The pathogenesis of the neurological complications of HIV-1 infection

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HIV-1 infection is complicated not infrequently by a number of sequelae that may involve the central and peripheral nervous systems even in the absence of opportunistic infections and neoplasms. Chief among these disorders are AIDS dementia complex, vacuolar myelopathy, peripheral neuropathy and myopathy as well as other less well appreciated complications such as seizures and transient ischaemic attacks.1 This review will explore the various possible explanations of such complications after a brief discussion of each entity.

Aids dementia complex (ADC)

This complication is known under a variety of terms such as HIV-1 encephalopathy, subacute encephalitis, AIDS related dementia and more recently HIV-1 associated cognitive/motor deficit.2 To understand various pathogenetic considerations it is first necessary to outline the critical features of the disorder: its broad clinical features, the timing of the dementia, the results of investigations and the effects of treatment.

While some controversy exists as to whether the disorder is consistently a cortical or subcortical dementia because of the recent demonstration of cortical neuronal loss,3-4 the clinical (rather than pathological) presentation of the patients is dominantly that of a subcortical process where there are complaints of poor concentration, disturbed short term memory, slowing of thought processes with motor incoordination and gait unsteadiness.5 Behavioural symptoms such as social apathy and withdrawal are less common and have a correlation with the severity of ADC that is similar to other disturbances such as limb tremor and urinary urgency (unpublished data). So called cortical symptoms such as aphasia, alexia and agraphia are distinctly unusual in ADC and when they do occur, they do so at an advanced stage of dementia where the deficit has become more global. ADC is most often a complication occurring at the phase of moderately advanced immunosuppression. In a personally examined group of ADC patients, the mean CD4 cell count was 94, SD 139 (unpublished data). Numerous other investigators have also observed its relatively late occurrence.

Investigations often reveal a number of abnormalities that are confirmatory of the diagnosis rather than diagnostic. Computed tomography (CT) of the brain often shows cerebral atrophy and magnetic resonance imaging of the brain may show periventricular T2 weighted abnormalities.7-8 Single photon emission computed tomography (SPECT) usually shows multifocal cortical and subcortical areas of hypoperfusion.9 Preliminary data suggest that SPECT is more sensitive than the other imaging techniques10; however, similar changes may occur very frequently in asymptomatic patients.11 At a more investigational level, positron emission tomography reveals hypometabolism of the basal ganglia early in the disease only to be replaced by global hypocaactivity late in the illness.12 Similarly, water suppressed proton magnetic resonance spectroscopic imaging shows significantly reduced N-acetylaspartate relative to choline and creatine in approximately 40% of cognitively impaired patients although there was overlap with asymptomatic patients.13

Just as various imaging techniques may reveal abnormalities in asymptomatic patients so too may cerebrospinal fluid (CSF) analysis where a host of disturbances may be found. These include a mononuclear pleocytosis, raised protein, oligoclonal bands, intrathecal IgG synthesis14-15 raised β2 microglobulin and neopterin concentrations.16-22 Of these, the latter two have been shown to be related to the severity of ADC as have the CSF concentrations of the excitotoxin quinolinic acid.23 Other markers of immune activation such as tumour necrosis factor24-25 remain controversial. Interleukins 1β and 6 have also been associated with both HIV-1 infection per se and with the presence but seemingly not the severity of ADC.24 Recently, anti-myelin basic protein antibodies have also been found to be elevated in the CSF of patients with ADC but there does not appear to be a relationship between the degree of elevation and the severity of ADC.26

With regard to the virological aspects of the CSF, the detection of p24, the core antigen of HIV-1, is quite specific but insensitive27-28 with approximately half of patients with severe ADC not having demonstrable p24 despite acid dissociation of immune complexes to remove any p24 that may have been "trapped". Thus far no one has been able to measure other viral antigens in the CSF such as gp120, nef and tat. Culture of HIV-1 from the CSF is also non-specific with approximately 30% of patients being culture positive despite the absence of cognitive abnormalities.29 As patients become more demented the ability to rescue HIV-1 from the CSF increases but does not exceed
approximately 50% despite the presence of severe ADC. Amplification of HIV-1 by the polymerase chain reaction from the CSF has also been explored but at the present time its utility is controversial as some groups have claimed that HIV-1 can only be amplified from patients who are neurologically abnormal whereas others have found the opposite.

Neuropsychological investigations may also be abnormal but again the underlying theme is that the abnormalities are often found in asymptomatic patients as well as those with ADC albeit in a less severe form. Thus disturbances in pursuit and saccadic eye movements become increasingly common with severity of systemic disease and with the presence of ADC. Brainstem auditory evoked potentials have similarly been found abnormal as well as long latency event related potentials. The significance of electroencephalographic (EEG) abnormalities is, however, less clear. Two studies have described an increased frequency of EEG abnormalities in asymptomatic patients but a larger and more rigorously controlled study has not supported these earlier findings. Moreover, the purported prognostic significance of EEG abnormalities in asymptomatic patients is presently only supported by one group.

The neuropathology of ADC has recently been revised and by consensus it may be divided into five categories which in individual cases frequently overlap with each other. The most common disorder in this classification is HIV-1 leukoencephalopathy where there is diffuse damage to the white matter, reactive astrocytosis, macrophages and multinucleated giant cells with minimal or no inflammatory infiltrates. These changes are predominantly subcortical in location and may be found in patients who are mildly demented. However, a similar leukoencephalopathy where evidence of HIV-1 infection in the brain tissue is absent is not addressed by this consensus classification because of the lack of definite association with HIV-1 infection. Nonetheless, the disorder occurs frequently in patients with ADC. Diffuse poliodystrophy is also a reasonably common finding and is defined as the presence of diffuse reactive astroglisis and microglial activation involving cerebral grey matter. The clinical correlation of this pathology has yet to be determined but it would seem likely to at least be associated with mild ADC. Less frequent is HIV encephalitis where there are perivascular inflammatory infiltrates of multinucleated giant cells again in a predominantly subcortical distribution. This finding correlates with the presence of significant ADC. Rarely, the pathology may be characterised by vacuolation throughout the white matter which has been termed vacuolar leukoencephalopathy, the clinical correlate of which has yet to be delineated. Lastly, cerebral vasculitis has been described but it would appear to be distinctly uncommon. The relationship between cortical atrophy with neuronal loss and the above neurological pathological sets is presently unclear although it is most likely associated with HIV diffuse poliodystrophy and HIV encephalitis. Moreover the precise interrelationships between the latter mentioned sets is unknown but it would seem that leukoencephalopathy forms a base upon which are added the changes of diffuse poliodystrophy and in moderate to severe cases of ADC, HIV encephalitis. The overriding principle, however, is that the neuropathological changes are dominantly subcortical and even within these subcortical areas there appears to be certain structures that are more commonly involved. Thus several investigators have noted the prominent basal ganglia involvement, especially the globus pallidus. Importantly, at least two researchers have noted that the distribution of pathology is inconsistent with a simple "centrifugal" spread of disease from the meninges. ADC can be treated successfully with zidovudine and possibly other nucleosides. While there is some controversy as to the optimal dose of ZDV for ADC there is no doubt that it improves and sometimes reverses cognitive impairment. Similarly, the importance or even the existence of resistance to didanosine at least in children although preliminary analysis of the efficacy of didanosine in adults has cast some doubt as to whether there is any significant effect (Portegies, personal communication). However, despite the encouraging reports of treatability of ADC it must be recognised that not all patients will respond to therapy even with zidovudine. The explanation for such variation in response is unknown but it may relate to resistance to the particular drug, inadequate penetration of the drug through the blood brain barrier and possibly the nature of a particular strain of virus; for example, the syncytium inducing virus strain is purported to be relatively insensitive to zidovudine or to develop drug resistance more rapidly. Furthermore, the precise neuropathological features of ADC that may or may not respond to treatment are unknown save for preliminary data showing that multinucleated cell changes and HIV leukoencephalopathy have become less frequent since the introduction of zidovudine.

With the latter background, it is possible to approach some of the pathogenetic considerations of HIV-1 brain involvement that serve as a base for the construction of a theoretical model. Firstly, subclinical involvement of the nervous system is common throughout the long course of HIV-1 infection as delineated by a number of investigators approaching the issue from different aspects. Minor neurological dysfunction has been found by several groups in the absence of any symptoms while other larger studies have not shown any significant deficit at a population level. Frequent abnormalities in the CSF of asymptomatic patients have also been described with a mild mononuclear pleocytosis usually of less than 100 mononuclear cells, an elevated protein and recovery of HIV-1
from the CSF in a small percentage of patients and rarely p24, the core protein of HIV-1.\textsuperscript{17,62} As previously mentioned, disturbances of neurophysiological function, EEG abnormalities long latency potentials and eye movement disturbances have also been found by a number of authors. Imaging studies of the brain have also delineated the presence of abnormalities by a number of different techniques in asymptomatic patients. Perhaps even more important than the wealth of data indirectly indicating central nervous system disturbance is the recent finding of neuropathological changes in the brains of patients who had been asymptomatically infected and who died accidental deaths.\textsuperscript{63} While there was no evidence of productive HIV-1 infection of the brain, there were changes of astroglia, vasculitis and a lymphocytic meningitis.

Secondly, although there is subclinical involvement by HIV-1 throughout the course of HIV-1 infection, the clinical expression of this involvement, namely ADC, is largely a feature of advanced HIV-1 disease when there is significant immunodeficiency. This is supported by earlier studies\textsuperscript{64} and by our more recent study where we found the mean CD4 cell count of patients with ADC was 94 SD 139 (unpublished data). Thus ADC is essentially an opportunistic complication of HIV-1 disease.

Thirdly, despite significant immunodeficiency, not every HIV-1 infected individual develops ADC. Prevalence figures vary for ADC as already mentioned but even before the introduction of zidovudine, prevalence estimates were not higher than approximately 66%. While one explanation may be that the majority of patients are not living long enough to develop ADC, this seems unlikely at least on an anecdotal level. Additionally, there is evidence for "neurotropism": most brain derived viral isolates from patients with HIV-1 encephalitis have been found to be macrophage tropic and it has been shown that HIV-1 will only replicate in microglia if it is macrophage tropic.\textsuperscript{65-69}

Fourthly, there is a superficially paradoxical correlation between ADC severity and certain markers of immune activation (especially of $\gamma$ interferon), namely $\beta$ microglobulin, neopterin and quinolinic acid.\textsuperscript{18-23} Moreover, the presence of ADC has been linked to certain cytokines in the CSF namely interleukin 1 and 6.\textsuperscript{62} Hence, ADC is related to increased immune activity in the form of cytokines at a time when there is decreased humoral and cell mediated immune function. This is mirrored in the systemic circulation in AIDS where there is evidence for excessive activity of cytokines.\textsuperscript{70}

Fifthly, the neuropathological changes are dominantly subcortical and perivascular in location with a specific vulnerability within those subcortical structures.\textsuperscript{41-49,71} Additionally, there is cortical neuronal loss mainly affecting the frontal lobes.\textsuperscript{5,7} Moreover, there are certain parts of the brain that seem peculiarly susceptible to the patho-logical changes, namely the globus pallidus.\textsuperscript{82}

Important from a pathogenetic view point is the absence of productive infection of the choroid plexus,\textsuperscript{52,60-72} Just as there is topographic localization of the neuropathology of ADC so too is there regionalization of the virological features. Thus productive infection is largely a feature of subcortical structures in accord with several investigators\textsuperscript{42,47,71} but in contrast to Gabuzda et al.\textsuperscript{73} The latter group, however, did not systematically sample the same areas as in the other studies and the number of samples was small. Indeed, there has been no large published study where cortical and subcortical tissues were examined that has shown that the cortex is preferentially infected over subcortical areas. The recent finding by several groups of cortical neuronal loss\textsuperscript{5,5} may therefore be an indirect consequence of subcortical infection as discussed by Achim et al.\textsuperscript{74} Moreover, the finding of Everall et al.\textsuperscript{75} that cortical neuronal loss occurred independently of HIV-1 encephalitis and in some patients without ADC suggests that cortical neuronal loss and HIV-1 encephalitis may be independent processes that variably contribute to ADC.

The sixth critical point is that productive infection of the brain is restricted to the mononuclear and macrophage cells and microglia. There is still controversy as to whether endothelial cells and oligodendroglia are infected but it is likely that the early reports of endothelial cell infection actually represent infection of the microglia as substantiated by double labelling experiments\textsuperscript{71} and the recent finding that microglia are a component of the perivascular glial barrier.\textsuperscript{75} Whether oligodendroglial cells are infected is also still open to speculation. The initial reports of such infection\textsuperscript{78-77} were open to considerable doubt\textsuperscript{79,80} but recent data from Esiri et al.\textsuperscript{80} has raised the possibility again although if infection of oligodendroglial cells does occur in vivo it is distinctly uncommon. Similarly, while most investigators agree that astrocytes can be infected in vitro\textsuperscript{81} it is not clear if the infection is low grade and mediated independent of the CD4 receptor and probably by way of galactosyl ceramide.\textsuperscript{82} How this relates to in vivo infection is entirely unclear but it would appear to have limited relevance since galactosyl ceramide is most abundant on oligodendroglial cells, the very cell type that at best is infected only very infrequently.

The seventh major point is that there is a clinical-virological dissociation in that the clinical severity of ADC is often greater than amount of productive HIV-1 infection found at necropsy.\textsuperscript{79} Indeed, in some cases of pae-diatic ADC there is no evidence of infection despite the presence of severe dementia.\textsuperscript{86} Moreover, there is viral-pathological dissociation wherein the pathology is more extensive than the amount of productive infection.\textsuperscript{50,85} While high levels of unintegrated HIV-1 DNA have been found in the brains of patients with ADC in one study\textsuperscript{87} only a small number of patients was studied and these all had severe ADC. Preliminary data from
Gadler et al.\(^9\) suggest that latent infection in the brains of ADC becomes more frequent with increasing ADC severity but that in less severe cases of ADC there may be little detectable latent infection.

The latter considerations can be summarised as follows: (i) the brain is involved early by HIV-1, (ii) there is selectivity of involvement in terms of the patient, the brain structures and the brain cells, (iii) direct viral infection of the brain is not the explanation of the clinical deficit, (iv) host mediated responses seem likely as candidate toxins and (v) certain viral products are involved in tissue damage.

With these considerations it is possible to construct an hypothetical model of the pathogenesis of ADC. It is proposed that HIV-1 enters the brain early in the course of the disease probably at the time of seroconversion. Entry is by way of blood borne infection and to a lesser extent by "spread" from chronic meningeal infection which in turn is likely related to low level infection of the choroid plexus. The latter is supported by experimental evidence showing that the choroid plexus may be infected.\(^72\) That productive infection of the choroid plexus cannot be demonstrated in patients with ADC is probably the result of the death of the original cells capable of supporting infection. Such low level infection is kept in check by a relatively intact immune system but as HIV-1 disease progresses, brain infection becomes unchecked and compensatory mechanisms are activated that result in the production of various cytokines that over time lead to central nervous system dysfunction. Additionally, the low level brain infection is now capable of being amplified by the similarly unchecked systemic disease thereby accounting for the perivascular distribution to the pathology of ADC. The tissue damaged by the cytokines then becomes secondarily infected both by the now unchecked local brain infection and by the systemically circulating infected cells. Moreover, as HIV-1 disease advances and there is a reduction in CD4 + cells there is a selection towards macrophage tropic isolates of HIV-1 that further infect the brain; essentially the brain cells that are of macrophage lineage namely the microglial cells. However, it should be stressed that macrophage tropism alone is insufficient to explain brain tissue invasion by HIV-1.\(^89\) The mechanism by which HIV-1 actually enters the brain is still conjectural but there are at least two possibilities, namely through trafficking of activated T cells, the so called "Trojan horse" mechanism,\(^89,91\) since these have been shown to be able to cross the blood-brain barrier. As well, since the blood brain barrier is disrupted in advanced HIV-1 disease\(^92\) cells harbouring HIV-1 and cell free virus could easily pass into the brain.

At the cellular level, the envelope glycoprotein of HIV-1 gp120 is toxic to rodent neurons\(^84\) and the neuronal killing is critically dependent upon the presence of cells of the macrophage lineage.\(^85\) Furthermore, the precise mechanism of neuronal damage is by way of activation of the N-methyl D-aspartate receptor with consequent influx into the cell of calcium and secondary synthesis of nitric oxide in those neurons containing nitric oxide synthetase.\(^96\) Not only do macrophage lineage cells serve to facilitate neuronal damage but it appears that they release neurotoxic factors as well. Some of these are as yet undefined,\(^77\) while others are arachidonic acid metabolites and platelet activating factor, that require cell-to-cell interactions for toxicity.\(^98\) Our group has also shown that quinolinic acid, an N-methyl D-aspartate receptor agonist, is elevated in the CSF of ADC patients\(^92\) and that in vitro HIV-1 infected macrophages can produce large quantities of quinolinic acid with this production being dependent upon the degree of macrophage tropism of HIV-1.\(^99,100\)

While these mechanisms serve to assist in understanding the pathogenesis of neuronal loss and dysfunction, they do not address the causation of the leukoencephalopathy. At present, it seems likely that the cerebral white matter is affected by the cytokines that are released by macrophage lineage cells in an attempt to control infection. Certainly similar leukoencephalopathic changes have been observed in patients receiving high doses of various cytokines as part of cancer chemotherapy. Another possible mechanism is the documented methylation defect\(^101\) in HIV-1 infected individuals that may lead to changes similar to cyanocobalamin deficiency. The third possibility, namely direct infection of oligodendrocytes, would seem to be unlikely as previously discussed and if present to be of minor significance.

Vascular myelopathy
Approximately one third of patients\(^102\) have a myelopathy usually manifesting as a spastic paraparesis without a definite sensory level although posterior column type sensory loss namely, proprioception and vibration disturbance is prominent. The disorder is largely confined to the legs and has a subacute to chronic onset over weeks to months leading on occasion to a wheelchair bound state. In most patients the myelopathy is associated with ADC. Importantly, vascular myelopathy is exceptionally uncommon in children who are HIV-1 infected.\(^103\)

Pathologically there are multiple vacuoles in the white matter of the posterior and lateral columns of the spinal cord, infrequent lipid-laden macrophages and separation of the myelin lamellae on electron microscopy. Despite the similarities with subacute combined degeneration of the cord serum vitamin B12 levels are normal. Recent studies have demonstrated that this disorder is probably not the result of productive HIV-1 infection and although controversy still exists,\(^106\) It is conceivable, however, that the latter studies may have focused on cases with combined multinucleated cell myelitis and vascular myelopathy since the two conditions frequently coexist.\(^41\) Multinucleated cell myelitis is characterised by multinucleated
The pathogenesis of the neurological complications of HIV-1 infection

337

cell infiltrates and is related to productive viral infection. Response of either of these disturbances to antiretroviral therapy is unknown but anecdotal experience suggests that vacuolar myelopathy does not respond while multinucleated cell myelitis does.

The pathogenesis of vacular myelopathy is unclear. Three possibilities exist namely, that it is (i) related to HIV-1 infection per se, (ii) secondary to another opportunistic infection and (iii) related to a metabolic abnormality. As to the first possibility, it would seem unlikely to be secondary to productive infection if one excludes multinucleated cell myelitis. Moreover, the recent report describing vacular myelopathy in immunocompromised non-AIDS patients strongly points away from HIV-1 per se being pathogenetically important. Nonetheless, other retroviruses such as human T-lymphotropic virus type I have been associated with a myelopathy as has human T-lymphotropic virus type II. The possibility that vacuolar myelopathy might be related to dual infection with HTLV-1 has been excluded. The second possibility that it is related to another opportunistic infection is conceivable considering that the disorder is so uncommon in children just as opportunistic infections in general are. The third possibility namely that it is secondary to an underlying metabolic abnormality is also conceivable as a methylation defect has been identified in HIV infection. However, this abnormality has also been described in HIV infected children the very group where vacuolar myelopathy is rare.

Peripheral neuropathy
HIV-1 related peripheral neuropathy may take the form of mononeuritis multiplex, inflammatory demyelinating polynueropathy, autonomic neuropathy and distal symmetrical polyneuropathy. The AAN working group has, however, only defined two conditions: HIV-1 related nerve root, meningeal, and ischemic demyelinating polyneuropathy, HIV-1 associated predominantly sensory neuropathy. Mononeuritis multiplex occurs in the context of a mild immunodeficiency and seems no different than its non HIV counterpart. It is important to distinguish this type of mononeuritis that occurs relatively early in HIV disease as opposed to mononeuritis that occurs late in HIV disease where the aetiology is almost certainly cytomegalovirus infection. Similarly, an inflammatory demyelinating neuropathy may occur acutely or chronically in the context of seroconversion to HIV or at a more advanced stage of HIV disease. Its features are no different from its non HIV counterpart with the exception of the finding of a CSF pleocytosis, probably the result of concordance of two disease processes namely the neuropathy and "background" HIV related CSF abnormalities. The latter neuropathies have been studied pathologically and the consistent finding has been the lack of evidence of significant productive infection of the peripheral nerve, the only exception being a patient who had productive infection in endoneurial infiltrates. Consequently, the pathogenesis of these neuropathies is considered most likely to be on an autoimmune basis.

An autonomic neuropathy has also been described. Its clinical manifestations of bladder and bowel dysfunction, sweating abnormalities and arrhythmias occur infrequently although a subclinical autonomic neuropathy has been found in up to 50% of HIV infected patients. Because this neuropathy often occurs in conjunction with the distal symmetrical predominantly sensory neuropathy, pathogenetic possibilities for both disorders will be discussed together.

Probably the most important of the HIV related peripheral neuropathies is the distal predominantly sensory neuropathy. This is largely a feature of advanced HIV disease and is common occurring in approximately 45% of such patients. Patients complain of numbness which is usually confined to the lower legs; only rarely are the arms involved. Significant weakness of the legs is distinctly unusual. In a small proportion of patients a painful distal sensory neuropathy develops which advances to the point where walking is difficult.

The pathogenesis of these neuropathies is also unclear. Productive infection of the nerve has not been convincingly demonstrated and although cytomegalovirus infection has been implicated in the pathogenesis of the distal painful sensory peripheral neuropathy on epidemiological grounds it is unlikely that cytomegalovirus is playing a significant role when one considers that the neuropathy may occur at a time when there is insufficient immunodeficiency for cytomegalovirus to be a pathogen. The significance of the rarity of peripheral neuropathy in HIV infected children is unknown but as with vacuolar myelopathy it may point to an indirect pathogenesis perhaps a metabolic disturbance or another opportunistic infection. A metabolic aetiology has support by way of the previously mentioned methylation defect that has been found in HIV infected patients. In a similar disturbance, abuse of nitrous oxide, the resulting methylation defect leads to a peripheral neuropathy and myelopathy. However, macrophages have been found to be prominent in the peripheral nerves of HIV infected patients arguing against a purely metabolic disturbance.

Myopathies
HIV-1 related myopathy is still a poorly defined entity. Patients usually present with slowly progressive proximal weakness that seemingly may occur at any point in their HIV-1 disease. Excluding zidovudine related myopathy the pathological findings can be grouped as follows: an inflammatory myopathy that is similar to if not identical with polymyositis and a non-inflammatory myopathy.
Pathogenetically, productive HIV-1 infection has not been found in the majority of studies with the exception of occasional evidence of infection of the infiltrating cells. Such data would seem to point away from a direct HIV-1 aetiology.

Seizures
Seizures may also complicate HIV-1 infection. They may be both partial and generalised although this author's experience is that they are most often generalised. Preliminary data indicate that they are largely a feature of moderately advanced HIV-1 disease and that there is an association with ADC (6, unpublished observations). The pathogenesis of such seizures at the moment is entirely conjectural but in view of the association with ADC it would seem that the role of excitotoxins in both disorders may be important Lipton.134

Transient neurological deficits and strokes
Transient ischaemic attacks in the absence of an underlying infection or neoplasm may occur in HIV-1 infection.135 136 These usually do not lead to clinically apparent strokes but at autopsy some 20% of patients have evidence of small areas of infarction in the basal ganglia.137 The pathogenesis of these vascular events is unknown but there is an association with antiretroviral antibodies.138 139

Conclusion
Thus the pathogenesis of HIV-1 related neurological involvement is complex and likely to be multifactorial. There is overwhelming evidence that the myriad of neurological complications is not simply a result of the viral burden of productive infection but more probably there is a complex interplay of cytokines, excitotoxins, toxic viral products such as gp120 and in some cases autoimmunity.


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