Acute lumbosacral polyradiculopathy due to cytomegalovirus in advanced HIV disease: CSF findings in 17 patients

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Abstract

Objectives—To describe the abnormalities in CSF from HIV infected patients with acute lumbosacral polyradiculopathy (ALP) caused by cytomegalovirus (CMV) infection.

Methods—Retrospective case notes and laboratory records were reviewed for 17 consecutive patients with CMV associated ALP admitted to specialist HIV/AIDS units at UCL Hospitals and Chelsea and Westminster Hospital.

Results—Infection with CMV was confirmed by detection of CMV DNA by polymerase chain reaction amplification in 15 patients (all of whom were negative by culture), by culture in one patient, and by objective clinical response to anti-CMV treatment in one patient. Only nine patients had a CSF pleocytosis 28–1142 (median 150) cells/mm³; in seven there was a polymorphonuclear (PMN) leucocyte preponderance. Protein concentrations in CSF were moderately or considerably raised in 13 patients; CSF: plasma glucose ratios were $\leq 50\%$ in five patients. Two patients had no pleocytosis, normal CSF:plasma glucose, and normal or near normal protein values.

Conclusions—Abnormalities in CSF in CMV associated ALP are varied: only 50% of patients have a "typical" PMN preponderant pleocytosis. The diagnosis of this condition should not rely on demonstration of a PMN preponderant pleocytosis, but on identification of CMV DNA in CSF and the exclusion of other opportunistic infections and lymphoma in order that specific anti-CMV treatment may be instituted.

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Acute lumbosacral polyradiculopathy, which is also known as cauda equina syndrome,¹ myeloradiculitis,² myelitis,³ and polyradiculomyelitis,⁴ is an uncommon but distinctive neurological syndrome that occurs in patients with advanced HIV disease.⁴ The clinical presentation is with the subacute onset of bilateral lower motor neuron leg weakness, which may progress to flaccid paraparesis, often accompanied by pain and paraesthesiae of the legs and perineum, areflexia, and sphincter dysfunction.

Abnormalities in CSF, most often a pleocytosis with a polymorphonuclear leucocyte preponderance, a raised protein concentration, and a reduced CSF:plasma glucose ratio, and detection of cytomegalovirus (CMV) by culture,⁵ *in situ* hybridisation,⁶ or the polymerase chain reaction (PCR)⁷ are often reported findings. Pathological studies show CMV infection of the lumbosacral spinal cord and cauda equina.^{8–10}

In some patients presenting with acute lumbosacral polyradiculopathy there is no detectable CSF pleocytosis, or if present it consists predominantly of monocytes. In this study we report the CSF findings in 17 consecutive HIV infected patients presenting with acute lumbosacral polyradiculopathy.

Methods

We studied 17 consecutive HIV-1 antibody positive patients admitted with severe lower motor neuron leg weakness to the specialist HIV/AIDS inpatient Unit at University College London Hospitals or Chelsea and Westminster Hospital, London from 1988 to 1995. All were homosexual or bisexual men. Their ages ranged from 29–53 (median 37) years; 16 patients had a previous AIDS defining illness. CD4 counts, which were available in 16 patients, ranged from 10–140 (median 10) $\times 10^6/l$; all but one CD4 count were below $100 \times 10^6/l$.

A diagnosis of acute lumbosacral polyradiculopathy⁵ was made on the basis of (a) bilateral or unilateral moderate or severe leg weakness which had developed over four weeks or less; (b) depressed or absent knee or ankle reflexes; (c) absence of clinical evidence of upper motor neuron abnormalities; (d) absence of abnormal neurological findings in the arms.

At the time of presentation with leg weakness five patients had concomitant CMV retinitis and one had CMV gastritis. In addition to retinitis one also had evidence of a CMV viraemia. Three other patients had previous diagnoses of CMV disease, proctitis in one, colitis in one, and retinitis in one. All patients underwent lumbar puncture. Thirteen patients also had radiological studies of the lumbosacral region of the spine (MRI in 12 and myelography in two; one patient had both investigations) and four patients had electrodiagnostic studies of the legs.

In all patients CSF protein and glucose concentrations were determined and the presence or absence of CSF pleocytosis was noted. The

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Table 1 Symptoms and neurological findings in 17 patients with CMV associated acute lumbosacral polyradiculopathy

	No of patients
Symptoms:	
Leg weakness	17*
Bladder and bowel dysfunction	8
Leg paraesthesiae	7
Low back pain	6
Neurological findings:	
Leg weakness	17*
Depressed or absent knee and ankle reflexes	17*
Sensory loss	15
Legs	10*
S4 and S5 dermatomes	5

*Left leg only in one patient.

CSF was examined cytologically for malignant cells and was stained histochemically and cultured for bacteria, mycobacteria, and fungi and assayed for antibodies to *Treponema pallidum* and *Toxoplasma gondii* and for *Cryptococcus neoformans* antigen.

An aliquot of CSF from each patient was inoculated into a cell culture of human embryonic lung fibroblasts. The presence of CMV was detected by the finding of a typical cytopathic effect. In addition, in patients presenting from January 1991 onwards (patients 1–15) CMV and herpes simplex virus type 2 (HSV-2) genome detection was undertaken by nested polymerase chain reaction (PCR) amplification using primers to detect CMV *gB* and HSV-2 *gG* sequences.^{11 12} Briefly, CSF samples were pelleted (15 000 *g* for five minutes); the supernatant was boiled for 10 minutes and cooled on ice and then 10 μ l was added directly to the first round mixture. Studies using a sensitive PCR for amplification of human DNA sequences (human pyruvate dehydrogenase and β -globin genes) showed that there was no detectable contamination of CSF supernatant liquid with cellular material after this procedure. Any CSF samples that were obviously bloodstained were also examined for inhibition of nested PCR by titration of dilutions of the positive controls in aliquots of these samples. The sensitivity of the PCR was assessed using tissue culture derived virus and purified CMV and HSV-2 DNA which was diluted in pooled CSF that did not con-

tain detectable CMV DNA. It was estimated that ≤ 10 copies of CMV and HSV-2 DNA could be detected after two rounds of PCR. The products of PCR amplification were analysed by ethidium bromide stained agarose gel electrophoresis. Appropriate positive and negative controls were included in each PCR run: pooled herpes virus negative CSF, distilled water, and the equivalent of 10 and 100 copies of CMV and HSV-2 DNA.

Results

Table 1 gives the patients' presenting symptoms and neurological findings. Serological tests for *T pallidum*, *T gondii*, and *C neoformans* were negative in all 17 patients. Staining and culture for bacteria, mycobacteria and fungi, and cytological examination for malignant cells were negative in all patients. Cytomegalovirus was isolated from only one patient by conventional cell culture. By contrast CMV DNA was detected in all 15 patients examined using nested PCR (patients 1–15; table 2). HSV-2 DNA was not detected in the CSF from the patients in whom genome detection was carried out (patients 1–15). The patient with negative results for CMV detection by culture (in whom PCR amplification was not performed) had concomitant CMV retinitis. In response to treatment with ganciclovir there was an improvement in power from MRC grade 4 to 5, a return of bladder and bowel function, a recovery of knee and ankle reflexes, and return of sensation in the legs. Of the 12 patients who had MRI, results were normal in six (table 2); myelography was normal in one patient (table 2). In all four who had EMG studies there were changes of acute denervation with a reduced number of motor units and the presence of abnormal spontaneous activities. Two patients also had nerve conduction studies and the findings in both were of diminished compound muscle action potentials and prolonged F wave latencies. Necropsy in four patients (patient numbers 1, 3, 4, and 16) performed between one and four months later confirmed the diagnosis of CMV associated lumbosacral polyradiculopathy and

Table 2 Results of CMV detection and imaging/electrodiagnostic studies in 17 patients with CMV associated lumbosacral polyradiculopathy

Patient No	CSF CMV detection PCR	Culture	CMV disease elsewhere	EMG	Lumbar myelography	MRI of cauda equina and lumbosacral roots		
						Gadolinium enhancement	Appearance	Enlargement of conus or clumping of roots
1	+	–	Gastritis (C)	ND	ND		Normal	
2	+	–		Abnormal	ND		Normal	
3	+	–		ND	ND		ND	
4	+	–		Abnormal	ND		Normal	
5	+	–	Retinitis (C)	ND	ND		ND	
6	+	–			ND		ND	
7	+	–	Colitis (P)	ND	ND	Yes		No
8	+	–		ND	ND	No		Yes
9	+	–	Proctitis (P)	ND	ND	No		Yes
10	+	–	Retinitis (C)	ND	ND		Normal	
11	+	–	Retinitis/viraemia (C)	Abnormal	ND		Normal	
12	+	–		ND	ND	Yes		No
13	+	–		ND	ND	No		Yes
14	+	–		ND	ND	Yes		Yes
15	+	–	Retinitis (P)	Abnormal	ND		ND	
16	ND	+	Retinitis (C)	ND	Thickened sacral roots		ND	
17	ND	–	Retinitis (C)	ND	Normal		Normal	

PCR = polymerase chain reaction; + = positive; – = negative; ND = not done; (C) = concurrent; (P) = previous.

Table 3 CSF laboratory findings, response to treatment, and survival in 17 patients with CMV associated acute lumbosacral polyradiculopathy

Patient No	CSF abnormalities				Response to treatment			Survival (months)
	WBC count (/mm ³)	% Polymorph leucocytes*	Protein (g/l)	Glucose CSF: plasma (mmol/l)	Recovery of feeling	Recovery of knee/ankle reflexes	Increase in power by ≥ 1 MRC grade	
1	40	75	1.2	2.8:5.5	No	No	No	1
2	288	80	3.0	2.1:3.7	No	No	No	2
3	149	97	3.3	1.1:6.6	No	No	No	4
4	150	44	2.1	2.6:4.4	No	No	No	1
5	4	100	0.3	3.4:5.0	Yes	Yes	Yes	8
6	2	0	0.3	3.2:5.4	No	No	No	4
7	0	0	0.55	4.8:ND	Yes	Yes	Yes	8
8	1	0	ND	2.7:4.8	Yes	Yes	Yes	12
9	92	90	1.75	1.9:6.1	No	No	No	2
10	3	0	0.9	3.0:5.0	Yes	Yes	Yes	12
11	0	0	0.9	2.7:5.3	No	No	No	7
12	0	0	0.38	2.6:5.7	Yes	No	No	3
13	28	0	1.09	2.6:ND	Yes	Yes	Yes	8
14	489	80	2.91	1.8:5.3	No	No	Yes	7
15	345	40	1.57	2.5:ND	No	No	Yes	3
16	1142	96	3.8	1.3:ND	No	No	No	2
17	2	0	0.81	2.7:7.4	Yes	Yes	Yes	4

*Remaining % of CSF WBC count = lymphocytes, except in patient 14, in whom remaining cells were lymphocytes (10%) and monocytes (10%) and patient 15 in whom remaining cells were lymphocytes (30%) and monocytes (30%).
ND = not done.

established that no other diagnoses were present.

At the time of lumbar puncture none of the patients were receiving foscarnet and only two were receiving ganciclovir: patient 15, with a previous diagnosis of CMV retinitis, was receiving oral maintenance treatment and patient 11 with concurrent CMV retinitis had begun ganciclovir five days previously.

Only nine of the 17 patients had a CSF pleocytosis (> 5 cells/mm³) and of these patients polymorphonuclear leucocytes accounted for most cells in seven patients; in one patient (patient 4) the predominant cells were lymphocytes (table 3). There was no correlation between the duration of symptoms, the severity of weakness, and the presence or absence of CSF pleocytosis.

Response to anti-CMV treatment, ganciclovir in all but patient 10 who received foscarnet, was variable (table 3). After treatment, despite the use of long term maintenance therapy, the overall prognosis was poor with a median survival of four months. Those patients with a polymorphonuclear leucocyte predominant pleocytosis did worse (median (range)) survival = 2 (1–7 months) than those without, (median (range)) survival = 7.5 (1–12) months. Death was due to progressive HIV disease and other supervening opportunistic infections rather than to the polyradiculopathy.

Discussion

In this study we sought to describe the laboratory abnormalities detected in the CSF of HIV infected patients with acute lumbosacral polyradiculopathy caused by CMV infection. All of our patients had presented with clinical features typical of this condition, all had advanced HIV disease, many had CMV disease at other sites, and CMV was identified by DNA amplification or culture of CSF in most patients; in the remainder an objective response was seen to specific anti-CMV therapy. The differential diagnosis of CMV associated acute lumbosacral polyradiculopathy includes other opportunistic infections includ-

ing HSV-2, which may present with urinary retention, radiculopathy, and an acute ascending necrotising myelitis: abnormalities in CSF are variable but a polymorphonuclear pleocytosis may occur.¹³ *T gondii* may cause a myelitis and a conus medullaris syndrome with subacute onset of development. Studies with MRI may show abscess formation and CSF abnormalities include a mixed pleocytosis with raised protein and depressed CSF: plasma glucose ratio.¹⁴ Rarely, meningo-myelitis presenting as subacute progressive paraparesis with areflexia and urinary retention may be due to mycobacterial infection.¹⁵ Syphilitic polyradiculopathy¹⁶ or myelopathy¹⁷ may present with a subacute onset. Analysis of CSF may show a lymphocytic or polymorphonuclear pleocytosis. Tumours, including lymphoma, may also mimic CMV associated acute lumbosacral polyradiculopathy.¹⁸ In this study we specifically sought evidence of these infections and lymphoma by the use of neuroimaging, staining, serological tests, culture, and cytological examination of CSF and were able to exclude them from the differential diagnosis.

Early reports of CMV associated lumbosacral polyradiculopathy commented on the almost universal finding of a CSF pleocytosis due to polymorphonuclear leucocytes. Some reports have used the presence of a CSF polymorphonuclear pleocytosis in patients presenting with subacute onset flaccid paraparesis as being diagnostic of CMV infection even in the absence of identification by culture of the virus in CSF.⁵ Of data available from 58 patients in previously published series and case reports 44 (76%) had a CSF pleocytosis with a preponderance of polymorphonuclear leucocytes.^{1–10 19–30} By contrast CMV infection of the CNS—for example, CMV encephalitis, rarely evokes a pleocytosis; if a pleocytosis occurs it is usually low grade, with < 40 cells/mm³, and consists predominantly of lymphocytes and monocytes.^{12 13} Neuropathologically the probable explanation for the polymorphonuclear pleocytosis, raised CSF protein, and reduced CSF:plasma glucose ratio in patients with CMV associated acute lumbosacral poly-

radiculopathy is the presence of CMV induced acute and chronic inflammatory changes in the ventral and dorsal roots of the lumbosacral spine with a polymorphonuclear and monocytic infiltration, oedema, and necrosis.^{2 8 24 32} By contrast with previously published reports only nine of the 17 patients in our study had a CSF pleocytosis; of these patients polymorphonuclear cells were the predominant cell in seven patients. These data suggest that if the presence of a polymorphonuclear leucocyte pleocytosis was used as a requirement for diagnosis of CMV associated acute lumbosacral polyradiculopathy in patients presenting with subacute onset of flaccid paraparesis then in about half, institution of specific anti-CMV treatment might be delayed pending the finding of CMV in CSF.

The data from our study contrast with those from a study of acute lumbosacral polyradiculopathy in 23 patients with AIDS by So and Olney.⁵ They reported that 14 patients had a pronounced pleocytosis with a preponderance of polymorphonuclear cells, mean count 756 cells/mm³, range = 81–1230 cells/mm³; in eight of these patients CMV was isolated from CSF by culture.⁵ In nine other patients there was a low grade CSF pleocytosis, mean cell count = 13 cells/mm³, range = 0–37 cells/mm³, consisting predominantly of monocytes; CMV was cultured from CSF in only one of this group of patients and two of these patients had lymphoma, identified by cytological examination of CSF, as the cause of their neurological presentation.⁵ It was reported that those patients with a monocyte predominant pleocytosis, who did not have lymphoma as a cause, had a slower clinical progression and a milder neurological deficit, and that spontaneous improvement without treatment was common.⁵ In our study eight patients had no pleocytosis and we were unable to show any correlation between the duration of symptoms or the severity of neurological deficit and the presence or absence or type of CSF pleocytosis. However, survival in those with a pleocytosis was worse than in those without. It is possible, even though negative culture of CMV from CSF does not exclude CMV infection, that some of the patients in the study by So and Olney who had a monocytic preponderant pleocytosis and no detectable CMV infection, did not in fact have CMV induced disease.

The reported CSF changes in response to treatment of acute polyradiculopathy with ganciclovir are varied.⁶ In those who respond clinically to treatment there is often an associated reduction in the CSF pleocytosis. Of our patients only two were already receiving ganciclovir at the time of lumbar puncture, one as long term oral maintenance, the other intravenously. Both patients had a polymorphonuclear leucocyte pleocytosis. Thus use of anti-CMV therapy does not explain the varied CSF pleocytosis seen in our patients.

In our study 13 patients had moderate or pronounced increase in CSF protein; however two patients had normal or nearly normal CSF protein without a pleocytosis or depression of the CSF:plasma glucose ratio. Clearly there is a

range of CSF inflammatory response seen in this group of patients which mirrors the range of severity of neuropathological damage induced by CMV.^{2 8 24 32} Several studies have shown the low sensitivity of conventional viral culture of CSF for identification of CMV and the high sensitivity and specificity of CMV DNA detection by PCR amplification in HIV infected patients with CMV associated neurological disease.^{7 11 12 22 28 31} In one study of 164 consecutive HIV infected patients undergoing lumbar puncture 26 had confirmed CMV associated neurological disease (encephalitis in 12, mononeuritis multiplex in nine, and polyradiculopathy in five). CMV DNA was detected in CSF from 24 of these patients and in only four patients without CMV associated neurological disease giving a sensitivity of 92%, a specificity of 94%, and a negative predictive value of 97%.³¹ In another study 39 of 111 consecutive HIV infected patients had suspected CMV associated neurological disease; CMV DNA was detected in CSF of 24 of the 39 (62%) and in only eight of 72 patients with alternative diagnoses.¹² Whereas it is known that there is a high prevalence of latent CMV infection in HIV infected patients these studies confirm that expression of CMV and detection of viral DNA in the CSF is strongly associated with the presence of CMV associated neurological disease. Our study confirms that DNA detection is more sensitive than culture for virus detection from CSF in HIV infected patients with acute lumbosacral polyradiculopathy and suggests that this method should be used for diagnosis.

In conclusion, in this small study, we have shown that the CSF abnormalities occurring in patients with CMV associated acute lumbosacral polyradiculopathy are varied. "Classic" changes of a pleocytosis consisting predominantly of polymorphonuclear leucocytes are present in only half of the patients; some patients may have a normal CSF without increased protein or depression of the CSF:plasma glucose ratio. In view of these findings patients with advanced HIV disease presenting with subacute flaccid paraparesis should have the diagnosis of CMV infection made by identification of CMV DNA in CSF by PCR amplification and by exclusion of other opportunistic infections and lymphoma, in order that specific anti-CMV therapy may be instituted promptly.

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