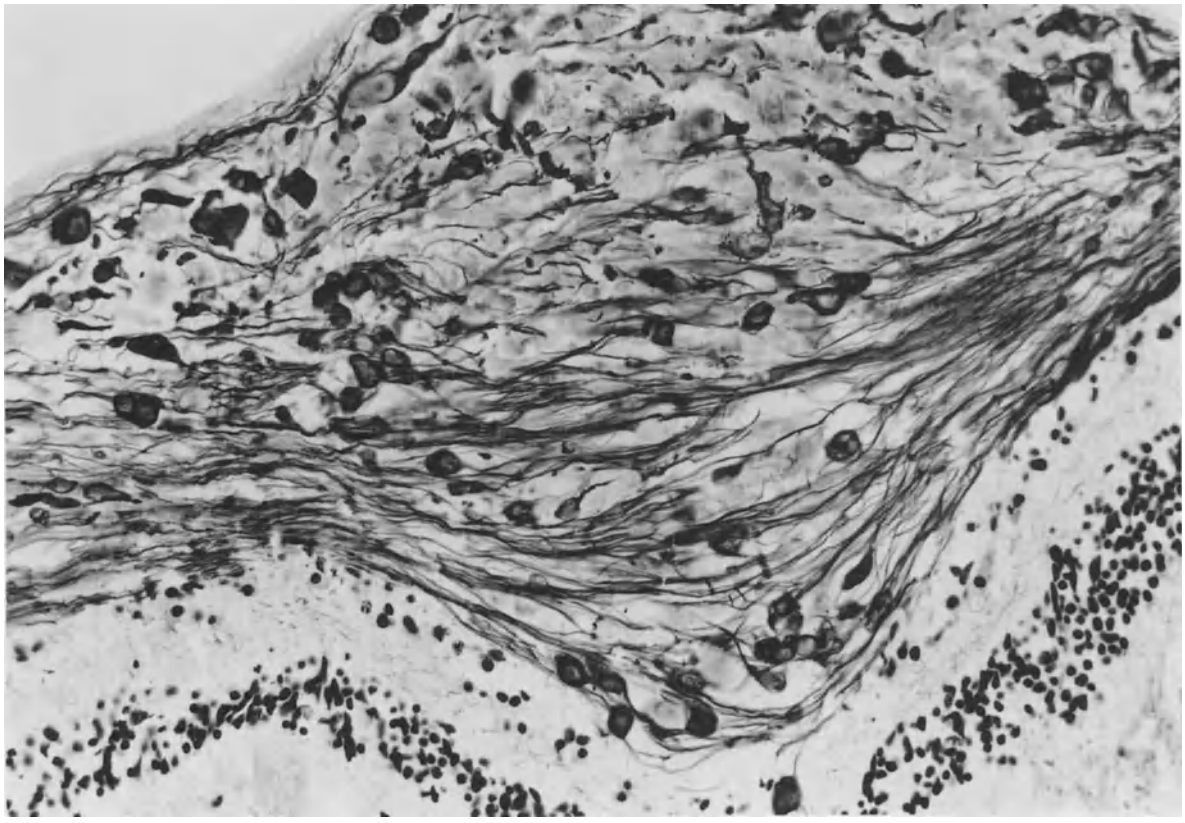

Fig. 5.2. Cotton-wool spots. Cross-section of retina showing axons running in nerve fiber layer at top. Note axonal swelling corresponding to site of cytoid bodies. Bodian, × 294

lating immune complexes associated with occluded blood vessels in the retina (Pepose et al. 1985) and other tissues (see review by Ammann 1989) also suggests an alteration in the microcirculation. Axonal swellings in the cytoid bodies are identical to axonal swellings described in the brain stem and spinal cord of patients with AIDS with acute occlusion of small blood vessels (Giangaspero and Foschini 1988; Johnson 1989).

Other ophthalmoscopic findings indicative of vascular disease include retinal hemorrhages and ischemic maculopathy (Mines and Kaplan 1986; Schuman et al. 1987; Holland and Krieger 1988; Freeman et al. 1989 a). Kestelyn et al. (1985) reported clinical evidence of perivasculitis in African children with the AIDS-related complex. Microaneurysms have been observed clinically by funduscopy-angiography and demonstrated pathologically by trypsin digestion preparations of the retina (Newsome et al. 1984; Pepose et al. 1985).

Macular edema associated with microvascular retinal disease (Palestine and Frishberg 1991) and branch retinal-artery occlusion have been observed (Yassur et al. 1988).

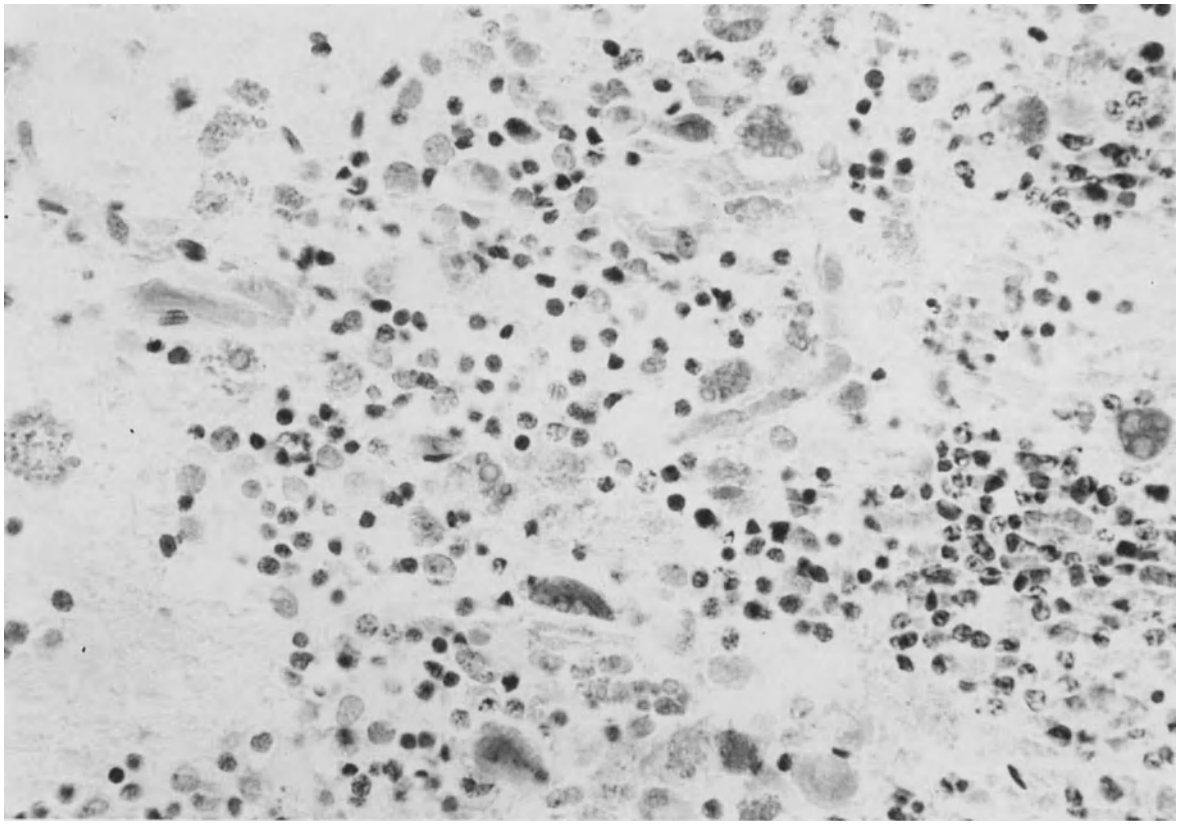

Fig. 5.3. Cytomegalovirus retinitis. Cross-section of mid-retina showing many CMV-infected cells with intranuclear and intracytoplasmic granular material. H&E, ×300

■ Infectious Agents

Viruses

A variety of infectious agents have been reported to infect the retina and choroid in patients with AIDS (see reviews by Culbertson 1989; Pavan-Langston 1990).

Cytomegalovirus Retinitis

The second most frequently observed clinical ophthalmological abnormality in AIDS patients is CMV retinitis, and CMV is the most common ocular infectious pathogen –15%–40% of cases (Dhermy et al. 1984; Mines and Kaplan 1986; Schuman et al. 1987; Bloom and Palestine 1988; Holland and Krieger 1988; Palestine 1988; Cantrill et al. 1989; Hennis et al. 1989; Jabs et al. 1989a; Bernauer and Daicker 1990; Cochereau-Massin et al. 1990; Schmidt-Gräff et al. 1990). The funduscopic appearance of early CMV retinitis is that of an irregular, well-demarcated, yellowish, flat lesion which occurs along the vascular arcades and generally begins at the posterior pole (Gass 1987; Bloom and Palestine 1988). As the infection progresses, there may be associated foci of hemorrhage. The histological appearance of CMV retinitis in AIDS patients is similar to that observed in individuals receiving immunosuppressive drugs and to that of newborns with disseminated CMV (Smith et al. 1966; Cogan 1977; Egbert et al. 1980). The early lesion consists of single, greatly enlarged cells with large viral intranuclear inclusions. The intranuclear inclusions have a homogeneous amphophilic hue on hematoxyllin-eosin preparation and may vary considerably in diameter (<1–10 μm; Fig. 5.3). A clear zone between the nuclear chromatin aggregated along the nuclear envelope and the intranuclear inclusions gives an owl's eye appearance. Intracytoplasmic granular inclusions of viral material can be well demonstrated with immunocytochemical reactions (Fig. 5.4). In the acute florid

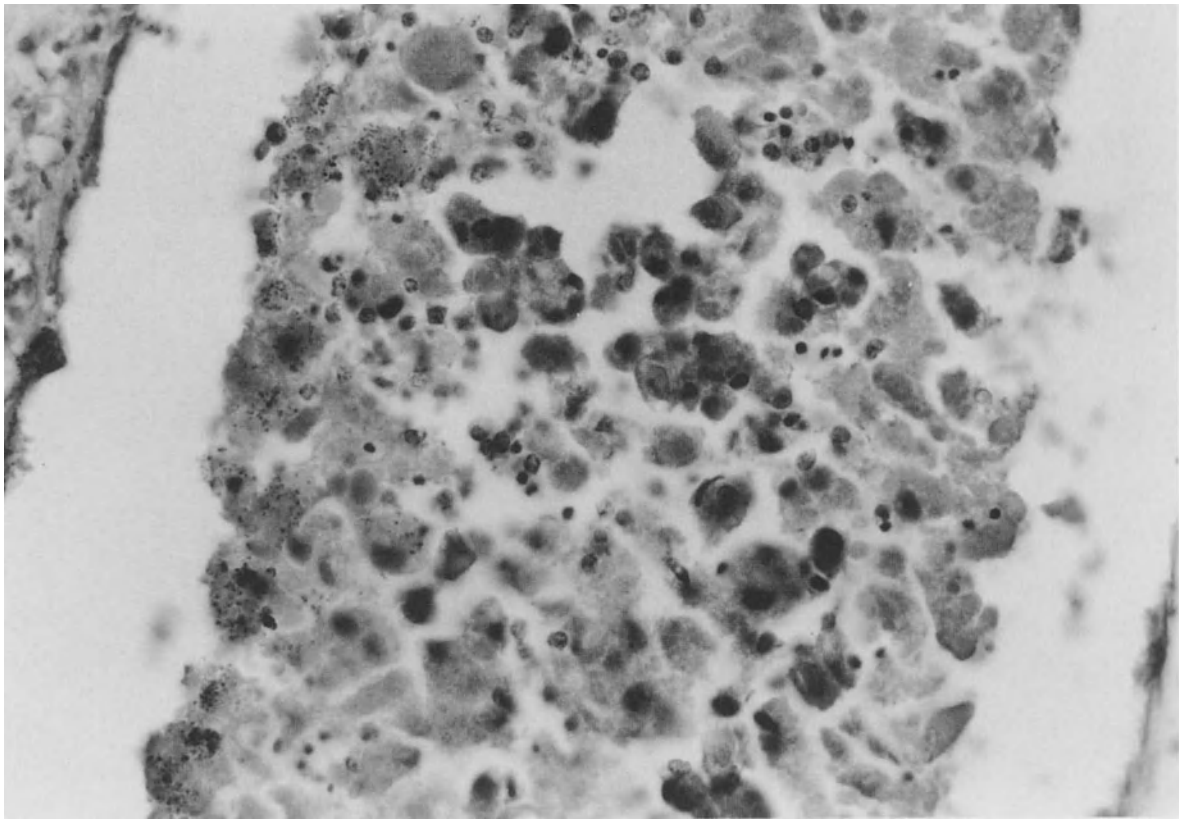

Fig. 5.4. Cytomegalovirus retinitis. Immunohistochemical localization for CMV shows viral antigen in the nucleus and cytoplasm of retinal cells. Anti-CMV immunoperoxidase, ×350

lesion there are multiple discrete foci of hemorrhagic necrosis in all layers of the retina, retinal pigment epithelium, optic nerve, and vitreous.

Even after intravenous treatment with ganciclovir with subsequent clinical improvement, ultrastructural and immunocytochemical investigation of the involved eye at postmortem may still demonstrate widespread infection (Teich et al. 1988). Intravitreal treatment with ganciclovir may prove to be a more effective method of treatment (Cantrill et al. 1989; Cochereau-Massin et al. 1990). By light-microscopic examination it is not always possible to be certain of the precise type of retinal cell that harbors the infection. Inclusions may be seen clearly in ganglion cells or cells having cytoplasmic extensions suggestive of glia. Infected cells can form syncytia and multinucleated forms. Ultrastructural and immunocytochemical investigations of CMV retinitis and CMV encephalitis have demonstrated conclusively that glia, neurons, and macrophages are capable of harboring the virus (Holland et al. 1983; Newman et al. 1983; Jensen et al. 1984; Palestine et al. 1984; Grossniklaus et al. 1987; Morgello et al. 1987). A recent study demonstrates infection of retinal endothelial cells by in situ hybridization and electron microscopy (Schmitt-Gräff et al. 1990). Surprisingly, in view of the extent of retinal destruction, there is remarkable little inflammatory response. We have observed a fairly constant mild to moderate chronic inflammatory response in the choroid. Older or treated lesions typically consist of foci of thinning out of the retina to the point that the normal layers– are no longer recognizable (Fay et al. 1988). There remains a plate of glial-fibrous tissue which may be heavily calcified (Fig. 5.5).

CMV retinitis is usually a late manifestation in AIDS although it has been reported as the initial presentation (Sison et al. 1991). Ganciclovir is an effective treatment for CMV retinitis, but up to 29 % of patients may still develop retinal detachment during or after treatment (Freeman et al. 1987). Despite successful surgical repair of the retinal detachments, significant recovery of visual function is often limited (Dugel et al. 1991; Fig. 5.6).

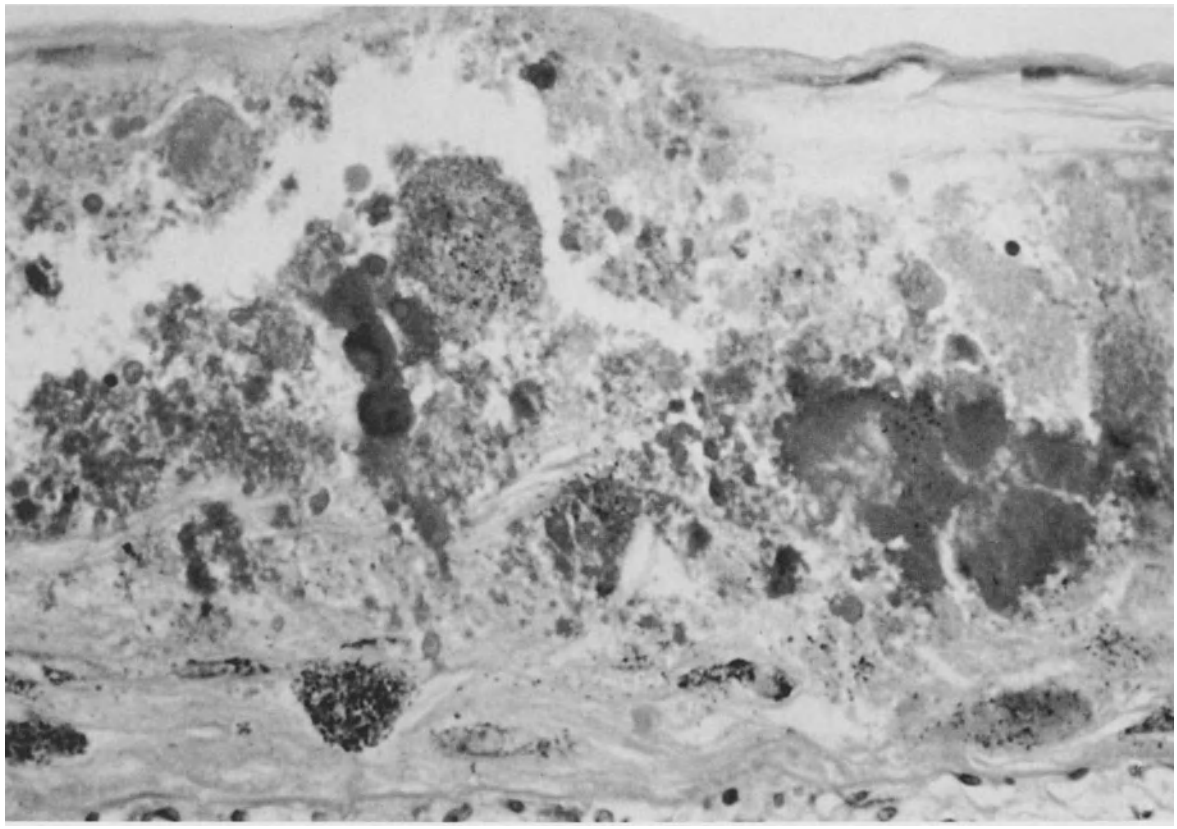

Fig. 5.5. Cytomegalovirus retinitis. Cross-section of severely destroyed retina showing multiple foci of calcification. H&E, × 350

HIV-1 Infection

Retinal infection with HIV-1 has been documented in five reports. Pomerantz et al. (1987) found no histological abnormality in the retina of the two cases examined. HIV-1 immunoperoxidase studies on frozen retinal tissue and virological search for HIV-1 on retinal homogenates successfully demonstrated the virus. The nature of the infected cells remains unclear. In a second study, Cantrill et al. (1988) detected HIV-1 by tissue culture methods and enzyme-linked immunosorbent assay in one retina, iris, conjunctiva, and cornea. In one of three cases HIV-1 was demonstrated in the retina by immunofluorescence (monoclonal antibody to HIV p24). Skolnik et al. (1989) reported two cases of dual retinal infection with HIV-1 and CMV by culture, immunofluorescence (anti HIV-1 polyclonal) and immunohistochemistry (monoclonal antibodies to gp120 and p24 antigens), including coinfection of individual cells. Culture for HIV-1 was positive in 8/13 retinas, both with and without ocular lesions. Cases with dual infection showed severe full-thickness necrotizing retinopathy. Immunohistochemical study showed CMV antigens in scattered cells in all retinal layers but not in retinal endothelial cells. HIV-1 antigens were detected in cytoplasm of scattered cells in all retinal layers, cytomegalic cells, retinal endothelium, and normal retina. In one patient, in whom the retinas were positive for HIV-1 antigens and culture, funduscopic examination showed CWS and retinal hemorrhages. In two other cases where retinal cultures were positive for HIV-1 no gross lesions were noted.

Qavi et al. (1989) demonstrated HIV-1 in retinal inflammatory lesions by immunofluorescent techniques (two cases) and in total retinal tissue by the polymerase chain reaction to detect HIV-1 DNA sequences (four cases, including two of the ones positive by immunofluorescence). In the fifth report (Schmitt-Gräff et al. 1990), p24 HIV-1 antigen was detected by the immunoperoxidase method in retinal glial cells of both eyes in a patient with coexistent CMV retinitis

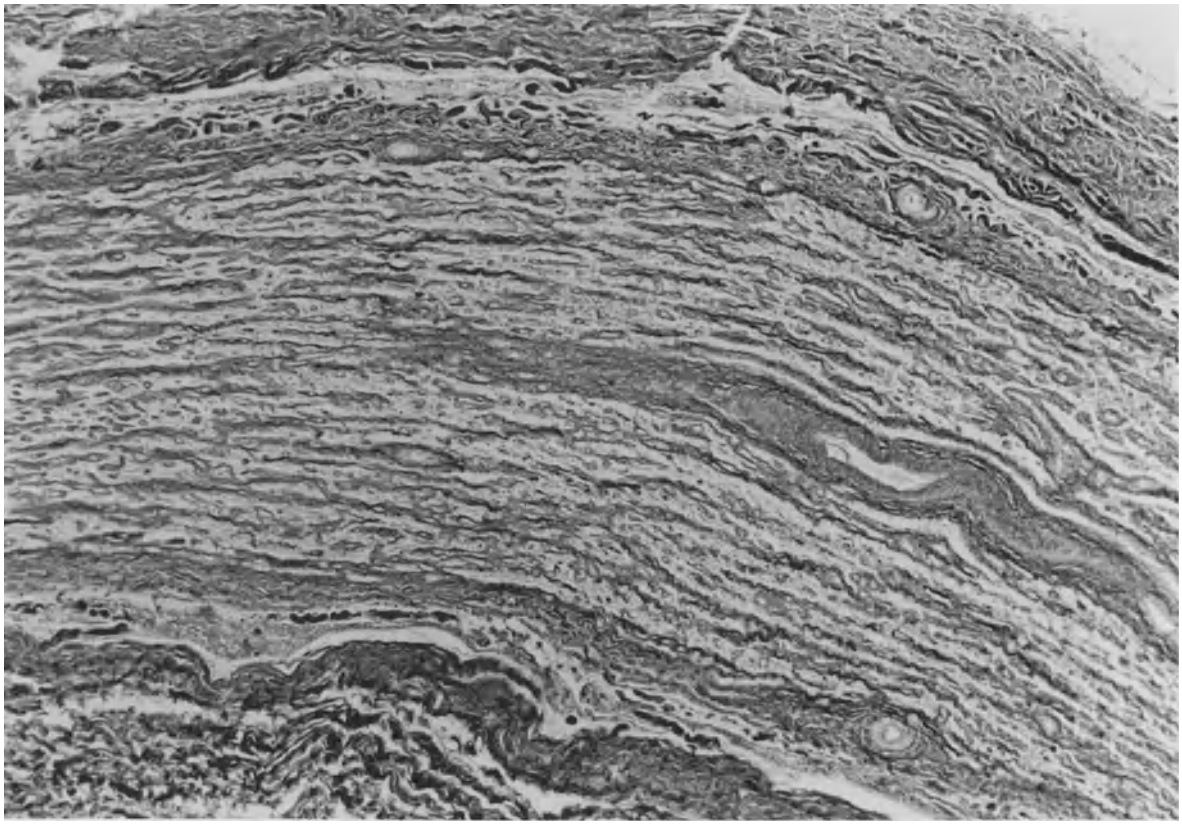

Fig. 5.6. Secondary effect of cytomegalovirus retinitis. Longitudinal section of optic nerve showing extensive loss of myelinated nerve fibers and prominent connective tissue septi. Bodian/LFB, × 50

and CNS toxoplasmosis. HIV-1 has been shown productively to infect human glial cells in tissue culture (Cheng-Mayer et al. 1987). The virus has also been identified in the tears (Fujikawa et al. 1986), conjunctival epithelium (Fujikawa et al. 1985), cornea (Doro et al. 1986; Salahuddin et al. 1986), and aqueous humor (Kestelyn et al. 1986) of affected individuals.

Herpetic Infections

Infection of the eye in patients with AIDS due to herpesviruses appears to be infrequent. Culbertson et al. (1986) described two cases of varicella-zoster virus necrotizing retinitis, confirmed by immunoperoxidase methods using a monoclonal antibody directed against the viral glycoprotein antigens. The virus was also cultured from the vitreous in one case. Similar cases of necrotizing retinitis were described by Forster et al. (1990). A dual retinal infection with CMV and herpes simplex virus was observed in a patient who was also shown to have herpes simplex virus and CMV in the brain by immunocytochemistry (Pepose et al. 1984). Herpes zoster ophthalmicus in the distribution of the first division of the trigeminal nerve has been noted clinically as an important and perhaps early manifestation of AIDS, especially in Africa (Cole et al. 1984; Sandor et al. 1986; Kestelyn 1990).

Varicella-zoster virus has recently been implicated in the development of a rapidly progressive necrotizing retinitis in AIDS patients, resulting in atrophic, necrotic retinae and optic nerve-head pallor. Although superficially similar to the acute retinal necrosis snydrome, it lacks certain features such as the paucity of iridocyclitis, vitreitis, or vascular sheating. The cherry-red appearance of the macula and the failure to develop vitreal bands or retinal detachments, is distinctive of patients with AIDS (Nussenblatt and Palestine 1991).

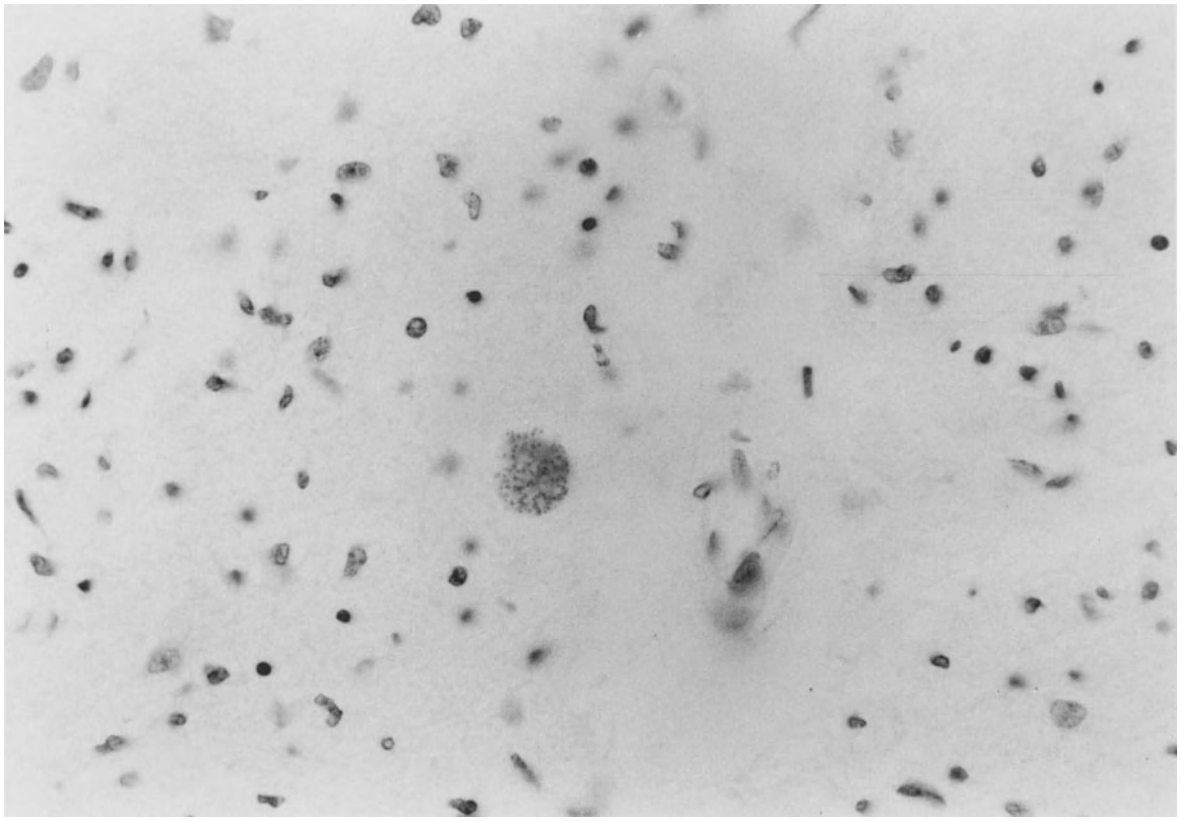

Fig. 5.7. Optic nerve toxoplasmosis. Cross-section of optic nerve showing extensive gliosis and encysted bradyzoite of *T. gondii*. H&E, × 350

Parasites

Although toxoplasmosis is the most common nonviral intracranial infection in AIDS patients (Anders et al. 1986; Navia et al. 1986), only a few cases of AIDS-related ocular toxoplasmosis have been documented histopathologically (Friedman 1984; Parke and Font 1986; Holland et al. 1988a; see reviews by Schuman and Friedman 1983; Weiss et al. 1986; Heinemann et al. 1986; Grossniklaus et al. 1987; Holland 1989; Pillai et al. 1989; Gagliuso et al. 1990). The organism can involve the retina and cause a necrotizing retinitis, chronic choroiditis and/or optic neuritis. In the eight patients of ocular toxoplasmosis studied by Holland et al. (1988b), five had coexistent intracranial toxoplasmosis. In two case series from Paris and Copenhagen in which a total of 68 postmortem cases with complete brain and eye examinations were carried out in every case, there was only one case which showed toxoplasmosis in both brain and eye (Fig. 5.7; De Girolami et al. 1989a, b; Jensen and Klinken 1989). A recent series reported 16 cases of ocular toxoplasmosis, 7 of whom also had CNS toxoplasmosis (Gagliuso et al. 1990). Since the retinal lesions were

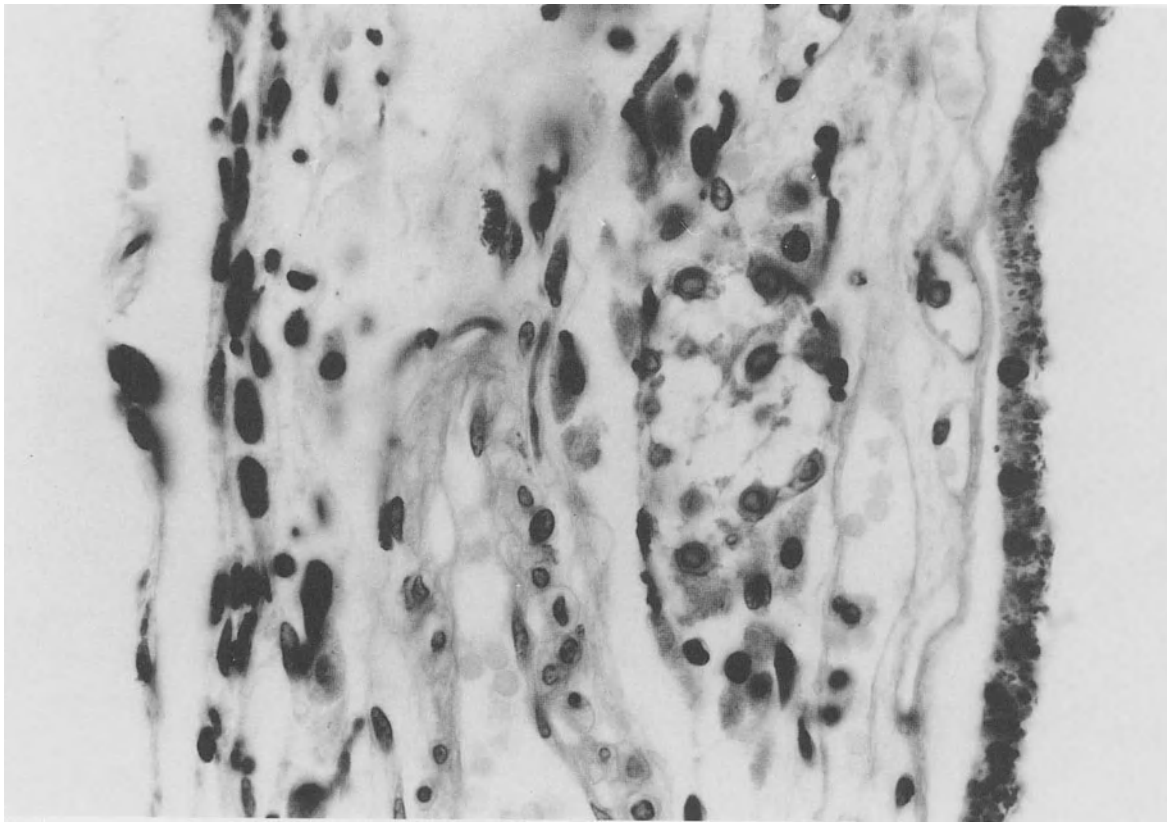

Fig. 5.8. Pneumocystosis in choroidal blood vessel. Patient with disseminated *Pneumocystis carinii* infection shows organisms in choroidal vessel demonstrated with specific immunoperoxidase reaction. (Courtesy of Prof. G. Grosse, Berlin) Anti-*P. carinii* immunoperoxidase, ×350

not associated with a preexisting retinochoroidal scar, it has been suggested that the lesions reflect acquired rather than congenital disease.

Pneumocystis carinii choroiditis has been documented in a few cases (Fig. 5.8; Freeman et al. 1989b; Rao et al. 1989; Dugel et al. 1990; Sneed et al. 1990).

Other Infrequent Infections

The following infectious agents have been described affecting the eye in single case studies: *Cryptococcus neoformans* (Fig. 5.9; Newman et al. 1983; Pepose et al. 1985; Carney et al. 1990), *Histoplasma capsulatum* (Macher et al. 1985; Specht et al. 1991), *Sporothrix schenckii* (Kurosawa et al. 1988), *Candida albicans* (Friedman 1984), *Microsporidium* (keratoconjunctivitidis; Friedberg et al. 1990), *Mycobacterium tuberculosis* (Croxatto et al. 1986; Blodi et al. 1989), *Mycobacterium avium intracellulare* (Pepose et al. 1985), and *Treponema pallidum* (Passo and Rosenbaum 1988; Levy et al. 1989). Rarely, bacterial retinitis may occur in the context of sustained immunosuppression with

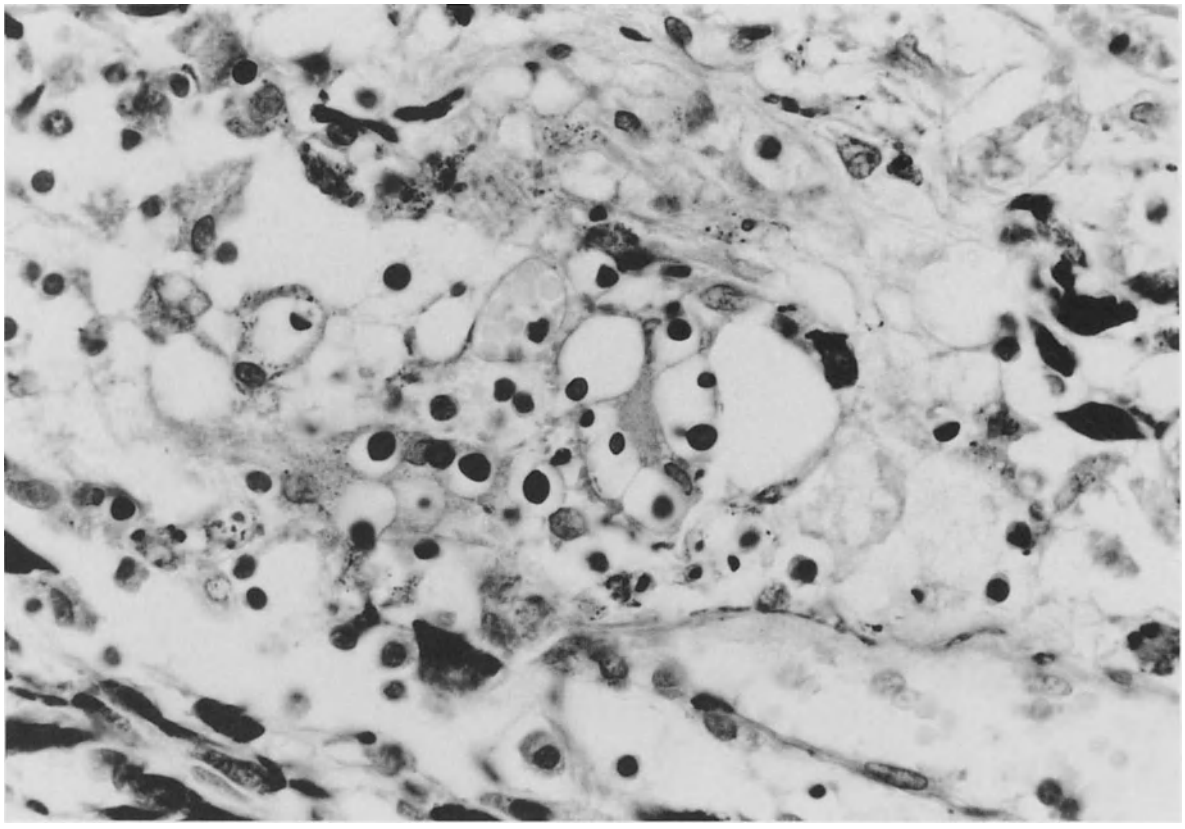

Fig. 5.9. Cryptococcosis. Section of choroid showing numerous cryptococci within the choroid in a patient with disseminated cryptococcosis and multiple opportunistic infections. (Courtesy of Prof. G. Grosse, Berlin) PAS, × 350

or without septicemia (Davis et al. 1989). Severe morbidity has also been reported with bacterial external disease (Shuler et al. 1989 a).

Ocular syphilis has been reported infrequently in HIV-1 infected hosts. A recent series (McLeish et al. 1990) presented nine patients with ocular syphilis and HIV-1 infection. Manifestations included iridocyclitis, vitreitis, retinitis or neuroretinitis, papillitis, optic perineuritis, and retrobulbar optic neuritis. A high frequency of neurological involvement has been noted in this patient group – 15 of 19 reported HIV-1 infected patients with ocular syphilis have had clinical or laboratory evidence of CNS syphilis, and five (33 %) of the 15 were symptomatic (McLeish et al. 1990).

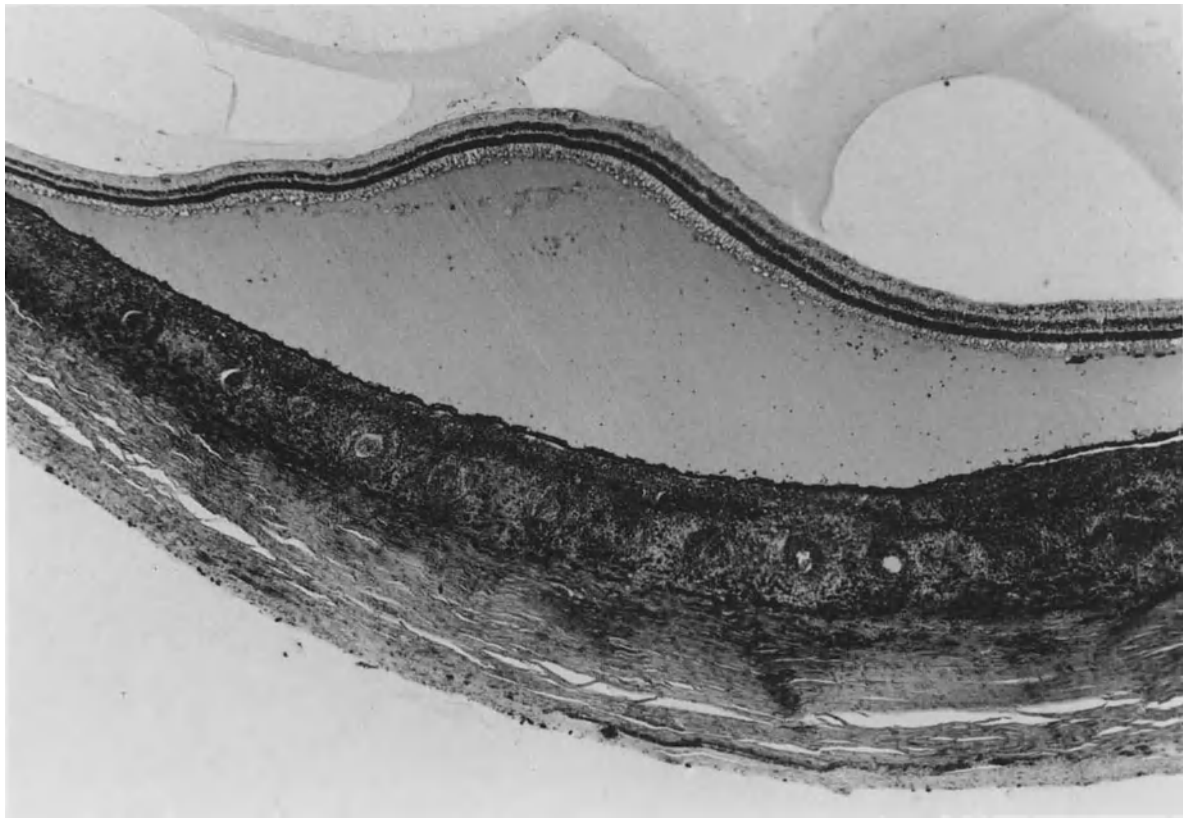

Fig. 5.10. Lymphoma. Patient with infundibular, diencephalic and air sinus B-cell lymphoma with involvement of eye and optic nerves. Section of entire globe embedded in celloidin. Note lymphomatous invasion of uveal tract and retain with retinal detachment. H&E, × 100

■ Corneal and Conjunctival Diseases

Keratoconjunctivitis sicca has been reported in 10%–15% of AIDS patients (Khadem 1984). The constellation of lacrimal gland involvement, salivary gland enlargement, perivasculitis of peripheral retinal vessels, and lymphocytic interstitial pneumonitis has been observed frequently in African children with AIDS, raising the possible etiological role of Epstein-Barr virus in these disorders (Kestelyn 1990). A nonspecific keratoconjunctivitis has also been reported with varying frequency in adult patients with AIDS (Newsome 1989).

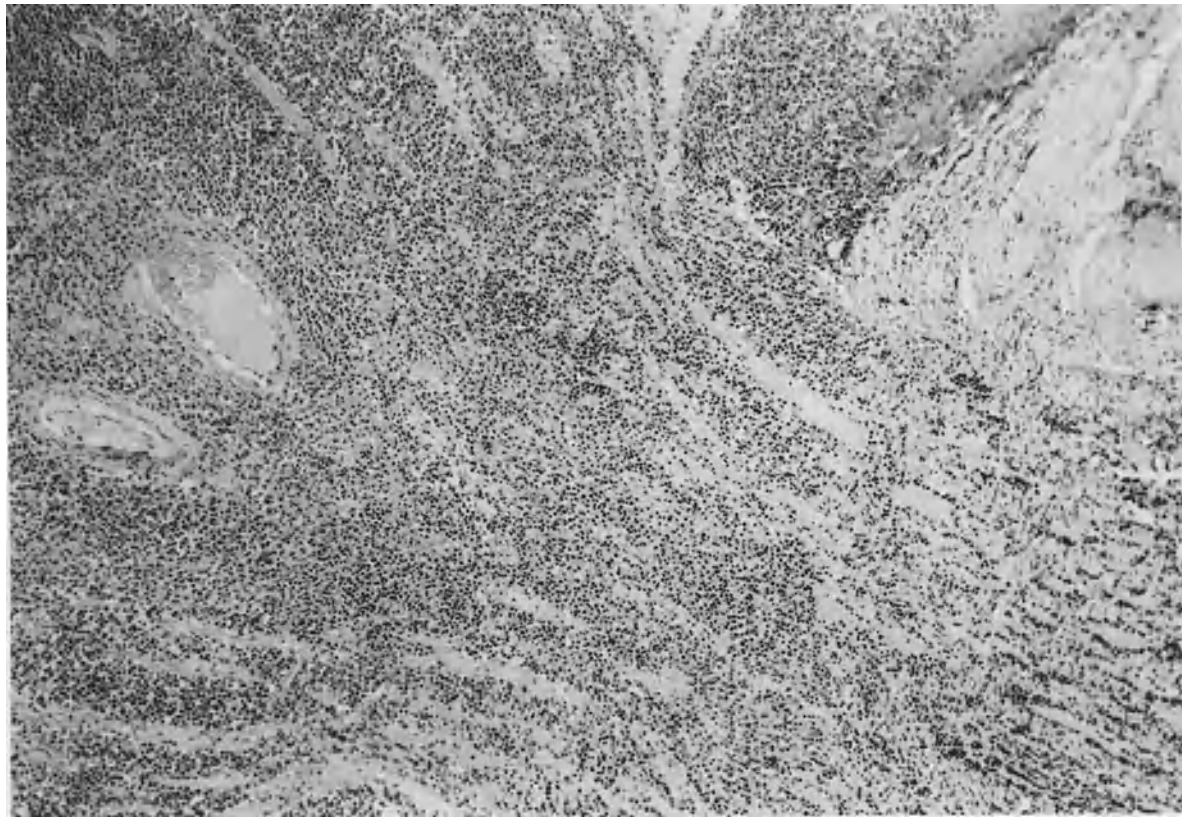

Fig. 5.11. Lymphoma. Longitudinal section of optic nerve showing diffuse infiltration of nerve by tumor cells. H&E, × 100

■ Neoplasms

Kaposi's sarcoma is the most frequent AIDS-associated tumor in general, and ophthalmic involvement occurs in 15 %–24 % of these patients (Reich et al. 1985; Jabs et al. 1989b; Shuler et al. 1989b). In our experience, the histological appearance of the lesion in the conjunctiva, eyelid, and orbit is identical to that observed elsewhere in the body. There have been several reports of orbital Burkitt's lymphoma in patients with AIDS (Brooks et al. 1984; Parrinello et al. 1987; Kamani et al. 1988). Burkitt's lymphoma can also involve the eyelids and conjunctiva. The first reported case of primary ocular malignant lymphoma occurred in a patient who also had a cerebellar mass detected by magnetic resonance imaging and neoplastic cells in the cerebrospinal fluid (Schanzer et al. 1991). We have also observed a case of large cell lymphoma involving the retina, optic nerve, and uveal tract in a patient with a CNS lymphoma, and similar cases are described by Lauer et al. (1988) and Jensen and Klinken (1989; Fig. 5.10–5.12).

■ Neuro-ophthalmological Disorders

The frequency of neuro-ophthalmic disturbances in AIDS patients is about 8 % (see review by Holland and Kreiger 1988; Jabs et al. 1989b; Keane 1991). These manifestations include optic nerve disease, retrobulbar neuritis, visual field defects, cortical blindness, pupillary defects, and ocular motor nerve palsies (Kestelyn 1990). Papillitis in HIV infection can be seen with CMV (Friedman 1984), syphilis (Carter et al. 1987; Passo and Rosenbaum 1988), hepatitis B (Farthing et al. 1986), and the acute retinal necrosis syndrome. Retrobulbar neuritis with HIV seropositivity has been described in patients with syphilis (Zaidman 1986; Zambrano et al. 1987) and CMV (Winward et al. 1989). Visual loss due to cryptococcosis may results either from direct fungal invasion of visual tracts or from prolonged papilledema associated with chronic meningitis (Ofner and Baker 1987). Severe optic atrophy can occur in patients with long-standing CMV re-

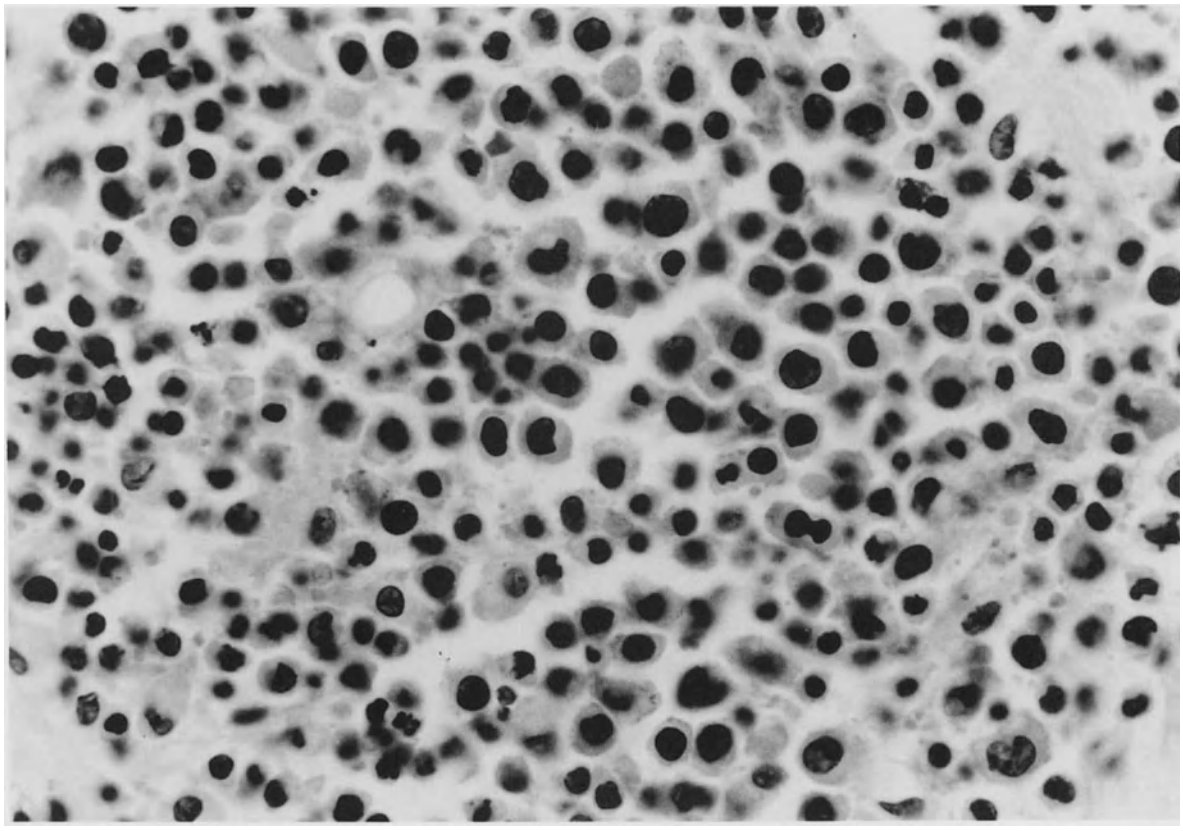

Fig. 5.12. Lymphoma. High magnification of infiltracting tumor involving the retina. H&E, × 400

tinitis (Palestine et al. 1984) or arachnoiditis (Lipson et al. 1989). Supratentorial lesions (infectious or neoplastic) which interrupt the course of visual tracts may, of course, give rise to visual field disturbances.

Although opportunistic CNS infections account for the majority of neuro-ophthalmological manifestations, less common causes include intracranial tumors, chiefly lymphoma, and HIV encephalopathy. We have seen one case of direct involvement of the optic nerve and tract by the microglial nodules and multinucleated giant cells of HIV encephalopathy.

Clinical observations and ocular motor monitoring studies have suggested the eye movement abnormalities to be an early sign of neurological involvement in HIV infection (Tervo et al. 1986; Currie et al. 1988; Hamed et al. 1988; Nguyen et al. 1989). A recent study reported one or more ocular motor abnormalities in 88% (15/17) of asymptomatic HIV seropositive patients, 69% (11/16) with AIDS-related complex and 100% (14/14) AIDS patients with or without dementia (Merrill et al. 1991).

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