Association between HIV distal symmetric polyneuropathy and *mycobacterium avium* complex infection

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Abstract

***Objectives*—Pronounced infiltration of activated macrophages occurs in the peripheral nerves of patients with HIV distal symmetric polyneuropathy (DSPN). *Mycobacterium avium* complex (MAC) is a common facultative intracellular parasite of the macrophage in advanced HIV disease and may induce macrophage activation. Whether MAC disease is associated with DSPN was examined prospectively.**

***Methods*—One hundred and fifty consecutive patients with HIV infection were assessed for the probability of DSPN. Blood cultures for MAC were performed, independently of neurological assessment, as part of the investigation of unexplained fever, anaemia, weight loss, or, less commonly, diarrhoea.**

***Results*—There were 20 patients with possible, 14 with probable, and 22 with definite HIV DSPN. Blood cultures for MAC were performed on 80 patients, of whom 39 were positive and 41 negative. The test for trend, when corrected for CD4 count, disclosed a significant association (P = 0·01). There was no statistically significant association between DSPN and cytomegalovirus (CMV) disease.**

***Conclusion*—Coinfection of the macrophage by MAC may further activate the HIV infected macrophage thereby accelerating the elaboration of neural toxins or MAC infection of the macrophage itself may lead to the production of neural toxins.**

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HIV distal symmetrical polyneuropathy (DSPN) is a common complication of HIV infection, increasing in frequency as systemic immunodeficiency worsens. In advanced immune deficiency (CD4 counts below 100 μl) meticulous clinical and electrical assessment has documented evidence of DSPN in 35%-80% of patients.[1-3] Moreover, neuropathological studies have shown axonal degeneration with a prevalence approaching 100% of patients with AIDS[4] and increased infiltration by macrophages, most of which are activated.[4] Although the cause of DSPN is unknown, a hypothetical model has been advanced wherein activated macrophages in the peripheral nerve produce neural toxins, which, in the presence of other systemic infections, lead to further activation of the macrophage, thereby augmenting the production of such toxins and worsening the neuropathy.[4]

Mycobacterium avium complex (MAC) is the most common opportunistic bacterial infection in late stage HIV disease. It is a common facultative intracellular parasite of macrophages in HIV disease; at necropsy, MAC has been cultured from tissue in 50% of patients with advanced immunodeficiency.[5] It has been our clinical finding that many patients, when this complication develops, complain of symptoms of DSPN, either new or an exacerbation of previously documented neuropathy.

Using one observer and well defined criteria for DSPN, we therefore chose to evaluate whether there was a relation between MAC disease in the late stages of HIV infection and DSPN.

Methods

From 1 February 1995 to 1 June 1995, all HIV positive patients admitted to a large urban teaching hospital were assessed by one neurologist (GN). The assessment was undertaken within 48 hours of admission. Provided there were no confounding medical or psychiatric complications each patient was examined for evidence of DSPN, the probability of which was determined on the basis of symptoms—namely, numbness, paraesthesia, hyperaesthesia, or dysaesthesia—or associated signs—namely, reduced or absent ankle jerks with reinforcement or impaired appreciation of temperature distally. The following criteria were used: *Possible*—symptomatic without signs or asymptomatic with either absent ankle jerks or mildly impaired appreciation of temperature distally; *probable*—asymptomatic with absent or reduced ankle jerks and mildly impaired appreciation of temperature distally or symptomatic with either absent or reduced ankle jerks or mildly impaired appreciation of temperature distally; *definite*—symptomatic with absent or reduced ankle jerks and distal impairment of sensation.

We chose not to use electrodiagnostic studies in our criteria, firstly, because, like others[6] we considered it not essential for the diagnosis; secondly, electrophysiological studies are insensitive for small fibre neuropathies; and thirdly, because we were assessing a large consecutive population, most of whom were admitted acutely for reasons other than neuropathy.

Excluded were those with confounding CNS disease relevant enough to influence the objective assessment of the sensory nervous system or with fluctuating, paroxysmal, or asymmetric sensory symptoms or a neuropathy presumed to be related to drugs including alcohol, vinca alkaloids, isoniazid, dideoxyinosine, or dideoxycytidine treatment. Patients with diabetes were also excluded. Not all patients had blood samples taken for MAC cultures.

When clinically indicated by unexplained fever, weight loss, malaise, or diarrhoea, blood was cultured for MAC, usually on three separate occasions, by the Bactec radiometric assay (Bactec 13A technique), using Middlebrook 7H13 (Bactec 13A) medium. Isolates were identified with standard techniques by a reference laboratory. The decision to perform MAC cultures was taken without knowledge of the neurological assessment. Conversely, the results of MAC culture were not known to the neurologist for at least seven and up to 42 days after the neurological assessment.

STATISTICAL METHODS

Logistic regression was used to check for a possible association between MAC and DSPN. A test for trend was used because if there was a true association between MAC and DSPN, then there should be an increasing proportion of MAC infections in the DSPN population: lowest in the "normal" to highest in the "definite" group. As both MAC infection and DSPN are known to be more prevalent in patients with low CD4 counts, the association between the two was adjusted for this variable, by including a term for the natural logarithm of CD4 count in the logistic regression model.[7]

Evidence of previous clinically relevant cytomegalovirus (CMV) infection (for example, retinitis or colitis) was retrieved from the case notes or the National HIV database for those patients who also had MAC cultures undertaken and similar statistical analysis with respect to a possible association with DSPN was performed.

Table 1 Relation between MAC culture positivity and peripheral neuropathy

	MAC culture			*Adjusted for CD4 count*
	−ve	*+ve*	*OR (95% CI)*	*OR (95% CI)*
Neuropathy:				
Normal	21	9	1·0	1·0
Possible	5	7	3·3 (0·82–13·09)	2·1 (0·46–9·51)
Probable	1	9	21·0 (2·31–191·2)	12·3 (1·25–121·3)
Definite	5	12	5·6 (1·52–20·61)	4·4 (1·1–17·24)
P (test for trend) = 0·002				P (test for trend) = 0·011

Table 2 Relation between CMV non-neurological disease and peripheral neuropathy

	CMV non-neurological disease			*Adjusted for CD4 count*
	−ve	*+ve*	*OR (95% CI)*	*OR (95% CI)*
Neuropathy:				
Normal	19	11	1·0	1·0
Possible	7	5	1·2 (0·31–4·84)	0·6 (0·13–2·99)
Probable	4	6	2·6 (0·61–11·23)	1·1 (0·21–5·89)
Definite	7	10	2·5 (0·73–8·34)	1·7 (0·45–6·35)
P (test for trend) = 0·095				P (test for trend) = 0·395

Both CMV and MAC are common opportunistic infections when CD4 counts are less than 50 μl. Therefore if the association between MAC and DSPN merely reflected a common link with advanced disease then a similar association should be anticipated between CMV and DSPN. This analysis was also adjusted for the CD4 count. Finally a Fisher's exact test was performed on the painful neuropathy subgroup to ascertain if there was a more specific relation with either MAC or CMV disease.

Results

One hundred and sixty three patients were admitted on 206 consecutive occasions. Thirteen patients were not assessed (two refused, one died, 10 were only admitted for a very brief period) giving a study population of 150. There were 145 men and five women. The median age was 37 years, mean 39 years, and range 23–62 years. The median CD4 count was 27 μl, mean 77 μl, and range 0–740 μl. The median and mean duration of HIV infection was nine years, range 1–14 years. The risk factors for HIV infection were male to male intercourse 139, intravenous drug use three, bisexual intercourse two, heterosexual intercourse two, uncertain four.

Of the 150 patients, 16 were excluded either because of mental changes preventing reliable assessment or other potential causes of a neuropathy. In the remaining 134, the assessment for HIV DSPN was normal in 78, abnormal in 56 (possible 20, probable 14, definite 22). The overall clinical estimation of DSPN was thus 56 of 134 patients (42%) with 17 of the 56 (30%) having symptoms of pain.

Cultures for MAC were performed on 80 of the 150 patients of which 11 were excluded for the reasons listed above, leaving 69. Thirty seven were MAC culture positive and 32 MAC culture negative; 32 had documented CMV disease and 37 did not.

Tables 1 and 2 show the statistical analyses of DSPN assessment with respect to MAC culture and clinical CMV disease. The test for trend, when adjusted for CD4 count, gave P values of 0·011 and 0·395 respectively.

A subsidiary analysis was carried out, in which the 63 patients who did not have MAC cultures undertaken, were assumed to be negative and included in the "negative" group. Two were excluded as the CD4 count was not available. Forty six patients did not have DSPN; it was possible in eight, probable in four, definite in five. Combining the MAC culture negative and "not tested" groups in this way produced an even more significant test for trend, corrected for CD4 count ($P < 0·001$).

Of the 39 patients with clinical DSPN who also had MAC cultures, 11 had pain, of which nine were MAC culture positive (82%); 19 of 28 without pain were MAC culture positive (67%; $P = 0·46$, Fisher's exact test). Eight of the 11 patients with pain and 13 of the 28 in the non-painful group had clinical CMV disease. ($P = 0·17$, Fisher's exact test).

Discussion

The overall prevalence rate of 42% for clinical DSPN in our population is slightly higher than previously published values, which averaged 30% although there is considerable variation,[1] a reflection of differing criteria as well as the population studied. Fuller *et al*[8] found an overall incidence of 11·5% in 1500 patients at all stages of HIV infection. There is evidence that the incidence of peripheral neuropathy has been increasing over the past three years,[6] which may be a reflection of improved survival as well as drug associated neuropathies.

With respect to MAC and DSPN, there is only one reference in the medical literature. Fuller *et al*[8] noted a possible association between MAC infection and non-painful peripheral neuropathy in his 54 patients with peripheral neuropathy (four of 13 with neuropathy *v* one of 30 controls, $P < 0·03$). Winer *et al*[3] found that the only significant association between the peripheral neuropathy group compared with the non-neuropathy group was isoniazid exposure (five of 13 *v* five of 65, $P = 007$). All, however, had been on adequate pyridoxine prophylaxis. As the major indication for isoniazid in that study was MAC, this was further indirect evidence for a relation between MAC and DSPN. Our study has confirmed this with a highly significant test for trend ($P = 0·011$ adjusted for CD4 count).

Although the association between MAC and DSPN does not necessarily prove a causal link, the fact that the association persisted after adjustment for CD4 count, the lack of an association between CMV and DSPN at the same stage of immune deficiency, and finally the meticulous exclusion of those with a possible drug related neuropathy, nevertheless implies that MAC disease may be a significant factor in the pathogenesis of DSPN, independent of the stage of immune deficiency.

The immediate question that follows from these findings is whether mycobacterial infection in isolation predisposes to a peripheral neuropathy. Some 30 years ago, triple therapy for *Mycobacterium tuberculosis*, which included isoniazid, produced such a neuropathy. The addition of vitamin B6 to the regime virtually abolished this complication. A literature survey from 1966 to the present failed to find any recognised association between the two, other than that as a consequence of treatment. Moreover, it should be emphasised that such patients usually presented with localised infection, typically pulmonary, rather than disseminated as occurs in HIV disease.

Griffin *et al*[4] recently presented the results of a comparative immunological and pathological study of peripheral nerve tissue obtained at necropsy from HIV seropositive patients with clinical evidence of DSPN in life compared with peripheral nerve tissue obtained at necropsy from an asymptomatic AIDS patient, HIV seropositive patients with a predominately sensory neuropathy from other causes, seronegative patients with a sensory neuropathy of comparable severity, and finally an HIV seronegative, non-neuropathy control group. It is of interest that in none of the HIV necropsies was there evidence of CMV in either nerve or ganglia.

Griffin *et al*[4] found that the common response to axonal degeneration, irrespective of the underlying aetiological factor, was a striking increase in the normal resident macrophage population of nerves. Many of these cells were "activated" and secreted cytokines including tumour necrosis factor-α (TNF-α) and interleukin-1 and interleukin-6. Activated macrophages seemed to enter the degenerating nerve to remove myelin and axonal debris by phagocytosis. The degree of macrophage infiltration parallelled the severity of the axonal degeneration, independent of the underlying aetiology of the neuropathy. However, the macrophage density was more intense in the HIV associated neuropathy for a given degree of axonal degeneration—that is, the response was "excessive". Another significant characteristic of the HIV associated macrophage infiltration was the exuberance of "activation" of individual macrophages. It seems that the macrophage in HIV infection is abnormally regulated and that the activation may be a direct "switching on" effect as well as perhaps a "switching off" of cytokines which normally inhibit the macrophage. Griffin *et al*[4] postulated that the macrophage "deactivating" cytokines interleukin-4 and interleukin-10 are deficient in patients with HIV infection, especially in neural tissue, including brain. This leads to a "hyperresponsive" state of the macrophage, with excessive production of other cytokines, including TNF-α.

How then could MAC infection influence this proposed interaction between HIV and the macrophage? It is known that macrophages and microglia support productive infection by HIV. These infected cells initiate the release of toxins that may activate adjacent macrophages as well as acting on other cell types which then produce additional toxins that damage neural tissue. Macrophages thus facilitate neuronal damage and probably release neural toxins themselves. Mycobacteria are also intracellular pathogens of the macrophage, which makes coinfection highly likely. Wallis *et al*[10] have discussed the various theoretical interactions between HIV, mycobacteria, and the macrophage and postulated that HIV may retard the immune response to mycobacteria by defective TNF-α production promoting dissemination of the organism and that mycobacteria may also stimulate HIV production.

In summary, it seems likely that these two intracellular organisms (HIV and MAC), by independently coinfecting macrophages in the terminal stages of HIV disease, induce a complex synergistic response in terms of cytokine production and ultimate neuronal damage. Both CMV and MAC occur at the same level of advancement of HIV disease and both may infect the macrophage. Yet the association with DSPN was only found with MAC, suggesting that MAC infection of the macrophage itself, may provoke the release of neurotoxins. What remains unknown are the initiating factors of nerve damage, the mechanism of

macrophage recruitment and activation into nerve tissue, and why the response is more intense in HIV DSPN. Our data suggest that infection of macrophages by MAC is a potentially common cause for the greater degree of activation of individual macrophages in the peripheral nerves of patients with DSPN. Of future interest is the question of whether early treatment of MAC and MAC prophylaxis may influence the development of DSPN.

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