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AIDS-Myelopathy

A Neuropathological Study

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SUMMARY

Vacuolar myelopathy belongs to the AIDS-associated diseases. It is characterized by vacuolation and infiltration of the long tracts of the spinal cord by macrophages. The clinical and morphological findings of 8 AIDS-patients with vacuolar myelopathy are reported here. The syndrome developed during the final stages of AIDS and was associated with HIV-encephalopathy in 5 cases. The vacuoles were mainly due to intramyelinic swelling and vacuolation. Vacuolated macrophages and axons contributed only to a minor degree. In one case only, HIV-antigens were detected immunohistochemically. The results are discussed in the light of modern pathogenetical concepts of HIV-related diseases.

Introduction

Neurological complications of the acquired immunodeficiency syndrome (AIDS) develop in up to 50 % of AIDS-patients[14]. They cause considerable morbidity and mortality and may be the main presenting manifestation of infection with the human immunodeficiency virus (HIV)[28]. HIV is related to diseases of the cerebrum, the spinal cord and the peripheral nerves[25] and seems to play a significant role in the pathogenesis of HIV-encephalopathy, the major morphological substrate of the AIDS-Dementia-Complex (ADC)[8]. The association of HIV-infection and vacuolar myelopathy (VM), however, is equivocal. This syndrome is characterized by a vacuolar degeneration of the white matter of the spinal cord and develops in up to 61 % of AIDS-patients. Common clinical symptoms are paraparesis, ataxia and incontinence[1,2,14]. Morphological and immunohistochemical findings in eight AIDS-patients with VM are reported here.

Material and Methods

Neuropathological investigations were carried out on 166 HIV-positive patients with and without AIDS[16]. Eight patients (5 %) with AIDS-manifestations had a VM and are the basis of this report. Clinical data and results of the general autopsy are given in Table 1. The postmortem interval ranged from 24 to 48 hours. All CNS-material was fixed in 10 % formalin for at least two weeks. The cerebrum was dissected in coronal, brain stem and spinal cord into horizontal slices. In only four cases was the whole spinal cord available for examination, in the other four cases only the upper cervical cord or medulla could be examined. After paraffin embedding the following stains or reactions were performed: hematoxylin eosin, Klüver-Barrera myelin stain, Nissl, PAS and Bodian silver stain. Selected slides were processed for immunohistochemistry by the avidin-biotin-immunoperoxidase complex (ABC) using diaminobenzidine as chromogen[7]. The following monoclonal antibodies were employed: KP 1, Mac 387, α1-antitrypsin, α1-antichymotrypsin directed against macrophages (M 814, M 747, A 012, A 022, all Dakopatts); GFAP (GFAP M 761, Dakopatts) and neurofilament protein

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(neurofilament M 762, Dakopatts). Rabbit polyclonal antisera to lysozyme (A 099, Dakopatts) were used. We performed virus detection studies with antibodies against HIV-proteins: Anti-HIV p17, Anti-HIV p24 and Anti-HIV gp 41 (NEA 9282, NEA 9283, NEA 9303, Dupont). Controls included omission of primary antibodies and simultaneous staining of positive material. Cytomegalovirus was investigated by in situ hybridisation (Enzo kit, BP 835).

Results

Clinical Findings

All patients were male, the average age at death was 32 years (range 20 to 43). Three patients were homosexual and five were intravenous drug addicts. All but two patients had a full-blown AIDS-syndrome at the time they developed their first neurological symptoms. The average duration of clinical AIDS was two years (range 1 to 4), when defining the onset of clinical AIDS as the time of presentation with the first opportunistic infection or Kaposi sarcoma. In two patients (patients 6 and 8 in Table 1) AIDS-infection was diagnosed only when neurological symptoms developed. These comprised an organic psychosyndrome (apathy, somnolence and dementia). HIV-associated myelopathy was suspected in five cases because of symptoms like gait disturbance caused by paraparesis, and neurogenic bladder. In the other three cases no spinal cord symptoms were present and the myelopathy was discovered only at autopsy (patients 2, 7 and 8 in Table 1). The spinal cord symptoms developed three to 18 months prior to death. Four patients had evidence of predominantly sensory neuropathy.

Morphological Findings

The general autopsy revealed infections and tumors typical for AIDS.

The macroscopic examination of the brain showed necrotic lesions in different lobes in cases 1 and 4 and -in a periventricular distribution- in cases 5 and 8 (Table 2). The gross appearance of the spinal cord and dura was normal in all cases.

Microscopically in five cases a HIV-encephalopathy with a maximum of changes in the deep white matter was found. Vacuolation of the white matter tracts was a conspicuous feature and involved the capsula interna in three cases (cases 2, 3 and 5 in Table 2). It was, however, always accompanied by macrophage infiltration with formation of multinucleated cells. Two cases presented with a metastatic aspergillus encephalitis and a CMV-encephalitis (Table 2).

The myelopathy was characterized by a vacuolation of the spinal cord white matter. The vacuoles were associated with lipid laden macrophages, which excluded a mere

Table 1. Vacuolar myelopathy (N=8): summary of clinical data and autopsy findings

Case Nr.	A/S	RF	general disease	neurological symptoms	CSF	DD/NS [years]	autopsy findings
1 (SN 182/89)	43 M	H	hepatitis A+B, Kap. sarcoma, PCP, diarrhea, lues	sensory neuropathy, sensory level (D8), spastic paraparesis	15/3 Cells	2/1,5	asperg.-pneumonia, septicemia, Kap. sarcoma
2 (SN 17/89)	31 M	H	oral thrush, AZT, lymphadenopathy	apathy, somnolence	0	1/2 Mo	liver fibrosis
3 (SN 129/89)	32 M	D	oral thrush, PCP, enteritis, hepatopathy, AZT, anemia	paraparesis, sensory neuropathy	0	2,5/1	enteritis, splenomegaly
4 (SN 223/89)	39 M	H	oral thrush, anal herpes, PCP, AZT	sensory neuropathy, peripheral paraparesis	15/3 lymphoc., 84 mg% prot., HIV-Ab, OKB	4/0,5	asperg.-pneumonia, septicemia
5 (NO 73/89)	34 M	D	Kap. sarcoma, septicemia	gait disturbance, sensory neuropathy, neurogenic bladder, apathy	0/3 cells, Pandy +, HIV-Ag. +	2,5/3 Mo	pneumonia, haemorrhagic cystitis
6 (NO 64/89)	31 M	D	0	gait disturbance, spastic paraparesis, incontinence, psychosyndrome	9/3 Lymphoc., Pandy +++	0	interstitial pneumonia
7 (NO 47/89)	20 M	D	cardiomegaly, genital herpes, condylomata acum.	hemiparesis, psychosyndrome	0	1/1	pneumonia, cardiomyopathy, cirrhosis
8 (NO 20/89)	26 M	D	virus pneumonia	incr. intracran. pressure (toxoplasmosis ?), retinitis	0	1,5/0,5	pneumonia

A = age, S = sex, RF = risk factors, H = homosexual, D = drug addict, DD = duration of disease, NS = duration of neurological symptoms, PCP = pneumocystis carinii pneumonia, AZT = azothymidin or zidovudine therapy, OKB = oligoclonal bands in cerebrospinal fluid, HIV-Ab = HIV-antibodies, HIV-Ag = HIV-antigen, 0 = not available.

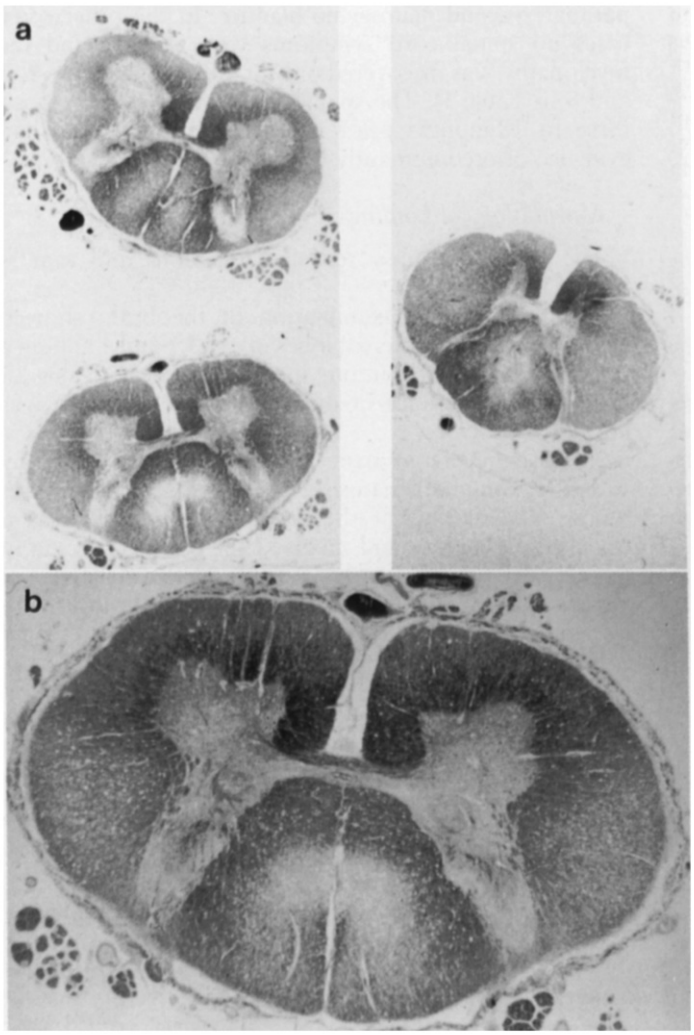

Fig. 1. a: Cross sections through the spinal cord at lumbar and thoracic levels. Vacuolar changes affect the posterior and to a lesser degree the lateral columns; the anterior columns are only slightly pale (Case 4 – SN 223/89 –, Kluever-Barrera). – b: Enlarged section of the upper lumbar cord (Case 4 – SN 223/89 –, Kluever-Barrera).

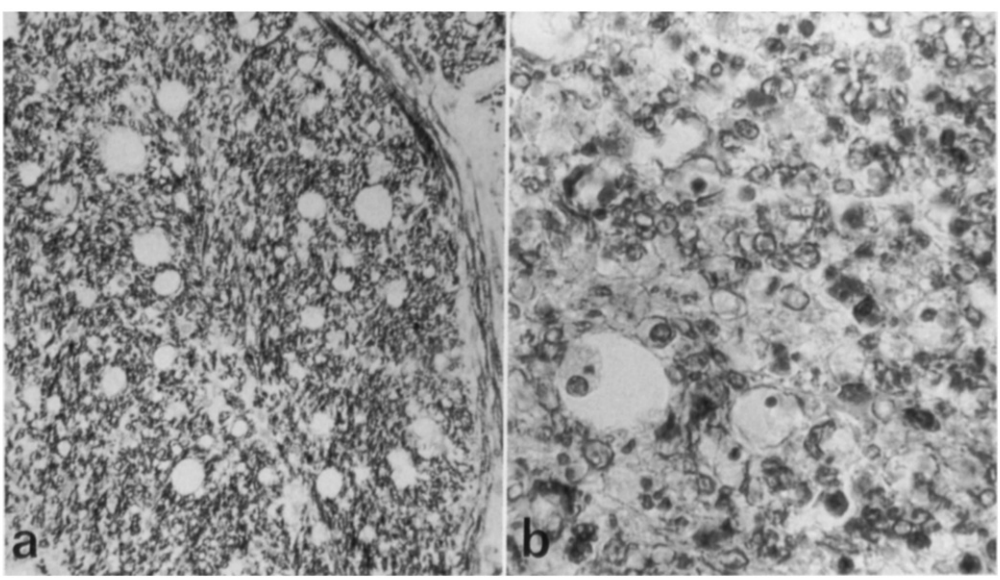

Fig. 2. a: In this case vacuoles are evident in the posterior columns of the cervical cord; they are surrounded by a thin myelin rim (Case 2 – SN 17/89 –, Kluever-Barrera, × 152). – b: Vacuolation of lateral columns of the thoracic spinal cord. Some of the vacuoles harbour macrophages with phagocytosed myelin debris (Case 4 – SN 223/89 –, Kluever-Barrera, × 470).

Table 2. Vacuolar myelopathy (N = 8) Neuropathological data

Nr.	spinal cord A/ L/ P	HIV-antigens	brain stem CS/ LM/ oth.	cerebrum	HIV-antigens	spinal roots/ ganglia
1 (SN 182/89)	C: +/++/+++ Th: +/++/+++ L: +/+/−	p 17: − p 24: − gp 41: −	−	asp.-encephalitis	p 17: − p 24: − gp 41: −	−/0
2 (SN 17/89)	C: +/++/++	p 17: + (MGC) p 24: + (MGC) gp 41: −	MB: ++/+/− P: ++/+/+* Med: ++/+/+**	HIV-encephalopathy (thalamus, int. caps., basal ganglia)	p17: − p 24: + gp 41: −	0
3 (SN 129/89)	C: +/++/+ Th: +/+++/+ L: +/++/+	p 17: − p 24: − gp 41: −	MB: − P: − Med: +/−/−	HIV-encephalopathy (int. caps., ant. commissure)	p 17: − p 24: − gp 41: −	−/−
4 (SN 223/89)	C: −/+/+ Th: +/++/+++ L: +/++/+++	p 17: − p 24: − gp 41: −	MB: − P: − Med: ++/−/−	asp.-encephalitis, gliosis of white matter	p 17: − p 24: − gp 41: −	−/−
5 (NO 73/89)	0	p 17: − p 24: − gp 41: −	MB: − P: − Med: +/−/−	CMV-encephalitis, HIV-encephalopathy (int. caps.)	p 17: − p 24: + gp 41: −	0
6 (NO 64/89)	C: ++/++/+ Th: +/+/+ L: +/+/−	p 17: − p 24: − gp 41: −	MB: − P: − Med: ++/−/−	HIV-encephalopathy	p 17: − p 24: + gp 41: −	+/0
7 (NO 47/89)	0	p 17: − p 24: − gp 41: −	MB: − P: ++/−/− Med: ++/−/−	HIV-encephalopathy	p 17: − p 24: − gp 41: −	0
8 (NO 20/89)	0	p 17: − p 24: − gp 41:	int. caps.: ++ 0 Med: ++/−/−	CMV-encephalitis	p 17: − p 24: − gp 41: −	0

C = cervical, TH = thoracic, L = lumbal, A = anterior, L = lateral, P = posterior (tracts of the spinal cord), MGC = multinucleated giant cell, CS = corticospinal tract, LM = medialis lemniscus, oth. = other tracts, MB = midbrain, P = pons, Med = medulla, CMV = cytomegaly, Asp. = Asergillus, * = Fasciculus longitudinalis medialis, ** = anterior spinocerebellar tract and inferior cerebellar peduncle, 0 = not available for examination, + = single vacuoles resp. positive reaction, ++ = numerous non-confluent vacuoles, +++ = confluent vacuoles.

post-mortem artifact (Figs. 1+2). PAS-positive mono- and multinucleated HIV-cells were only found in case 2 (Table 2). The changes were distributed throughout the spinal white matter in a multifocal and sometimes asymmetric fashion without restriction to anatomic tracts. The vacuoles were mostly found in the posterior and lateral columns where they showed confluence to the so-called "Lückenfelder" in some cases. The anterior and anterolateral fiber tracts were the least involved. No isolated degeneration of the posterior columns was found. The evaluation of the longitudinal distribution of changes is limited by incomplete tissue sampling. In all cases but one (case 6 in Table 2) midthoracic levels were especially severely affected; but also the neighbouring cervical or lumbar sections showed severe changes. The spinal roots were unremarkable; only in one case a modest focal demyelination of some lumbar posterior roots was seen. The posterior root ganglia of only two cases could be investigated and were morphologically normal. The vacuolation involved also motoric and sensory tracts of the brain stem; in the medulla oblongata the pyramids showed marked involvement in five cases (Table 2). A systematic degeneration of the distal parts of the fiber tracts, suggesting a dying back phenomenon, was lacking. The picture also differed from Wallerian degeneration because axonal spheroids were only seldom found at the level of the most severe degeneration and there was no clear craniocaudal gradient of degeneration. The vacuoles were of different origins. Most of them consisted of swollen myelinated fibers and were characterized by a thin myelinic rim. The majority of vacuoles were optically empty, others contained normal looking axons, which were located either at the center or at the periphery of the vacuole. Some vacuoles harboured lipid laden macrophages (Figs. 2b and 3a). Axonal spheroids were only found in areas of severe vacuolation, which also displayed some activated astro-

cytes. Some vacuoles were swollen macrophages or axons which were detected by the immunoreaction to CD 68 resp. neurofilament protein (Fig. 3b and 4). The macrophages behaved the same way as activated tissue macrophages and showed a positive reaction with α-1-antitrypsin, α-1-antichymotrypsin and lysozyme, whereas they did not react with MAC 387. The applied antibodies against HIV-core (p 17 and p 24) and envelope-proteins (gp 41) reacted with cytoplasmic epitopes in mononuclear and multinucleated cells in the cerebrum in three of five cases with HIV-encephalopathy, whereas multinucleated HIV-cells of the other two cases did not react with these antibodies. Only case 2 (Table 2) showed few HIV-positive cells in vacuolated regions of the spinal cord. This patient had a severe HIV-encephalopathy which extended into the caudal brain stem. The most reliable HIV-marker in our hands was anti-p 24, whereas anti-p 17 was positive in only one case, anti-gp 41 was negative in all cases.

Discussion

Neuropathology has helped to define a HIV-specific disease – HIV-encephalitis or HIV-encephalopathy – which is associated with a productive HIV-1 infection; some critical aspects of its pathogenesis, however, remain puzzling. In contrast the relation of HIV-associated tissue

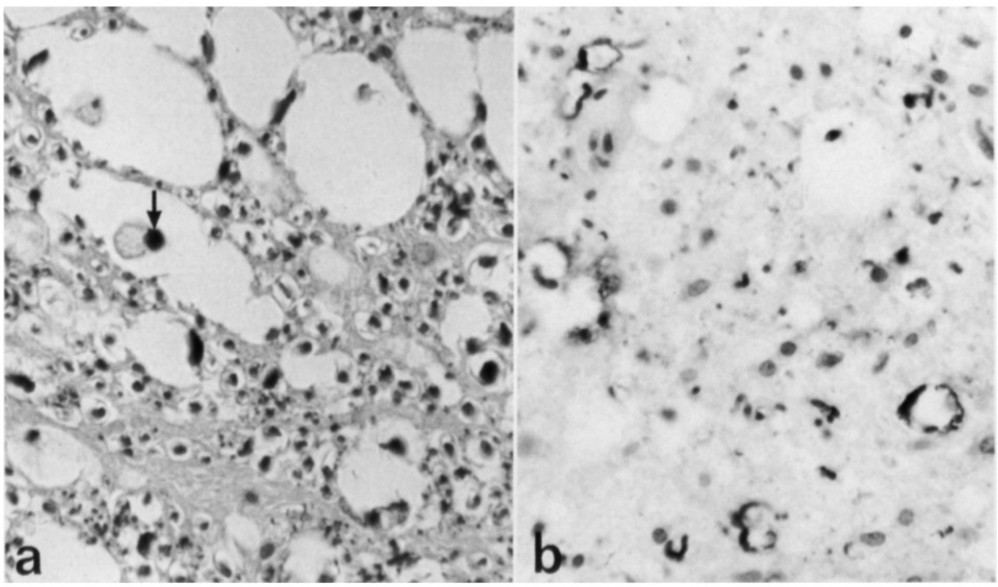

Fig. 3. a: This picture of the cervical spinal cord shows vacuoles with peripherally located axons. A macrophage is nestling against an axon (arrow; Case 4 – SN 223/89 –, neurofilament, ABC, × 485). – b: Vacuolated axons in the lateral columns of the thoracic spinal cord are easily indentified by neurofilament protein reaction (Case 1 – SN 182/89 –, ABC, × 390).

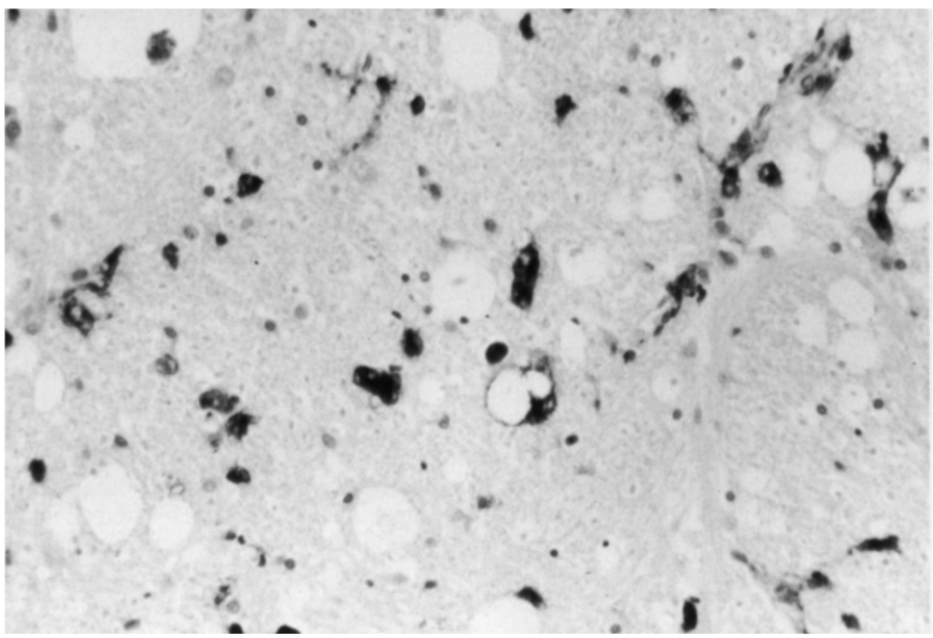

Fig. 4. Some vacuolated macrophages are present in the posterior columns of the cervical cord of this case. (Case 2 – SN 17/89 –, KP 1, ABC, × 255).

syndromes like vacuolar myelopathy (VM) or leucoencephalopathy (VL) to HIV-infection is still disputed[6].

VM is a fairly uniform morphological syndrome of the spinal cord, which was first described by Goldstick et al.[12] in 1984 and in more detail by Petito et al.[32]. It can be found in up to 61 % of autopsied AIDS-patients[2], whereas the incidence of VM in children with AIDS is around 8 % according to the data given by Dickson et al.[9] and Sharer et al.[41]. Morphologically it is characterized by a vacuolar, non-inflammatory myelinopathy affecting the long tracts of the spinal cord. The vacuolated areas are infiltrated with lipid-laden macrophages. The process is reported to affect mainly the lateral and posterior columns of the midthoracic[32] or cervical and thoracic[1,2] spinal cord. These vacuolar changes are neither specific for VM nor are they confined to the spinal cord of AIDS-patients. A vacuolar leucoencephalopathy (VL) has been described in the brain stem and the cerebral hemispheres of patients with and without VM. VL can occur as diffuse[27] or multifocal white matter change[32,34,40]. Moreover HIV-encephalopathy features not only microgranulomatous foci of mononuclear and multinucleated macrophages but sometimes also vacuolation mainly in the cerebral white matter, which can display diffuse pallor[4,16,17]. On the other hand, histopathological changes of HIV-encephalopathy can encroach on the spinal cord without showing vacuolar changes[41]; an isolated HIV-myelitis without corresponding alterations in the brain has been reported by Geny et al.[11]. Because of significant overlap between these syndromes it is not entirely clear whether we are dealing with disease entities or parts of a spectrum of tissue damage.

The neuropathological picture in our eight patients is in accordance with literature reports. The predilection for the thoracic cord described by Petito et al.[32], however, was not so striking. Gracile tract degeneration recently described by Rance et al.[33] in AIDS-patients, which appears to be a sequel of sensory neuropathy and is therefore different from VM, was not seen in our series.

According to Artigas et al.[2] the vacuoles can be divided into different types. The intramyelinic type, caused by splitting of the myelin lamellae[32], was the most frequent type in our series. Without electron microscopy this type was difficult to differentiate from the periaxonal type, which is caused by widening of the periaxonal space. Artigas et al.[2] reported this type as the most frequent one, whereas vacuolation of macrophages and axons contributed only to a minor degree to the vacuolar degeneration.

Clinically the patients affected by VM complain of gait disturbance, leg weakness, bladder and bowel incontinence. The syndrome develops usually during the final stage of HIV-infection after the immunological disorder is well established, although a myelopathy as the first clinical manifestation of the infection has been described by Honig et al.[19]. On physical examination, spastic paraparesis, ataxia and minor sensory impairment are detected. Some degree of spasticity, bladder and bowel disturbances are also features of the AIDS-Dementia-Complex (ADC), which develops frequently in AIDS-patients[8]. Therefore spinal symptoms of AIDS-patients are often attributed to cerebral lesions or general debilitation, which is normally present in these patients; this was the case in three of our patients. A close clinicopathological correlation in some of our patients was not possible because of incomplete tissue sampling. The clinical differential diagnosis of VM can be difficult and has to consider all causes of a paraparesis-paraplegia syndrome. In AIDS-patients opportunistic infections of the spinal cord must be excluded: myelitis due to herpes simplex, herpes zoster, cytomegalovirus, treponema pallidum and toxoplasma gondii have been described in AIDS-patients. Also lymphomatous tumors or vascular necrosis of the cord are common causes of spinal cord syndromes in AIDS-patients[14]. Myelopathic syndromes in AIDS-patients rarely result from myelomalacia due to disseminated intravascular coagulation[10].

Etiology and pathogenesis of VM are still disputed. Ho et al.[18]. isolated HIV from the spinal cord of a patient with VM, and HIV-antigens were detected in vacuolated areas of the spinal cord[5,23,35]. HIV-1 nucleic acid sequences have been found in macrophages infiltrating vacuolated areas and the level of HIV-1 RNA expression correlated directly with the extent of spinal cord pathology and clinical findings[45]. HIV-encephalopathy is frequently associated with VM. All these findings favour an etiological role of HIV in the pathogenesis of VM.

Other studies, however, found a dissociation of AIDS-related myelopathy and HIV-infection of the spinal cord[13,24,38]. The results of our study would support the latter accounts since we detected HIV-immunoreactive cells in only one case. However, a limited expression of HIV-1 not detectable with the currently available methods could play a role in the development of VM. Also not in accordance with a possible role of HIV are the reports that VM can be found without HIV-infection of the brain and has been seldom described in children with AIDS. Moreover, VM was reported in 12 immunocompromised non-AIDS-patients[22].

That macrophages might be important in the pathogenesis of VM is suggested by the frequency with which they are found in the vacuolated areas. These cells are the main target of HIV-infection in CNS[39] and produce in vitro large amounts of cytokines like IL-1, IL-6 and TNFα in response to infection which in turn can increase HIV-expression. TNFα and IL-1 are able to induce myelin damage and could therefore play a role in the pathogenesis of ADC and VM[26]. Whether HIV-positive macrophages are really pathogenetically relevant to vacuolation or are only unspecifically attracted to a spinal cord lesion brought about by unrelated mechanisms, is an open question.

Although the histological picture of VM differs somewhat from classical Wallerian degeneration, supraspinal pathology may not be insignificant for the development of this syndrome. An association between VM in the lateral columns and the severity of brain lesions especially in the capsula interna has been reported[13,34]. In five of our patients VM was associated with HIV-encephalopathy and partly severe involvement of the capsula interna. This might indicate Wallerian degeneration as a cofactor in the pathogenesis, although other morphological findings argue against this. As in the study of Grafe et al.[13],

vacuolation of the posterior column was not related to pathology in the spinal roots or ganglia.

Another pathogenesis is suggested by the clinical and morphological resemblance of VM and subacute combined degeneration (SCD) due to Vit. B_{12} – or perhaps folic acid deficiency. Both deficiencies cause vacuolation of myelin; the most severe lesions occur in the posterior columns of the lower cervical and upper thoracic cord[31,36]. Vacuolation and demyelination of the cerebral white matter, rarely seen in SCD, are held responsible for the dementia which develops in some of the vitamindeficient patients. Although most AIDS-patients are in a malnourished and often cachectic state, Vit. B_{12} and folic acid levels, however, were normal in most reported cases[32]. In our patients Vit. B_{12} levels were not investigated. SCD has also been reported in patients with normal serum B_{12} levels in Lupus erythematodes, with a familial defect in cobalamin metabolism and after prolonged exposure to nitrous oxide (for review see Petito et al.[32]). These disorders were not found in our patients, nor have they been reported in conjunction with AIDS. None of our patients was exposed to toxic agents known to produce spinal cord lesions like hexachlorophene, intrathecal gentamycin, isoniacid or clioquinol[32]. Metabolic disorders known to produce spinal cord pathology – hepatic disease with portocaval shunt, nicotinic acid deficiency and severe nutritional deficiencies – were also not present[15,31,43]. Moreover these states cause Wallerian degeneration or a dying back process but no vacuolar myelopathy. However, toxic or metabolic cofactors are probably relevant to the pathogenesis of VM and VL and could also relate to the reported regional variation in incidence of VM[6].

Finally infection with other viruses can produce similar tissue damage; HTLV-1 for instance, sharing considerable biological similarity and some genetic homology with HIV-1, most probably produces a chronic myelitis with minimal involvement of midbrain, cerebellum and cerebrum and in the spinal cord sometimes vacuolation of long tracts[37]. The severity of the inflammatory infiltrate correlates roughly with the duration of the disease process[20,29]. HTLV and HIV-1 share common risk factors; seroprevalence rates of HTLV-I in intravenous drug abusers of up to 49 % have been described. To date 6 individuals with dual infection of HIV-1 and HTLV-I/II have been reported[3]. However, HTLV-I myelitis varies morphologically from VM, has a limited geographical distribution and shows clinically only a slowly progressive spinal cord syndrome with positive HTLV-I antibodies in serum and CSF. Chronic leucoencephalitis with demyelination and vacuolation of the cerebral and spinal cord white matter is caused in sheep and goats by the visna virus[21]. In animal experiments vacuolation of the spinal cord can be induced by infection with corona virus JHM-CC[44].

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