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The pathology of the posterior root ganglia in AIDS and its relationship to the pallor of the gracile tract*

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Summary. The spinal cord and the thoracic and lumbar posterior root ganglia (PRGs) of 14 HIV-positive men and 7 age- and sex-matched controls were studied by routine histology, morphometric analysis of the number of nodules of Nageotte (nN) and the diameters of sensory ganglion cells, immunohistochemistry and in situ hybridization. In 7 patients (2 of whom had evidence of cytomegalovirus ganglionitis) there were increased numbers of nN and diffuse, mild infiltration with $CD45R^+$ T lymphocytes; no B lymphocytes were observed. Macrophages were increased in number in all cases. Whenever more than one ganglion was examined from the same patient, the appearances were similar in all. There was no alteration in the distribution of ganglion cell diameters. Changes in the spinal cord included vacuolar myelopathy (5 cases), HIV myelitis (1 case), microglial nodules (3 cases) and pallor of the gracile tracts (GTP) in 7 cases, in 6 of whom it co-existed with increased numbers of nN. Seven cases had no abnormalities, except the increase in number of macrophages in PRGs. In spite of a correlation between sensory nerve cell loss and GTP our findings suggest that other mechanisms, such as 'dying back' may contribute to the pathogenesis of GTP. Moreover, sensory disturbances were found most commonly in association with nerve cell loss; however, loss of sensory ganglion cells was not necessarily associated with evidence of sensory impairment.

Key words: AIDS – HIV – Posterior root ganglia – Gracile tract pallor

The frequent involvement of both the central and peripheral nervous systems (CNS and PNS) in AIDS has been known since the early report by Snider et al. [39]. In the years that have followed, progress has been made in our knowledge of the pathogenesis of the disease, although more has been learned about the CNS than the PNS. Posterior root ganglia (PRGs) have not been as extensively investigated as the brain and the spinal cord, one reason being, perhaps, the difficulty in removing them. Furthermore, the few reports which include a description of PRGs [5, 8, 16, 30, 31] give only very brief accounts of the pathological findings; in particular, they do not include any detailed information about the degree and type of inflammation or of the extent of ganglion cell loss. The latter is particularly important in cases with associated peripheral neuropathy and pallor of the gracile tract (GTP), to understand whether there is any correlation between these changes. GTP, described by Rance et al. [30] in four HIV-positive patients who presented with sensory disturbances of the lower extremities, consists of loss of myelinated fibres in the upper part of the fasciculus gracilis. In the single case in which PRGs were available for examination, the authors described mild reduction in number of sensory neurons and presence of nodules of Nageotte (nN).

In this report we describe changes in the PRGs in 14 patients with and without clinical signs of peripheral neuropathy and correlate these findings with those in the spinal cord.

Materials and methods

Brains, spinal cords and PRGs were taken at post-mortem from 14 HIV-positive patients and 7 age-matched controls; the former, aged between 25 and 59 years (mean 36.8 years) were all male; 13 were homosexual; one of them (case 5) was also an intravenous drug user; as for patient 13, no risk factor could be ascertained. All patients were admitted to the same hospital and underwent several thorough neurological examinations by the same team of neurologists. Four patients (1, 6, 7 and 12) had presented, at various stages of their illness, with sensory disturbances. Their clinical data are summarized as follows: (1) patient 1. Five months before death, he developed leg weakness, reduced sensation over the L5 and

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S3–5 dermatomes, absent ankle and knee jerks and, eventually, right foot drop. The myelogram appearances were consistent with arachnoiditis and CSF contained 1142 white blood cells/mm^3, 95 % of which were polymorphs. (2) Patient 6. He presented 6 months before death with reduced light sensation and vibration sense in the toes but with preserved knee and ankle jerks. (3) Patient 7. Eight months before death, he noticed impotence and poor urinary stream. The ankle jerks were depressed. Subsequently he developed difficulty in walking and paraesthesiae in both lower limbs, weakness of the right leg with foot drop, absent ankle jerks and reduced sensation in the S1 region on the right and L1–4 on the left side. (4) Patient 12. He was admitted to hospital with an 8-month history of difficulty in walking. On examination, he showed mild spastic paraparesis with brisk knee jerks, absent ankle jerks and extensor plantars. Vibration sense was reduced in both feet. Subsequently, he developed paraesthesiae below the knees and increasing weakness in both legs. CSF was normal and EMG showed signs compatible with a demyelinating neuropathy.

Details of the salient clinical and neuropathological findings are summarized in Table 1. The control patients (aged between 21 and 68 years, mean 45.2 years) were male and had died after road traffic accidents; none of them had any present or past history of neurological disease.

The organs were fixed in 10 % buffered formalin for periods varying from 3 weeks to 2 months. Blocks of spinal cord included at least three (upper, middle and lower) thoracid and two lumbar segments and, in cases 4 and 6, one cervical segment; in addition, the cauda equina and a variable number (one to six) of PRGs were examined. The latter were thoracic and/or lumbar and, in case 14, included one cervical ganglion. All these specimens were part of an extensive neuropathological examination which included at least 15 blocks of cerebral and cerebellar hemispheres and brain stem. Peripheral nerves were not available, either as biopsy or at post-mortem. Paraffin sections were stained with routine neuropathological staining techniques. Immunohistochemical methods were applied using antibodies to glial fibrillary acidic protein (GFAP), S-100 protein, B (L26) and T (UCHL1) lymphocytes (all from DAKO, High Wycombe, UK), macrophages (HAM56, Enzo Biochem, New York, USA) and to a core HIV protein (p24, Dupont, UK). In situ hybridization for cytomegalovirus (CMV) was performed with a biotinylated cDNA probe (Enzo Biochem.). The probe was visualised according to Schmidbauer's modification of the manufacturer's protocol [36].

Morphometric studies

A number of 5-μm serial paraffin sections from each ganglion were cut and mounted on slides; the 1st, 5th, 9th and 13th of these were stained with haematoxylin and eosin (H&E) according to the method used by Chung and Coggeshall [2].

Counts of nodules of Nageotte. nN can be used as an indicator of sensory ganglion cell loss [34]. All nerve cells with a recognizable nucleus and all nN were counted. The nN are defined as aggregates of closely packed satellite cells with scanty cytoplasm and small nuclei [41]; they differ from clusters of lymphocytes by their elongated nuclei and lack of immunoreactivity with lymphocytic markers; and from tangentially cut rings of satellite cells which do not show closely packed hyperchromatic nuclei.

Table 1. Salient clinical and neuropathological details

Case no.	Age/risk group	Clinical findings		Neuropathology
		Neurological	Other	Brain
1	36/H	CMV retinitis, peripheral neuropathy, CMV radiculopathy, CT: atrophy	Bronchopneumonia, cystitis, MAI infection	No lesions
2	59/H	None CT: ND	KS lung, anaemia	CMV ventriculitis MGN in cortex
3	32/H	Terminal seizures, CT: atrophy	Bronchopneumonia, anaemia	No lesions
4	39/H	Encephalitis, CT: atrophy	KS lung & skin, Septicaemia, severe anaemia	MGN with CMV in cortex
5	31/H & IDU	Seizures, CT: atrophy	Severe anaemia	No lesions
6	50/H	CMV retinitis, peripheral neuropathy, CT: atrophy	KS, myopathy	Lymphoma
7	32/H	Psychosis, radiculopathy, CT: atrophy	PCP, pneumothorax	HIVE
8	50/H	None, CT: ND	Widespread KS	MGN in basal ganglia
9	30/H	None, CT: ND	Enteropathy	No lesions
10	38/H	Focal signs, CT: focal lesions	Pneumonia	Lymphoma
11	34/H	None, CT: ND	KS lung & skin, myopathy, MAI, diarrhoea	No lesions
12	33/H	Cognitive impairment, spastic paraparesis, demyelinating neuropathy, CT: atrophy	Renal failure, pneumonia	Non-specific reactive gliosis
13	26/N	Recurrent cryptococcal meningitis, CT: normal	Bronchopneumonia	Ischemic/anoxic changes
14	39/H	Mania CT: ND	Diarrhoea, emaciated, lung abscess	CMV encephalitis

H, homosexual; IDU, intravenous drug user; N, none; ND, not done; CMV, cytomegalovirus; KS, Kaposi's sarcoma; MAI, –; HIVE, HIV encephalitis; MAI, Mycobacterium avium-intracellulare; MGN, microglial nodules

Nerve cell diameters. The outlines of nerve cells with identifiable nuclei and nucleoli were traced on the digitising bit-pad of a mini MOP linked to an IBM computer; this was programmed to convert areas to mm^2 and determine the diameters assuming circularity of the cross sectional profiles. Histograms were prepared showing distribution of cell diameters.

Density of B and T lymphocytes and macrophages. UCHL1-, L26- and HAM56-positive cells with recognizable nuclei were counted using a ×25 objective in ten areas containing exclusively ganglion cells and the mean was obtained. A graticule inserted into the eyepiece of the microscope was used to define the size of the area in which the cells were counted and the cell density per mm^2 was calculated.

Results

Neuropathology

In addition to the changes in the spinal cord, cauda equina and PRGs (see below), neuropathological findings in the HIV-positive patients included CMV infection of the brain (cases 2, 4 and 14), primary brain lymphoma (cases 6 and 10), HIV encephalitis (case 7), presence of a few microglial nodules in the basal ganglia (case 8), multiple ischaemic foci in the cortex (case 13) and diffuse cortical and subcortical gliosis (case 12). Details of these changes are summarised in Table 1.

Table 2. Pathology of the ganglia and spinal cord

	Ganglia			Spinal Cord				
	% nodules of Nageotte	UCHL1 + cells/mm^2	HAM56 + cells/mm^2	GTP	VM	MGN	HIV myelopathy	root lesions
HIV +								
1 L	18.8 [2]	42.2 [2]	132.8 [2]	+	−	+	−	+
2 L	5.1 [1]	ND	ND	−	−	−	−	−
3 L	4.1 [3]	1.7 [2]	156.0 [2]	−	−	−	−	−
T	4.5 [1]	ND	ND					
4 L	12.6 [3]	33.0 [3]	114.7 [3]	+	+	+	−	−
T	6.3 [1]	38.0 [1]	106.0 [1]					
5 L	6.9 [1]	1.4 [1]	121.0 [1]	−	−	−	−	−
6 L	1.6 [2]	6.3 [2]	ND	+	−	−	−	−
T	1.6 [1]	4.0 [1]	100.0 [1]					
7 L	13.8 [3]	15.9 [3]	108.3 [3]	+	+	−	+	−
8 L	2.7 [2]	22.5 [2]	96.5 [2]	−	−	+	−	−
T	1.3 [1]	80.0 [1]	85.0 [1]					
9 L	8.3 [3]	ND	80.7 [3]	−	−	−	−	−
T	8.6 [1]	ND	73.0 [1]					
10 L	12.3 [1]	10.9 [1]	115.0 [1]	(+)	−	−	−	−
11 L	1.9 [1]	65.0 [1]	118.0 [1]	−	−	−	−	−
12 L	15.5 [2]	56.5 [2]	124.5 [2]	+	+	−	−	−
13 L	4.9 [3]	37.9 [3]	209.0 [3]	−	+	−	−	−
T	2.6 [3]							
14 L	23.7 [3]	65.0 [3]	124.0 [2]	+	(+)	+	−	−
T	22.3 [2]	ND	ND					
C	28.7 [1]	ND	ND					
Lumbar								
mean	9.44 [30]	29.86 [25]	125.0 [27]					
range	(1.5–25.0)	(1.4–66.4)	(76–233)					
Total				7	5	4	1	1
Thoracic								
mean	6.74 [10]	40.6 [3]	88.0 [3]					
range	(1.3–24.0)	(4.0–80.0)	(73–106)					
Control S mean and range								
Lumbar								
mean	4.62 [14]	4.06 [5]	60.0 [8]					
range	(1.8–7.5)	(1.6–13)	(15–72)					
Thoracic								
mean	2.69 [10]	1.4 [3]	26.0 [2]					
range	(0.5–7.4)	(0.7–2.6)	(15–37)					

GTP, Gracile tract pallor; VM, vacuolar myelopathy; MGN, microglial nodules; L, lumbar; T, thoracic; C, cervical; [ ], number of ganglia examined; ND, not done; +, positive; (+), mild; −, negative

Light microscopy

The results of a morphometric study on PRGs and the spinal cord pathology are summarised in Table 2.

Spinal cord. Vacuolar myelopathy (VM) was observed in five patients (4, 7, 12, 13 and 14). It had the typical localisation to the postero-lateral columns and was severe in all except case 14.

Multinucleated giant cells (MGC), some of the latter reacting with p24 antibody, were observed both in grey and white matter of case 7 (Fig. 1a), in which they were sometimes intermingled with changes of VM. In patients 1, 4, 8 and 14 there was an occasional microglial nodule which, in case 14, included a CMV inclusion (Fig. 1b).

GTP was seen in seven cases (1, 4, 6, 7, 10, 12 and 14), including those with sensory disturbances (1, 6, 7, 12). It was most conspicuous at thoracic level (Fig. 2a), where it involved the funiculi symmetrically, whilst it was only mild or absent in the lumbar cord (Fig. 2b). In the two cases (4 and 6) in which the cervical cord was also available, pallor was recognisable only at this level (Fig. 2c). The region affected showed rarefaction of myelinated fibres with slight increase in number of GFAP-positive cells and macrophages but no obvious signs of active degeneration. In cases in which VM and

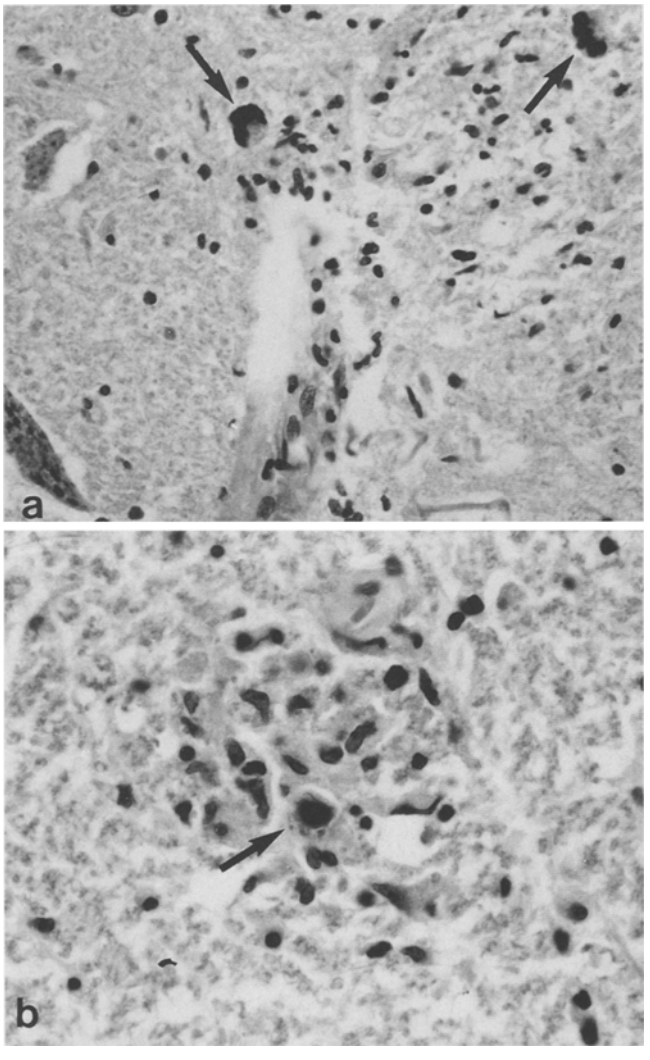

Fig. 1a, b. Spinal cord of HIV-positive patients showing inflammatory nodules. In **a** the nodule, which involves both grey and white matter, includes two multinucleated giant cells (*arrows*). In **b** the nodule is smaller, cells within it are more densely packed and the nucleus of one of them contains a cytomegalovirus (CMV) inclusion (*arrow*). **a, b** H&E, × 300

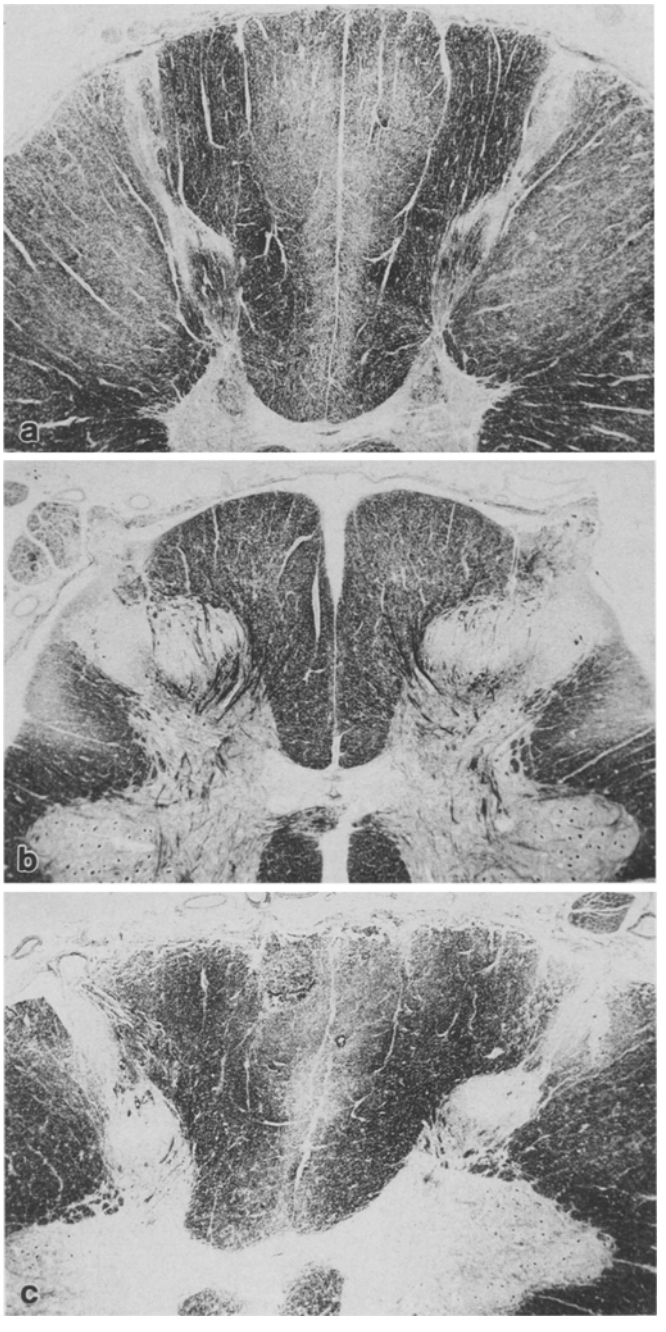

Fig. 2a–c. Various levels of spinal cord illustrate the localisation of pallor of the gracile tracts (GTP). **a** Thoracic cord showing pallor sharply circumscribed to the gracile tract. **b** The lumbar cord of the same patient (case 12) shows mild diffuse pallor. **c** Cervical cord of patient 6, the only level where the pallor could be seen. **a–c** Luxol fast blue/cresyl violet, × 6.5

GTP were present in the same cord, they affected different areas, except in case 7 were they were co-localised. In case 6, the subarachnoid spaces contained deposits of lymphoma cells, which were also seen around an occasional vessel in the cord.

Neither chromatolysis nor other signs of degeneration were seen in the nerve cells of the spinal cord. Lesions of the roots were observed only in case 1, in which the cauda equina showed patchy areas of axonal loss and proliferation of Schwann cells.

Posterior root ganglia

Nerve cell loss. The main abnormality recognisable with routine methods in seven patients (1, 4, 7, 9, 10, 12 and 14), including three of the four with clinical signs of peripheral neuropathy, was an increased number of nN (Fig. 3). In cases for which more than one ganglion per patient was available, counts of nN were comparable in all; therefore, in Table 2 the mean lumbar and, whenever available, the mean thoracic values are given for each patient.

In the AIDS group as a whole, the density of nN in the lumbar ganglia was considerably higher (mean 9.44 %) than in controls (mean 4.62 %).

Counts of B and T lymphocytes and macrophages. These could be performed thoroughly in 12/14 cases, as shown in Table 2. The number of T lymphocytes was increased in the AIDS group (mean 29.8 cells/mm^2) as compared with controls (mean 4.06 cells/mm^2), 9 of the 12 cases examined (1, 4, 7, 8, 10–14) showing an increased density of positively stained cells. In contrast, whereas T lymphocytes were increased in the AIDS group, no B lymphocytes were detected in either AIDS patients or controls. HAM56 expression was increased in all cases (Fig. 4a, b). Although the number of thoracic ganglia examined was smaller than that of the lumbar, it appeared that the density of nN, T- and HAM56-positive cells in each patient followed the same trend described in the latter.

Of the seven patients with increased percentage of nN, six had GTP; in the seventh (case 9) the increase of nodules was only moderate. Four of the seven also had VM, whereas in one (case 13) VM was seen in the absence of any other type of spinal pathology. Four of the patients with GTP (1, 6, 7 and 12) showed clinical evidence of sensory disturbance, whereas two (4 and 10) did not; as for patient 14, it could not be established whether sensory symptoms were present. VM was present in only two of the three cases with both sensory disturbances and GTP. The number of nN in the group with GTP was much higher (mean 14.04 %) than that in the whole group of HIV-positive patients (mean 9.44 %) as well as that in those without GTP (mean 4.84 %), in whom it did not differ from that of the control group (4.62 %). There was no association between the presence of GTP and expression of UCHL 1 (with GTP 32.83 cells/mm^2, without GTP 25.7 cells/mm^2)

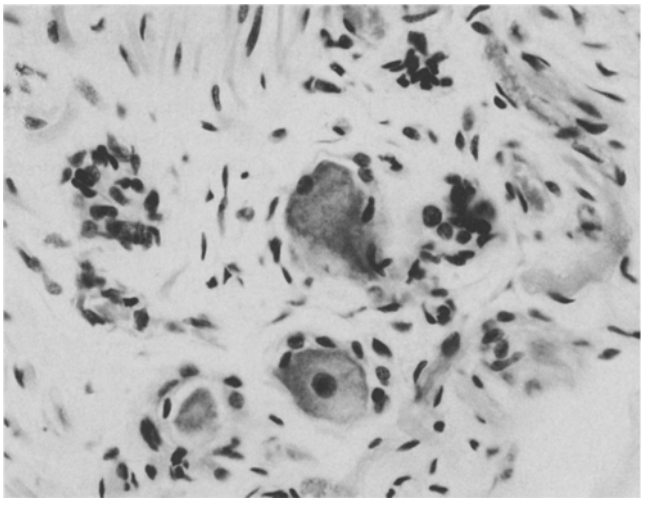

Fig. 3. Section of primary root ganglion (PRG) showing nodules of Nageotte adjacent to normal ganglion cells. H&E, × 300

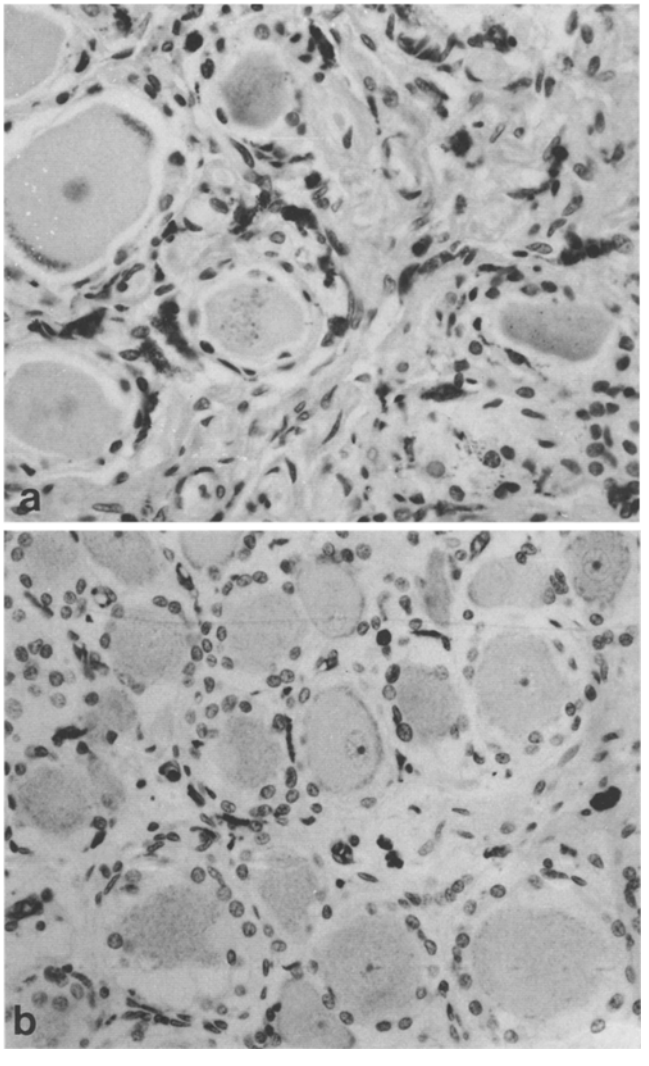

Fig. 4. Photomicrographs showing the distribution and density of HAM56-positive cells in HIV-positive patients (**a**) and in controls (**b**). The localisation of these cells to the endoneurial spaces and perineuronal region is similar in both. However, in **a**, cell density is considerably higher. **a**, **b** × 300

or HAM56 (with GTP 119.88, without GTP 130.2 cells/mm^2) in the ganglia.

Nerve cell diameter. There was no difference in the distribution of ganglion cell diameters between HIV-positive (including those with CMV ganglionitis, see below) and control patients, both in lumbar (Fig. 5a) and thoracic (Fig. 5b) ganglia.

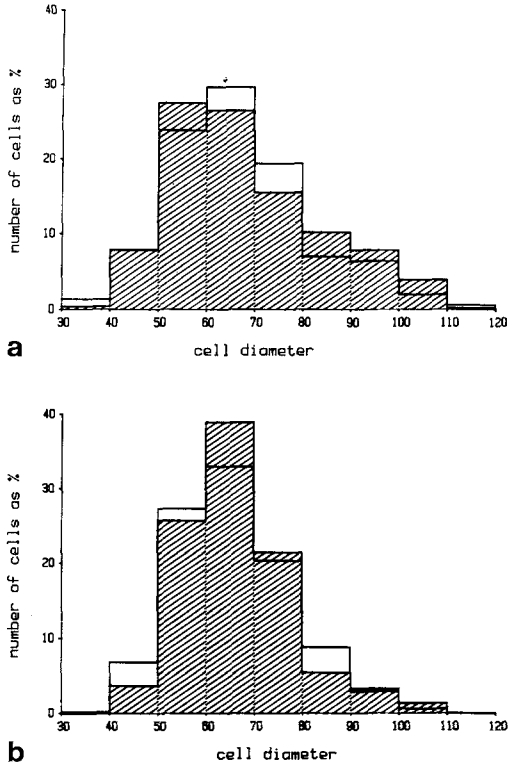

Fig. 5. Histograms showing the distribution of the diameters of lumbar (**a**) and thoracic (**b**) sensory neurons in the ganglia of HIV-positive patients (*hatched*) and controls (*open*). At both levels, the distribution of the diameters (*indicated in μm*) is similar in the two groups

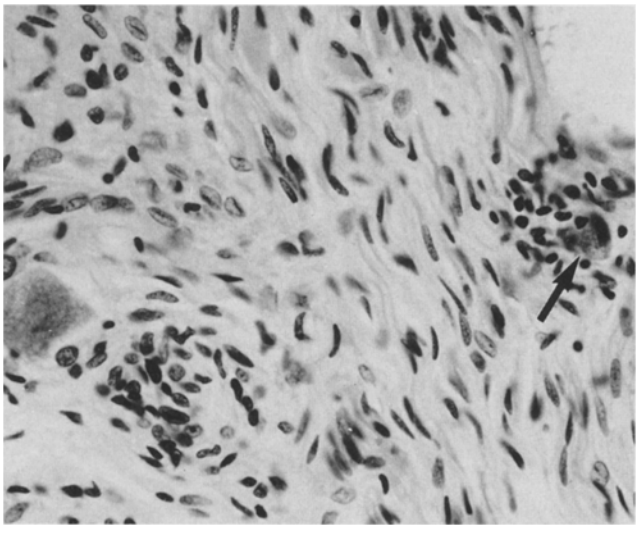

Fig. 6. Photomicrograph of one PRG of patient 14 showing a cell (probably a satellite cell) with an eosinophilic intranuclear inclusion of CMV (*arrow*). H&E, × 400

No HIV antigen could be detected by immunohistochemistry and no organisms were observed in any ganglion, with exception of cases 1 and 14, in which an occasional cell appeared enlarged and contained eosinophilic inclusions of CMV (Fig. 6). The nature of the organism was confirmed by in situ probe. These were also seen in the filum terminale of case 1 and in one root of case 14.

Discussion

Posterior root ganglia

This study has shown that 7 of 14 HIV-positive patients had pathological changes in the PRGs, the most obvious of these being an increase in number of nodules of Nageotte (nN).

Although similar findings were described by several authors [5, 8, 16, 30], the lack of morphometric analysis in their studies made it difficult to establish a correlation between morphological changes and clinical findings. The density of nN was increased in 50 % of our cases, which included three (cases 1, 7 and 12) of the four with clinical evidence of sensory disturbances. This finding is in agreement with a previous study [5] in which 48 % of the cases showed nodules. Our results show that, whereas sensory impairment in AIDS was associated with loss of PRG cells, the opposite was not always the case; indeed, in less than half of the cases with changes in the ganglia was there evidence of sensory loss. In our case 14, with the highest density of nN, the absence of recorded sensory disturbances was probably due to the poor condition of the patient, which made neurological examination of little value. These results are in keeping with those of Fuller et al. [10], who found high percentages of degenerating fibres in peripheral nerves of both symptomatic and asymptomatic patients. Moreover, they showed that the loss involves fibres of all diameters, a result similar to ours in relation to ganglion cells.

Ganglionitis, as reported by Elder et al. [8], could be seen in our study only in case 14, in association with CMV infection. In the other cases, immunocytochemistry revealed the presence of T and complete absence of B lymphocytes. These appearances may correspond to the diffuse inflammatory changes reported by Cristina et al. [5]. Despite the fact that previous work [38] demonstrated that UCHL1 also stains cells of the myelomonocytic series, we concluded, on the basis of the distribution, number and morphology of UCHL-positive cells that these were T lymphocytes. Although these were scattered in the endoneurium, their density, in nine patients, was higher than in controls. Our findings (including absence of B lymphocytes) in normal individuals confirm previous results [9] in normal ganglia. Macrophages, previously reported in normal PRGs [9, 35], showed a twofold increase in HIV-positive patients; however, the present morphometric investigation revealed that macrophages are increased in all

cases, irrespective of the co-existence of other pathological changes.

Spinal cord

The slightly higher incidence of VM [14, 28] in our series (35 %), compared with 29.6 % reported by Petito et al. [27] might reflect the fact that, in our study, patients with neurological involvement were preferentially submitted to post-mortem examination.

Since VM has been consistently reported in association with AIDS-dementia complex (ADC) [21, 28], it has been included in the definition of ADC [24–26, 29]. Indeed, Weiser et al. [42] found a direct correlation between VM and the level of HIV1-RNA expression by in situ hybridization. However, an association between VM and HIV detection is not supported by the present investigation.

Pathogenetic considerations

Pallor of the gracile tract. In AIDS this abnormality was variously considered as secondary to a process of 'dying back' [40] of sensory neurons [30], CMV radiculitis [37] or HIV-induced changes of PRGs [8]. Indeed, the high percentage of nN in six of seven of our cases with GTP suggests that loss of PRGs could play an important role in this type of cord lesion. On the other hand, in case 6 GTP and sensory disturbances co-existed with a low number of nN. This patient, who suffered from lymphoma, could have developed a paraneoplastic syndrome; however, the lack of severe involvement of PRGs [7] makes this unlikely. The suggestion by Rance et al. [30] that a dying back process could contribute, alone or in association with other causes including nerve cell loss, to the production of GTP is supported by the fact that, although the loss of PRGs was equally severe throughout the whole spine, in two cases pallor involved only the cranial part of the gracile funiculus. This region is known to contain the most distal segments of the longest axons of the sensory neurons.

Posterior root ganglia. Rance et al. [30] considered a number of viruses as possible causative agents of the sensory neuropathy in AIDS: HTLV-1, aetiologically linked to tropical spastic paraparesis and HTLV-1-associated myelopathy in Japan [18], can in a number of cases [1, 32] be associated with HIV. However, patient 4 of Rance et al. [30], who had abnormalities of the PRGs, was HTLV-1-negative. Furthermore, no evidence could be found of herpes viruses, including CMV.

Our cases can be divided into two groups on the basis of detectable virus: the first includes two cases (1 and 14) with CMV infection in both PRGs and roots. Inclusions of CMV in the ganglia were previously described by Robert et al. [31] in a patient suffering from a 'progressive neuromuscular disorder'. Moreover, evidence of an association between CMV and peripheral neuropathy [11, 15] was supported by successful treatment of two patients by Miller et al. [22]. On the other hand, Mahieux et al. [20] found CMV inclusions only in roots, but none in PRGs in a case of acute myeloradiculitis. The second group includes the remaining cases in which no virus was detected. The only evidence for the susceptibility of PRGs to HIV is an experimental observation [19] showing that satellite cells derived from human fetal PRGs are susceptible to HIV infection. The small number of cases with successful isolation or visualisation of HIV in the peripheral nervous system [12, 17, 23] raises the question of the pathogenetic mechanism producing the lesions. Indeed, Cornblath et al. [4] and Said et al. [33] suggested an immunopathogenetic mechanism, similar to that proposed for lesions in the central nervous system. Alternative hypotheses (see [6]) includede a 'bystander effect', with a mechanism similar to that by which Theiler virus produces demyelination [3]. Work by Giulian et al. [13] support this possibility. The increased numbers of T lymphocytes and macrophages in PRGs in our cases is in keeping with a cytopathic effect on both satellite and sensory cells, although the lack of correlation with the presence of sensory impairment and increased number of nN suggests that these changes may be a non-specific reflection of HIV infection.

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