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# Non-Neurotropism in Variable Host Cell /Hiv-1 Interactions Determining Neuronal Susceptibility

Lawrence, M. Agius
Department of Pathology St Luke's Hospital, Gwardamangia,
University of Malta, Msida, Malta, Europe

**Abstract:** A simple concept of directly operative viral neurotropism appears inadequate to explain a full spectrum of phenomena associated with the creation of a viral reservoir as occurs with central nervous system HIV-1 infection. Indeed, a full series of directly and indirectly operative steps would involve peripheral blood monocytes, CNS perivascular cells, vascular endothelia, and resident microglia. In an overall context of a highly integrated CNS and immune system responsiveness, viral encephalitis might actually constitute shifting levels of involvement ranging from dysregulation of cytokine production to autoimmune reactivity to potentially evolving pathways of secondary neuronal injury as by reactive oxygen radicals and phagocytic activity. HIV-1 infection of the CNS, in addition, would appear to add attributes of viral genomic integration and of possible emergence of resistance to anti-retroviral drug therapy to various other mechanisms arising from a central role played by CNS macrophages and microglia beyond a strict concept of viral neurotropism. It appears significant that long-term nonprogressors are selectively predetermined at an early stage in the development of the HIV-1 infected state.

**Key words:** Neurotropism, nervow, system, variable host, neuronal susceptibility

## INTRODUCTION

Neurotropism involves a selective susceptibility of neurons and especially of certain groups of neurons to particular strains of virus such as HIV in the establishment and progression of a series of cellular lesions related both to localization and subsequent integration and replication of the HIV.

Such a phenomenon would include also latency and occult infection phases of involvement of the susceptible neuronal groups to HIV. In AIDS neurons are lost without productive HIV infection being established in these cells[1].

## POSSIBLE PARTICIPATING ROLES OF METABOLIC AND MITOTIC ACTIVITIES OF NEURONS IN VIRAL ENCEPHALITIS

In the neonatally Borna-virus-infected Lewis rat model a neuronal pathology involving particularly apoptosis is dissociated from any inflammation or active viral infection of specific neuronal subgroups. In terms of developmentally related abnormalities, a global CNS activation of the microglial population operatively induces apoptosis of specific neuronal subpopulations of the dentate gyrus, Purkinje cells and pyramidal cortical neurons.

This contrasts with Borna virus infected adult Lewis rats that develop an immune-mediated biphasic behavioral disease[2].

Strictly regional neuronal pathology in a setting of global CNS involvement by the Borna virus in the neonatal Lewis rat possibly relates to specific susceptibility traits of the neurons in a context of the actively developing nervous system. Virally induced cytolysis of neurons does appear to be significant in HIV encephalitis and there appears to operate a complex of host cell factors culminating in AIDS dementia[3]. Such susceptibility relates also to interference with the proper supply of growth factors to neurons, to micronutrient insufficiency, and also possibly impairment of the immune system[4] .

Vulnerability of defined neuronal subpopulations varies according to the stage of development of neurons and CNS as a whole, relative to time of occurrence or exposure to an injury or infection. The actual pathobiologic processes of CNS development is characterized by attributes arising from immaturity of the neurons and glia of the brain and of a vast range of other immature organ systems. Dysfunctional inflammatory and immune responsiveness operates in a context of developmental exposure to the injurious agent.

Indeed, integration of immune and nervous system responses appears central to many physiologic and pathologic states[5] that primarily affect the developing

**Corresponding Author:** Lawrence, M. Agius, 27 Guzeppi Caruana Street Tal-Virtu, Rabat, RBT 09 Malta, Europe

nervous system. It is also significant to note that the immunologically quiescent mononuclear cell state carrying integrated HIV-1 provirus is recognized as a major obstacle to elimination of the infection.

The inflammatory/immune systems in neonatal Lewis rats operates in a setting that renders them aberrant in their directed response against viral infections and to trauma or ischemia of the CNS.

In view of the global microglial response in Borna-virus infected neonatal rats, neuronal apoptosis would depend on specific biologic attributes of development and of metabolic activity of various susceptible neuronal subpopulations.

What would render such neuronal subpopulations susceptible to selective apoptosis? In the case of HIV-1 infection, for example, the HIV-1 envelope protein gp120 appears capable of inducing neuronal apoptosis in the neocortex of the adult rat[6], through the generation of reactive oxygen species by glia[7]. The fact that HIV-1 Envs in brain cannot be distinguished from those in blood on the basis of coreceptor usage, number or position of N-glycosylation sites is against simple neurotropic mechanisms for HIV-1 in AIDS patients[8].

It is conceivable, for example, that mitotically active neurons such as the dentate gyrus cells and the cerebellar granule cells, are especially susceptible to injury in a setting of a globally activated microglial population, as seen in the Borna-virus-infected neonatal Lewis rat[2]. Whether, for example, viral infection occurs more readily in actively dividing neurons remains unclear. This neuronal susceptibility may be significant in spite of the post-mitotic neuronal phenotype in the HIV-infected adult since evidence of the presence of neuronal progenitors has been suggested in various experiments.

It is conceivable that neurotropism, as a basic pathobiologic phenomenon, is linked to biologically active neuronal populations, besides mitotic activity. Virus production appears accelerated in actively replicating cells such as lymphocytes. Also, viral latency is induced in immunologically quiescent cells[9] and HIV-1 replication is an important mechanism in inducing CNS damage and dementia via the participation of multinucleated giant cells[10].

In general, high metabolic activity, including such phenomena as highly oxygenated states of exposure and utilization of glucose by specific neuronal populations, might constitute important circumstances conducive to progressive neuronal pathology, as seen, for example, in viral encephalitis, and perhaps also with trauma and ischemic injury to the central nervous system and also with bacterial, fungal and parasitic infections.

The virally infected cells with affected DNA/RNA expression would participate in different potential systems of progression in the production of even more viral particles. Much of the circulating HIV-1 free cell-viral load in the body in fact derives from short-lived, actively replicating cells rather than from chronically infected or activated cell pools[11] or blood monocytes.

Also, a concomitantly active metabolic state of the virally infected cell would perhaps tend to increase cellular production of even more virus particles.

The metabolic state of the infected cells, and also the mitotic activity, perhaps are important parameters in determining selective vulnerability to viral infection of defined neuronal subpopulations, beyond simple neurotropism or membrane receptivity.

DNA/RNA transcription pathways, membrane-bound endocytosis and exocytotic vesicles might evolve as various predilected pathways that predetermine neuronal susceptibility. HIV-1 encephalitis as a reservoir system of virus elicits significant inflammation and immune responsiveness.

This is analogous to selective susceptibility of CD45RO memory T lymphocytes over CD45RA naïve lymphocytes where the latter appear incapable of complete HIV-1 reverse transcription.

Viral infections evolves in relation to a drop in T helper lymphocyte counts as relevant to protein synthesis, DNA transcription, and dynamic membrane vesicle formation. Modulated HIV-1 transcriptional activity correlates with eukaryotic or viral heterologous factors[11].

CD14+/CD16+ blood-derived monocytes in HIV-1-associated dementia accumulate in CNS perivascular spaces and also in nodules or diffusely in white matter. These cells constitute a major CNS reservoir of HIV-1 infection[12] in a context of selective susceptibility to infection and to neuronal apoptosis.

A simple concept of neurotropism might be insufficient to account for the marked susceptibility patterns to neuronal injury as seen across a vast range of forms of involvement in viral encephalitis developing within a dynamic context of a globally activated microglial cell population.

Diminished viral replication in systemic tissues help account for an apparent loss of neurotropism in certain cases of encephalitis[13]. Also, it may significant that pseudotyping of the HIV-1 particles with rhabdovirus envelope glycoproteins does not in fact confer the expected powerful neurotropic attributes of the lyssaviruses[14]. Dysregulation of signaling pathways are possibly a general mechanism of HIV-1 induced neuronal injury as suggested by gliosis in HIV-1 gp120 Transgenic

mice and humans with HIV-1 encephalitis[3]. Besides gliosis, CNS changes include microgliosis, microglial nodules, loss of neuronal subpopulations and of presynaptic terminals, and degeneration of dendrites.

## VIRAL NEUROTROPISM IS AN EXQUISITELY DIRECT FUNCTION OF SPECIFIC BIOLOGIC PROCESSES CHARACTERIZING A SPECIFIC CELL SUBPOPULATION

An essential link appears to exist between selective viral neurotropism with specific biologic attributes of neuronal subsets. Basic biologic attributes would presumably account for specific susceptibility traits.

The large anterior horn motor neurons of the spinal cord are particularly vulnerable to infection by the poliovirus not only with regard to specific membrane receptors, but especially because of certain well-defined biophysiologic attributes of the large motoneurons in the anterior horns of spinal grey matter[15].

Such membrane receptors would determine developmental characterization and subtyping pathobiologically.

Specific viral neurotropism may partly arise from low levels of Major Histocompatibility Complex (MHC)-II surface expression as induced by HIV-specific mechanisms. Suppression of MHC-I surface expression contributes to a suppressed immune response[16].

In an analogous fashion, the exquisite tropism of HIV-1 for T-helper subset of lymphocytes is fundamentally related to certain basic biologic properties besides specific HIV-1 receptors on the cell membrane.

Whereas the degree of viral load does not necessarily correlate with the presence of the symptomatic phase of the infection, CD4+ cell killing, whether virally induced or through cytotoxicity, strongly correlates with HIV-1 replication[11].

Hence, viral infection is essentially a pathobiologic process dictated by, and, in turn, primarily directed against, distinct cell subpopulations that render such cells particularly vulnerable to virus.

In this regard, high regional variation in HIV-1 RNA has been noted within the brain in cases of neuroAIDS, although, overall, presence and severity of HIV-1 associated dementia correlate more with levels of productive HIV-1 replication within the brain[17].

## MICROGLIA PLAY A PIVOTAL ROLE IN THE INITIATION AND PROGRESSION OF NEURONAL INJURY IN VIRAL ENCEPHALITIS

The microglial and macrophage cell population are an initial site of action leading to neurodegeneration in cases of HIV-1 encephalitis[1,18].

Macrophage tropism of HIV-1 isolates from brain and lymphoid tissues produces neurotropism independent of coreceptor specificity[19]. In addition, neurotropic strains of HIV-1 are not necessarily neurovirulent[20].

Whereas the beta-chemokine receptor CCR5 is essential for establishment of the chronic HIV-1 infected state, disease progression often depends on utilization of the CXCR4 alpha-chemokine receptor in a non-essential manner. The expression state of the surface coreceptors contributes to modulation of susceptibility to HIV-1 in mononuclear cells[9].

Much of the damage inflicted during the course of a viral encephalitis may be initiated and subsequently maintained primarily by action of microglia. This would apply in terms of beta-chemokines interfering with HIV-1 entry and replication[21]. Much of the clinical impact and subsequent course of viral encephalitis depends on a central participation of microglia as mediators of effects of various cytokines, complement components and interferon gamma, besides nitric oxide. Indeed, Interferon gamma appears to process against lethal neurotropic viral infection but promotes inflammation and associated neurodegeneration[22].

An inflammatory microenvironment appears to provide an immunological setting for driving HIV-1 replication and progression of the infected state[9]. In addition, there is evidence that increased immune activity is associated with increased expression of human endogenous retroviruses; these latter have, in addition, been implicated as causative agents in inflammatory brain diseases such as multiple sclerosis[23]. Although the role of human herpes virus 6 in multiple sclerosis remains controversial, it may possibly be a cofactor in progression of HIV-1 disease[24].

Active microglial nodules in cases of viral encephalitis might respond to neuronal injury and also induce neuronal injury subsequent to activation.

Both initiation and progression of the neuronal damage in HIV-1 encephalitis lie exclusively or mainly with active implication of the microglial cell population. Such a role of the microglial or other brain resident target cell is central in the selection of specific viral strains in the development of HIV-1 encephalitis[25].

It is probably also significant that the same inflammatory cytokines (interferon gamma, tumor necrosis factor alpha, and interleukin 1 Beta) that induce endothelial cell responsiveness to Tat also activate HIV-1 replication[26].

Such a resident microglial cell population is particularly significant in terms of inducing and maintaining progression of neuronal injury. Since a vast microglial repertoire of secretory cytokine potential exists,

this correlates with an exquisite tendency for microglial nodule formation as distributed globally in the central nervous system.

## MACROPHAGES ARE ACTIVELY RECRUITED SUBSEQUENT TO CNS PARENCHYMAL DAMAGE AS INDUCED BY INFLAMMATION AND MICROGLIAL RESPONSIVENESS

An autoimmunity based primarily on the prior creation of sustained inflammatory changes in CNS parenchyma would determine a series of steps linking microglial activation to macrophage phagocytosis.

Microglia might be primarily concerned with activation arising from antigen presentation and proinflammatory cytokine production in particular[27,28].

On the other hand, perhaps, macrophages are fundamentally a cell type that is subsequently recruited as phagocytes in relation to damaged CNS parenchyma. This would relate closely to a deterioration in immune response (as evidenced by a drop in helper T-lymphocyte counts) and an increase in viral replication[11] .

In this sense, perhaps, an essential distinction between resident microglia in the CNS parenchyma and macrophages would necessarily revolve around attributes of a series of tissue changes initially induced by such inflammation. This would prove significant especially in view of the intimately related life cycle of HIV-1 to the activated state of the host cell[9].

Perivascular cells in the CNS are potential sensors of perturbations of the CNS immune system; they are activated in cases of CNS inflammation, autoimmune disease, and neuronal injury or death. Indeed, perivascular cells appear a primary target for HIV-1 in neuroAIDS[29].

Proinflammatory cytokine production is an amplified phenomenon resulting primarily from an initial participation by resident microglia that subsequently results in significant CNS parenchymal damage.

It is only then that macrophages, as essentially active phagocytic cells, would react to CNS tissue damage that includes also significant axonal damage.

## ABERRANT RE-STRUCTURING OF THE MYELIN SHEATH INDUCED BY AN INFLAMMATORY RESPONSE TO VIRALLY LADEN CNS MACROPHAGES

The essential susceptibility for development of an autoimmune response in encephalitis that is recognizable as subacute relapsing demyelinating episodes of a persistent nature might concern itself with aspects of the immunologically privileged status of the CNS, particularly in terms of dynamics of ingress and egress of macrophages into and out of the brain and spinal cord[30]. For example, chemokine receptors on cerebral vascular endothelial cells might be central to the initial process of HIV-1 invasion of the CNS[31]. There is evidence for a relationship between HIV-1 phenotype, viral replicative rate, and immune response in initial stages of the infection that would predetermine and characterize slow progressors from progressors as the infection becomes established[11].

Also, the primary site of any compartmentalized inflammation predisposes to HIV-1 disease progression as seen in patients with either cryptococcal or tuberculous meningitis.

Preferential expression of CCR5 coreceptor expression, as seen in African patients, may possibly contribute to increased expression of HIV-1 strains.

In this sense, as also presumably in patients with AIDS, the occurrence of Progressive Multifocal Leukoencephalopathy in the setting of immunodeficiency might serve as a basic model that is relevant to multiple sclerosis as an aberrantly induced inflammatory response involving a possibly persistently active viral mechanism.

AIDS-associated Progressive Multifocal Leukoencephalopathy may very well implicate viral persistence with lymphocytic latency. Indeed, JC and BK human polyomavirus replication appear enhanced by HIV-1 coinfection[32].

Heightened cellular activation in a context of progressive antigenic presentation to lymphocytes would perhaps facilitate not only clonal expansion of cell subsets but also propagation of cell injury mediated by both proinflammatory cytokines and the HIV-1 itself[9].

Infection by the human polyomavirus JC virus remains latent during childhood, but may be reactivated in conditions of immunosuppression and cause lysis of glial cells.

A whole series of factors might determine such reactivation of JC virus ranging from direct and indirect participation of a dysregulated immune system, and also interaction with other viruses such as HIV-1[33].

The presence of exogenous stimuli in a context of immune activation would have significant impact on HIV-1 phenotype and genotype, cell apoptotic rate and HIV-1 disease progression[9].

It is therefore in terms of abnormal aspects of an inflammatory response that is transformed from a viral clearance to a paradoxically effective mechanism of viral persistence that one might consider the real dynamic creation of conditions that, on the one hand, allow persistence of the virus in the CNS, and, on the other, the

progressive mounting of an autoimmune response directed specifically against membranes and lipid membranes in particular, as included in the myelin sheath. Such a possible phenomenon might perhaps be better understood in the context of increased amounts of cell-free virus in plasma rather than in terms of ratio (mean transcriptional activity) or provirus copy number or specific viral transcript molecules as detected for example in peripheral blood monocytes[9].

In a fundamental sense, the dynamic interactions of peripheral macrophages and of CNS resident microglia might actually constitute a pivotal point of involvement in the pathogenesis and possible control of virally associated demyelination, whether this latter is clearly induced by an active viral infection or by a system of transformation of the inflammatory response associated with persistent viral particles. Tumor Necrosis Factor-alpha appears implicated in the pathogenesis of many autoimmune diseases and also in CNS inflammation ranging from multiple sclerosis to bacterial meningitis and HIV encephalopathy[28].

This phenomenon would occur after an initial highly variable period of clinical latency reflecting shifts in equilibrium between viral replication and deteriorating immune effectiveness[9].

Persistent JC rather than BK human polyomavirus is found principally in the brain in cases of HIV-1 infection, confirming etiologic participation in neurologic disorders associated with immunodeficiency [34].

## ENDLESS CYCLES OF REACTIVATED IMMUNITY IMPLICATING CD8+ LYMPHOCYTES IN INDUCED IMMUNODEFICIENCY IN COMBINED HIV-1/OPPORTUNISTIC INFECTIONS

Microglial activation as an induced change of the resident cell population in the CNS would involve neuroprotection inherent to the pathogenesis of encephalitis in AIDS patients beyond simply evolving dynamics of either the HIV-1 infection itself or of the opportunistic infectious agents involved[35].

Indeed, chromosomally integrated provirus persists together with defective viral forms and replication-competent HIV-1 genomes in a manner linking macrophages to neurotropism in AIDS[36]. Also, for example, cerebrospinal fluid isolates of HIV-1 subtype E tend to show more diversity in V1/V2 variable regions and of envelope gp 120 sequence in contrast to blood isolates. Indeed, evolution of V1/V2 variable regions of CSF isolates might directly influence developing infection of the CNS by HIV-1. On the other hand, conservation of the genetic distance in V4 and V5 regions of CSF isolates might be necessary during the process of HIV-1 infection of the CNS[37].

Certainly, microglial activation as a phenomenon that is potentially suppressed in AIDS patients might reflect induced pathology by the HIV-1 infection involving virion multiplication that drives the microglia along pathways of progressively aberrant activation and reactivation. In this regard, Tumor Necrosis Factor alpha appears to constitute a primary disturbance affecting immune responsiveness and to lead to depletion of CD4+ lymphocytes[9].

It is to be noted that neurological disease is the first manifestation of AIDS in 10% to 20% of symptomatic HIV-1 infection.

Opportunistic infections of the CNS are common in AIDS patients and include particularly toxoplasma encephalitis, cryptococcal meningitis, cytomegalovirus encephalitis and Progressive Multifocal Leukoencephalopathy[38].

Microglia in AIDS patients are primarily affected by HIV-1 infection as a dysregulation of activation kinetics resulting in an endless series of reactivation phenomena leading to immunodeficiency. Accelerated evolution of the HIV-1 infection is reflected in dynamic viral molecular indices[11].

The Simian-human immunodeficiency virus in the rhesus macaque brain induces apparently both macrophages and Interleukin-4 in the CNS microenvironment. Interleukin-4 in particular appears supportive of the CNS pathology[39].

Endless reactivation of microglia as a basic cause of immunodeficiency in AIDS patients perhaps predetermines dynamics of the HIV infection itself and of the consequent opportunistic infections in the CNS.

Certainly, the clinical and pathologic features of HIV-1 infection implicate fundamental disturbances of macrophage and microglial involvement by the HIV-1 as a series of patterns directly resulting in depletion of immuno-competent cells.

Amplification of the immune response directly implicates the macrophage and the microglial cell as primary features of secondarily provoked repeated opportunistic infections.

The onset of progressive immunodeficiency in AIDS involves CNS macrophages in productive viral infection. They might be stimulated and even result in a self-sustaining series of macrophage dysregulation and of subsequent emergence of various neurological complications[29].

Persistence of the HIV-1 infection itself is a fundamental form of progression that depends on a macrophage/microglial participation[40]. An endless series

of reactivation phenomena leads to immunodepletion, based not only on lysis of CD4+ T lymphocytes but especially on effects exerted by cytotoxic CD8+ T lymphocytes as endlessly reactivating events[41].

CD8+ suppressor lymphocytes as a subset of lymphocytes contributing to a progressive depletion of immune response, account for aberrantly induced responsiveness. Amplified systems of proinflammatory cytokine effect would predetermine integration of the HIV-1 provirus in a manner particularly conducive to complete reverse transcription[9]. Also, immune activation perhaps is instrumental in HIV-1 pathogenesis.

Functional restoration of HIV-1 and Epstein-Barr virus-specific CD8+ T cells during active anti-retroviral therapy is associated with an increase in CD4+ T cells[42]. HAART appears to improve antigen responsiveness of both HIV-1- and EBV-specific T cells, with also an increase in CD4+ T cells.

## EMERGENCE OF HIV-1 RESISTANCE TO CURRENT ANTI-RETROVIRAL DRUG THERAPY IN THE CONTEXT OF A FULL GENOMIC INTEGRATION

The concept of emergence of resistance of HIV-1 virus to anti-retroviral drug therapy[43] revolves around integration of the HIV-1 within the infected cell in the absence of plasma rebound levels of HIV-1 RNA. This is a major obstacle to virus containment and may account even for transitory improvement in immune responsiveness in treated patients[11].

It is perhaps in terms of the genome of the infected cell that one can better explain the biology of emergence of drug resistant strains of the HIV-1 within a sphere of operatively induced drug pressure on a replicating pool of HIV-1[44]. Certainly, within the context of a pool of effectively integrated HIV-1, there might develop a situation that would protect the integrated virion from any anti-retroviral therapy. In addition, subsequent emergence of specific resistant strains of the HIV-1 would depend on patterns of interaction between anti-retroviral agents and the integrated viral genome.

Pressure selection exerted by anti-retroviral drugs results in the emergence of resistant strains of the HIV-1 simply because of integration of the virus, through a process of adaptive mutagenicity; the latter phenomenon would develop as a result of the integration of the HIV-1 within the infected cell genome, as contrasted with susceptibility of free HIV-1 virions in the body fluids to the anti-retroviral drug treatment. In this regard, HIV-1 DNA sequences have been detected in hippocampal neurons isolated from postmortem AIDS brains that are consistent with latent infection by this virus; indeed, neurons might show a selective vulnerability for HIV-1 infection and even promote the development of a neuronal reservoir of HIV-1 infection that is potentially reactivated[45].

It might be true to consider the infected cell genome as an effective mechanism directly facilitating emergence of resistant strains of the HIV-1 virus. HIV-1-associated dementia tends transform to a more protracted illness due to effects of HAART that prevents frank neuronal cell death[46]

A concept of interactive effects arising directly from a combined virally induced and immunologically mediated series of cellular injuries helps better account for both neuronal and CD4+ T lymphocyte killing.

## CONCLUSIONS

It is evident that the understanding of how neuronal membrane receptivity predetermines susceptibility to HIV-1 encephalitis might necessitate considerations of how integration of the viral genome depends on various biologic mechanisms. Pathways determining entry within cells, and subsequent trafficking to sites in the nucleus would be against a simple concept of neurotropism primarily or solely determined by membrane receptivity. Viral infection of neurons as seen in various forms of encephalitis might simply evolve as a neuronally determined sequence of events primarily predetermined more by the infected neuron rather than simply by interactive binding of a virion with the neuronal surface membrane receptor.

Indeed, a complex interplay of variably activated systems of progression in determining neuronal injury in HIV-1 encephalitis might involve inflammation and immune responses that participate in integrative incorporation of the viral genome by specific neuronal subsets in the brain. A basic concept of a viral CNS reservoir would perhaps account for some features of persistent permutation in neuronal handling of viral particles that may affect not only DNA/RNA transcription and translation systems but particularly the expression of various metabolic and even mitotic type events of various other cell types in the central nervous system ranging from microglia to lymphocyte subsets and vascular endothelia.

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