Nature, incidence and prognosis of neurological involvement in the acquired immunodeficiency syndrome in central London

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Summary: Clinical neurological involvement at various times throughout the illness was recorded in 52% of 122 patients seen in central London who died from acquired immunodeficiency syndrome (AIDS). Various metabolic encephalopathies, dementias, focal encephalopathies, retinopathies and peripheral nerve pathology were the most frequent manifestations. Seven of 9 patients with a neurological presentation had no other major systemic illness. The median time from diagnosis of AIDS to death was 9 months and from onset of neurological symptoms to death 4 months. Human immunodeficiency virus dementia, central nervous system opportunistic infections, presence of Kaposi sarcoma, neurological presentations and minor symptoms were not associated with major change in survival time.

Introduction

Neurological involvement in the acquired immunodeficiency syndrome (AIDS) has been described in large clinical¹⁻⁶ and neuropathological⁷⁻¹⁰ series, mainly from the USA. There is no published neurological series from the United Kingdom and in the available clinical series the incidence of neurological involvement has not been determined in relation to a defined end point. We present our experience on the nature, incidence and natural history of neurological involvement in 122 patients with AIDS seen in Central London, throughout the length of their illness. This sample represents 20% of the total number of patients with AIDS who had died in the United Kingdom by 31 September 1987.¹¹

Methods and material

The register of patients with AIDS in the East Riverside district at the John Hunter Clinic at St Stephen's Hospital was searched. One hundred and thirty such patients had died up to 31.09.87. The records of 122 were available and reviewed. Sixty-four cases with neurological symptoms or signs

recorded at any time during the illness were analysed in detail. The following information was extracted: demographic data (date of birth, date of death, risk factors for AIDS, date of human immunodeficiency virus [HIV] positive result), general medical and neurological manifestations.

The date of diagnosis of AIDS was taken in accordance with the Communicable Diseases Center guidelines.¹² The date of onset of neurological symptoms was taken from the recorded history. For neurological diagnosis all clinical, radiology laboratory and, when available, pathology investigations were taken into account. The neurological picture has been classified by the predominant topographical syndrome *at presentation* according to standard neurological practice (e.g. diffuse encephalopathy, focal encephalopathy etc.) and then by aetiology. The neurological syndromes were judged minor if not clinically prominent and self limiting, either not warranting investigation or with negative results. Syndromes clearly attributable to pathology other than AIDS were labelled as unrelated. Virological confirmation of direct involvement by HIV was not available in the neurological syndromes. However, HIV has been presumed to be involved when no other cause has been found and the clinical picture and relevant investigations have fitted available descriptions of dementia,¹³⁻¹⁴ myelopathy¹⁵ and peripheral neuropathy.¹

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Post-mortem neuropathological examination was available in 14 cases. A further three had cerebral biopsies.

The Mann-Whitney-U-test was used for statistical analysis of time parameters.

Results

Demographic data and risk factors

The mean age at onset of neurological symptoms was 40.5 years (S.D. 9.0, range 22–63). All 64 patients were male; 58 were homosexual, 4 bisexual, 1 probably heterosexual and 1 unknown.

In twenty patients in whom the number of partners was recorded it was 100 or more in 18, with a range of up to 3000. A further 12 were recorded as promiscuous or as having multiple partners. No information was available in the remainder. Fifty (78%) were recorded as having other venereal disease in the past; their mean number of episodes of venereal disease was 3.3. Four had required hospital admission following rectal trauma.

Neurological involvement

The nature and incidence of the neurological involvement by neurological syndrome at presentation and by aetiology is presented in Table I. Patients often had more than one diagnosis.

Diffuse encephalopathies There were 27. Fifteen had a confusional state without focal signs and with a temporal relation to significant abnormalities of blood gases, biochemistry or appropriate drug ingestion and were classified as metabolic encephalopathies. Eight of these 15 had computed tomographic (CT) scans, in 5 some degree of cerebral atrophy was reported. Post-mortem examination was carried out in 2: one with hypoxia showed areas of slight myelin pallor in the hemispheres, the other with hypoglycaemia showed white matter gliosis with perivascular cuffing; both had multinucleated giant cells.

Progressive intellectual impairment was prominent both clinically and socially in 12 patients. Nine were considered to have the AIDS dementia complex,^{13–14} in 2 with associated myelopathy. Seven of the 9 had CT scans of which 5 revealed atrophy. Post-mortem examination was carried out in 5 cases. Three showed multinucleated giant cell encephalitis. One patient presented with a clinical picture indistinguishable from multi-infarct dementia and post-mortem examination revealed a chronic basal meningitis and vasculitis associated

with multiple cerebral infarcts.¹⁶ Of 2 with intellectual deterioration in the last month of life one had histologically proven CMV encephalitis and in the other the cause was unknown.

Focal encephalopathies Toxoplasmosis accounted for 5 of the 15 seen. All presented with hemiparesis. The diagnosis was established by CT scan and response to treatment ($n=3$), biopsy or autopsy ($n=2$).

The cases of primary central nervous system (CNS) lymphoma were confirmed by biopsy ($n=2$) or autopsy ($n=1$). Combined CMV and HIV encephalitis was confirmed pathologically in 2 patients. These last 2 and 2 with primary CNS lymphoma presented with brain stem syndromes. Another case with CNS lymphoma and one with pathologically confirmed progressive multifocal leukoencephalopathy (PML) and multinucleated giant cells both presented with unilateral hemisphere signs.

The cause of the focal encephalopathy was uncertain in 4 patients; one presented with clinical and CT scan features of recent cerebral infarction, 1 died from acute intracranial hypertension and 2 had low density lesions in one hemisphere (one of them also in the brain stem) on CT scanning which were of uncertain nature.

Meningitis All 5 cases with a clinical presentation of meningitis were diagnosed by cerebrospinal fluid (CSF) examination (Table I) and 1 had post-mortem examination. In a further one, a diagnosis of chronic basal meningitis was only made post-mortem (see section on diffuse encephalopathies above).

Myelopathies Two patients had acute myelopathies with partial or complete recovery, normal myelograms and CSF pleocytosis with mild elevation in protein and negative virological investigations in blood and CSF; one of them had also evidence of lower sacral root involvement. A slowly progressive irreversible paraparesis with pyramidal and posterior column signs was associated with dementia in 2 patients; both had normal CSF examination and one a normal myelogram.

Peripheral nerve involvement Three patients had mild signs of a predominantly motor peripheral neuropathy after treatment with vincristine for Kaposi sarcoma. One patient had an alcohol-related peripheral neuropathy antedating HIV seroconversion. The neurological signs were thought to be HIV-related in one patient with a symmetrical, painful, mainly sensory, peripheral neuropathy and in another with absent ankle jerks and impaired

sensation in the feet, in both associated with dementia. One patient had a fatal acute ascending inflammatory demyelinating neuropathy with predominantly neutrophil CSF pleocytosis, elevated CSF protein, normal myelography and electrophysiological evidence of proximal conduction

delay. In the remaining three (sensory, sensorimotor and mononeuritis multiplex) no cause was found.

Herpes zoster infection was seen in 11/64 neurological cases. Three had chicken pox, all after the onset of AIDS but before they developed neurological symptoms. The other 8 had zoster radiculo-

Table 1 Neurological involvement in AIDS in Central London by site, aetiology and prognosis

	<i>n</i>	<i>%</i>	<i>AIDS to death</i>		<i>Neurology to death</i>	
			<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>
<i>Diffuse encephalopathy</i>	27	46				
Metabolic	15	25	8	1-24	2	0.5-12
Hypoxic	7	12				
Dehydration	4	7				
Others*	4	7				
Dementia	12	20				
HIV	9	15	16	5-22	5	3-22
CMV	1	2	9		5	
Vascular	1	2	7		7	
Unknown	1	2	3		0.5	
<i>Focal encephalopathy</i>	15	25				
Toxoplasma	5	8	10	7-16	4	1-12
Primary CNS lymphoma	3	5	8	3-12	3	0.5-7
Progress multifocal leukoencephalopathy	1	2	2.5		2.5	
CMV/HIV	2	3		4-12		3.5-4
Unknown	4	7	10	1-42	2	0.1-5
<i>Meningitis</i>	6	10				
Cryptococcus	2	3		1-17		1-10
Tuberculosis	1	2	20		20	
Lymphoblastic leukemia	1	2	2		1.5	
Acute aseptic	1	2	9		0.1	
Chronic basal	1	2	7		7	
<i>Myelopathy</i>	4	7				
Acute, viral?	2	3		4-27		4-15
Chronic, HIV related?	2	3		15-22		7-22
<i>Peripheral nervous system</i>	19	32				
Peripheral neuropathy						
Unrelated	4	7	14	5-42		
Other	6	10	9	5-22	5	2-22
Radiculopathy	11	19				
Herpes zoster	8	14				
Other	3	5				
Cranial neuropathy†	3	5				
<i>Miscellaneous</i>						
Retinopathy	20	34				
Cotton wool spots	11	19				
CMV	9	15				
Optic neuritis	1	2				
Seizures unknown cause	8	14	17	3-24	6	2-15
Seizures known cause	8	14				
Headaches	9	15				

Percentages are calculated from 59 (after exclusion of 5 cases with exclusively minor neurology). Time in months.

*Drugs, hyponatraemia, hypoglycaemia, hepatic encephalopathy; †Unilateral VII (Kaposi sarcoma invasion in the face); III, VI, IX, X, XII (lymphoblastic leukaemia) and III (TB meningitis).

pathy, usually in the thoracic region, preceding AIDS in 1 and other neurology in 5. Symptoms and signs of a unilateral S₁ radiculopathy for which no cause was found were seen in 2 cases; one had elevated CSF protein, a normal myelogram and an abnormal ipsilateral sural sensory nerve action potential, the other had transient symptoms and a normal CSF.

Retinopathies Cotton wool spots were seen in 11 patients. Nine had a progressive retinopathy characterized by acute exudates and haemorrhages along the course of blood vessels, classified as cytomegalovirus (CMV) retinitis; one, without other neurological signs, showed a few non-specific areas of myelin pallor in the hemispheres at post-mortem.

Miscellaneous Seizures were recorded as of unknown cause in 8 patients; one was focal. CT scans were performed in all, of which 7 showed atrophy and 1 was normal. Electroencephalograms were performed in 5 cases, 3 of which showed epileptic activity which was focal in 2. Three showed a diffuse abnormality, theta in 2 and theta-delta in 1. Three of the 8 patients later developed a diffuse encephalopathy (2 with HIV, one with CMV). In addition, 8 other patients had seizures from recognized intracerebral causes.

During the course of their illness 16 patients had minor or unrelated neurological complaints. Nine cases complained of headache, 4 were non-specific, 4 were related to fever and 1 was diagnosed as migraine; 5 had CT scans, of which 4 were normal and 1 showed mild atrophy. CSF was examined in 4, two had raised protein but the results were otherwise normal. The other minor complaints were (1 patient each) paraesthesiae, meralgia paraesthetica, weakness, hysterical fugue, depression, loss of memory (minor). The neurological complaints were *exclusively* minor in 5/64 patients (8%).

Neurological presentations The neurological manifestations fulfilled or antedated the formal diagnostic criteria for AIDS¹² in 9 patients who were HIV antibody positive or had AIDS-related complex. These were 2 meningitis (tuberculosis, cryptococcal), 2 HIV encephalopathies, and visual failure (CMV retinitis), acute myelopathy (viral), PML, vasculitis with chronic basal meningitis and primary CNS lymphoma (1 each).

Associated general medical manifestations

The following were seen in 57 cases: *Pneumocystis carinii* pneumonia 60 episodes in 39 patients (61%); cytomegalovirus (CMV) pneumonitis 7 (11%); oral

candida 23 (36%); visceral candidiasis 9 (14%); cryptosporidial diarrhoea 7 (11%); CMV of gastrointestinal tract 12 (19%); *Mycobacterium avium-intracellulare* 8 (12.5%); persistent lymphadenopathy 35 (55%); Kaposi sarcoma 24 (37.5%), disseminated in 12 (19%); skin lesions other than Kaposi 14 (22%); lymphomas and leukaemia 2 (3%). Four cases who presented and died with neurological disease had no general medical manifestations. Three further patients, also with neurological presentations, had only oral candida or persistent lymphadenopathy throughout the illness.

Prognosis

The median time from diagnosis of AIDS to death was 9 months (range 0.1–42 months). The median time from onset of neurological symptoms to death was 4 months (range 0–22 months). The survival function from the time of diagnosis of AIDS in neurological patients and in 2 subgroups is given in Figure 1. The subgroup with CNS opportunistic infections ($n=22$) showed no significant difference in time from AIDS to death when compared to those without ($n=41$) ($P=0.55$) although their median time from onset of neurology to death was 2 months longer ($P=0.05$). The median and range for time from diagnosis of AIDS to death and from onset of neurology to death for various diagnostic categories appear in Table I. In those with a neurological presentation ($n=9$) the median time to death of 4 months (range 1–22) was not significantly different to those with other presentations ($P=0.13$).

A longer median time from AIDS to death was seen in neurological patients with a diagnosis of HIV dementia ($P=0.056$) and in those with Kaposi sarcoma (Figure 2). However, the median time from onset of neurological symptoms to death was not significantly different from the rest for the first ($P<0.08$) or second (Figure 2) subgroups.

Eighteen cases lived longer than 6 months from onset of neurological symptoms; 3 had treatable CNS infections (cryptococcal and tuberculous meningitis and toxoplasmosis), 2 had the AIDS dementia complex and myelopathy, 2 had CMV retinitis and 1 a primary CNS lymphoma. The remainder had unrelated symptoms ($n=7$) or seizures of unknown origin ($n=3$).

In 5 cases who had exclusively minor neurological symptoms the median time from AIDS to death was 4 months (range 2–9), and from onset of neurological symptoms to death 1 month (range 1–4).

Six patients received zidovudine and died 5, 2 and 1 ($n=4$) months after it was started.

There was no significant difference in mean age in the various subgroups considered above.

Figure 1 Time from diagnosis of AIDS to death. Survival function for the following groups: all neurological patients (○), CNS opportunistic infections (+), patients with Kaposi sarcoma and neurological symptoms (×).

Discussion

This sample of 122 patients represents nearly 30% of the total number of AIDS cases reported dead in the four London National Health Service regions by the 31 September 1987. Only 6 of them received zidovudine during life. The findings are therefore representative of the natural history of neurological involvement in AIDS as seen in Central London.

The 52% incidence of neurological involvement detected in this group is higher than other large clinical series,¹⁻⁶ probably because we considered all recorded neurological findings throughout the illness. It is lower than the 70-80% incidence quoted in neuropathological series^{7,8,9} probably for several reasons. Firstly, the neurological symptoms may be minor in relation to major systemic illness and may be under reported, especially minor cognitive impairments.¹⁷ Secondly, several patients died outside hospital and may have developed neurological manifestations that were not recorded. Thirdly, neuropathological changes may not always have clinical expression.

The spectrum of neurological disease seen in this series is similar to that of the USA.¹⁻⁶ Cryptococcal meningitis (1.6%) was significantly less common than the largest American series (5.4%)⁵ ($\chi^2=3.86$, $P<0.05$). The frequency for toxoplasmosis (4.1%) was not significantly different from

Figure 2 Box plots of time from diagnosis of AIDS to death (a) and from onset of neurological symptoms to death (b) in AIDS patients with ($n=24$) and without ($n=39$) Kaposi sarcoma. The box contains the middle 50% of data values between the lower and upper quartiles and the median (transverse bar). Vertical bars extend to points within 1.5 times the interquartile range. Mann-Whitney-U-test statistics are also shown.

the pooled data from USA (2.7%),⁵ though in Florida its frequency is much higher (25%).⁶ These differences may reflect the local prevalence of the organisms in the community. The incidence of PML and primary CNS lymphomas was similar to that seen by others.¹⁻⁶ The proportion of AIDS patients with neurological presentation (7%) is also similar to that quoted by others.^{2,5}

Only 10% of 122 cases were considered to have progressive intellectual impairment that was significant both socially and clinically. This is much lower than other estimates.^{13,14,17,18} Two other patients with combined HIV/CMV encephalitis presenting with brain stem syndromes later developed generalized intellectual dysfunction. Patients with subtle

cognitive impairment¹⁷⁻¹⁸ may have gone unrecorded and cases with cerebral atrophy in the CT scan but without intellectual deterioration clinically, like 7/8 of those with seizures of unknown cause, were not included. Further, in terminally ill patients, often with associated metabolic encephalopathies, it is frequently not possible to be certain of the underlying mental state. Our 2 patients with clearly documented hypoxia and hypoglycaemia who had histological evidence of HIV encephalopathy illustrate this point. The previously noted increased sensitivity to metabolic abnormalities and drugs² was also seen in our cases and may reflect less severe degrees of HIV or CMV encephalopathy.

Our retrospective series included only patients with AIDS who had died by a specified date. Cases with longer survivals would have been excluded. However, the prognosis in this group was poor irrespective of the cause of the neurological involvement and whether it was treatable or not. This is consistent with one series of cerebral toxoplasmosis¹⁹ which had a median survival of 3.75 months (range 8 days–12 months) in 18 treated cases and with another of 24 cases of cryptococcal disease²⁰ with 5 survivors for periods of 11 weeks to 9 months. In these series, as in our cases, successful treatment of neurological opportunistic

infection was often followed soon by some other fatal systemic manifestation. Our longest survivals after treating cerebral toxoplasmosis, primary CNS lymphoma and cryptococcal and tuberculous meningitis were 12, 7, 10 and 20 months respectively (Table I). The time from AIDS to death in cases with toxoplasmosis, meningitis and primary CNS lymphoma was not significantly different from that of the rest of the series. The median times from AIDS to death in patients with HIV dementia and with Kaposi sarcoma and from neurology to death in those with CNS opportunistic infections were significantly longer, or nearly so, but the differences from the rest of the series were clinically trivial. Fifty per cent of metabolic encephalopathies occurred in the last 2 months of life, but duration of the disease (time from AIDS to death) in these patients was not significantly different from the rest. Interestingly, patients with exclusively minor neurological symptoms did not appear to have a better prognosis.

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