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Abnormal Systemic Immune Reactivities Underlying a Predetermined Progression of HIV-1 Encephalitis or Infection

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Abstract: It would appear that a resident microglial population in the central nervous system might actually account for essential dynamics of an HIV-1 infection that transforms and amplifies various systemic forms of influence that bypass real participation by specific neurotropic mechanics. Indeed, one might perhaps view HIV-1 encephalitis as a true form of systemic infection that integrates a lymphocytic depletion with repetitive cyclic reinfection of neurons based on evolving dynamics of involved microglial cells. Indeed, as far as a conceptual rendering of HIV load quantification might in various ways influence such microglial participation in neuronal reinfections by HIV-1, one would in addition also recognize how viral antigen presentation is essentially inseparable from a whole series of integral immune reactivities that primarily evolve and transform as HIV-1 replicates and progressively spreads within the body. Indeed, one might recognize systemic processes as pathways that might predetermine various modes of involvement of the central nervous system. One would perhaps associate a concept of selective vulnerability of neuronal subsets in the central nervous system with essential attributes of systemic involvement that would predetermine how transformed immune reactivities influence even HIV-loading of brain microglia. One might perhaps even consider blood stream spread of the HIV-1 a simple series of inducing change that depletes not only T lymphocyte helper subset but especially induces a transforming role for microglia as a substitute cellular reservoir for the HIV-1. Indeed, systemic determinants in establishment of HIV-1 encephalitis would in various ways perhaps amplify microglial participation in not simply exposing neurons to the virus but in rendering such neuronal infection a widespread phenomenon of cell loss. Effective participation of T lymphocyte helper subset depletion would in multiple ways constitute an active participation in the establishment of neuronal HIV-1 infection in specific modes of predetermined progression towards widespread cell loss of the ADIS dementia type as an abnormally transformed systemic immune reactivity.

Key words: Immune, abnormal, reactivity, HIV-1, encephatotes

INTRODUCTION

Is a high error rate of HIV replicative origin reflected directly in high mutation rates of the HIV-1 infected lymphocyte?: HIV-1 would apparently constitute a system of specifically progressive genetic instability in terms particularly related to replication of the virus, and as probably influenced by cellular and humoral immune responses in the genital mucosa [1]. This may be linked to the fact that HIV replication, HIV-specific T cell responses and T-cell activation each contributes to outcome in untreated HIV infection[2] .

Indeed, such high error-prone features of replicating HIV-1 might prove particularly significant in terms also of integrated provirus within the genomes of actively dividing host cells. In terms indeed of actively dividing and of repetitive cell cycling, integrated provirus of HIV-1 type might implicate a tendency towards progressive genetic instability that would correlate with depletion of the T helper inducer lymphocytes on the one hand, and on the other, with a tendency for development of high grade nonHodgkin's lymphoma.

In terms indeed of amplification pathways affecting integrated HIV provirus that would specifically incorporate modes of a high error rate in terms of point mutations, one might perhaps realize an integral system of expression versus nonexpression attributes of the HIV proteins reflected in an immune reactivity that is conditioned by such high rates of generated genetic error.

In terms, therefore, of very high error rates of the integrated HIV-1 concurrent with lymphocyte multiplication, there would perhaps tend to subsequently develop a progressive state of instability of the involved lymphocyte's genome reflected especially in a depletion of such T helper/inducer cell subset.

In this regard, HAART administration has contributed to improvement of response rates and survival in ADIS-related nonHodgkin's lymphoma[3].

Indeed, one might perhaps envisage a duality of either depletion of T helper-inducer lymphocyte subsets, on the one hand, or of a tendency for high grade lymphomagenesis, on the other, as simply expressions of the high error initiation rate of HIV-1 particles that are integrated in the host lymphocyte.

Cyclical alterations of latency to reactivation inducing disorganized immunoreactivity in ADIS: Immunodeficiency as a system that progressively depletes systemic immunoreactivity might actively constitute different combined types of evolving cellular injury ranging, in particular, from genomic interference in replication to a specific state of persistent viral infection that is latent. Also, effective HIV vaccination would need to stimulate directly both in mucosal and systemic compartments[4]. Mucosal vaccines may appear an optimal approach to attain sustainable immune response at mucosal sites of HIV inoculation[5].

In terms indeed of a provirus that is integrally part of the host cell genome somehow combined with coating of the CD4 receptor on that cell's surface by envelope protein, perhaps one might envisage pathways of a latent infection that specifically can alternate from persistently chronic to actively acute forms of cellular injury. In this regard, also, transcutaneous immunization appears effective in inducing strong mucosal production of antibody and of cytotoxic T lymphocytes[6].

Indeed, in terms not simply of an infection of immune cells or even of specifically T helper cell type, B lymphocytes or macrophages, but especially with reference to infected antigen-presenting cells, one might perhaps view the evolving ADIS state as a depletion of precursor cells in conjunction strictly of disorganized immune reactivity. In such a context, visceral leishmaniasis has increasingly complicated HIV infections in Mediterranean countries[7].

One might speak of an essentially disorganized immunoreactivity in patients infected by HIV-1 in a manner that would constitute a paradoxical form of protection to T helper cells. Various immune systems are prone to induce a latency of the HIV infection in terms particularly of such dysregulated immune reactivity.

Also, higher viremia and stronger immune activation would act synergistically to accelerate evolving drug resistance systemically[2]. This would be coupled to the various immune evasion tactics of HIV involving antigenic diversity, and rapid integration within host cell DNA.

Conformationally restricted HIV-1 Env and gp120 immunogens may allow the development of broadly cross-reactive antibodies to HIV[8].

Indeed, perhaps, one might view various stages of maturation and of multiplication of precursor lymphoid cells as dependent on essential attributes of an abnormal antigen-presenting phenomenon that actively provokes subsequently a progressive masking of HIV-1 infected cells affecting macrophages and microglia within a context of alternating latency and reactivation with progression of the HIV-1 infection. In this manner, intestinal B cell hyperactivity in ADIS patients is protected against by effective anti-retroviral therapy[9].

It is perhaps in terms of such essential cyclical pathways of alternating latency and reactivation with progressive infection by the HIV-1 that one might better understand modes of participation of cytokines such as Tumor Necrosis Factor and Interleukin 6 that evolve to constitute depletive transformation affecting both antigen presentation and immunoreactivity.

HIV brings about altered immune responsiveness to tuberculosis with changes in cytokine production in these latter patients, with increased systemic levels of Th1 cytokine levels[10].

The very dynamics of central nervous system involvement might be suggestive of specific modes of manipulative participation of interactions between antigen-presenting and immunoreactivity phenomena influencing resident pools of cells whose primary role would determine the nature of latency to reactivation transforming phases of the HIV-1 infection.

B lymphocytes may be unable to upregulate key immune proteins including MHC II molecules after exposure to antigen induced cytokine action with increased susceptibility to HIV both in drug abusers and patients on morphine [11].

One might recognize not simply a masking of the provirus in an evolving context of a coated CD4+ receptor by the envelope proteins of the HIV-1 virion, but a specific evolutionary system of adaptation of the virus in terms both of multiplying capability and especially of amplified genomic replication that paradoxically incorporate essential phenomena of cyclical alteration between latency and reactivation of cellular and tissue HIV-1 infected states.

An essential inbuilt system of self-amplified immune reactivity in establishment of progressive HIV-1 infection: It would appear that target cells for HIV-1 infection, including in particular, T lymphocytes (CD4+), Langerhans cells and macrophages, would constitute a self-amplifying system of associated mucosal reactivity arising especially with reference to previous episodes of infection including sexually transmitted disease[12]. In this regard, CD95L is a key molecule in the development of

immune privilege or tumor cell survival and costimulator of T cell activation. CD95L is associated with HIV infection, autoimmunity and various malignancies[13].

In this regard, mucosal reactivity as constituted by associated increasingly active target cell populations for the HIV-1 might specifically concern immunologically active sets of lymphoid and macrophage populations in a close relative functionality implicating specific antigen-presenting cells such as Langerhans cells. Combined chemokine/cytokine action may potentially help target antigen to antigen presenting cells and steer immune responses toward Th1 and CD8CTL action and even enhance effective memory responsiveness[14].

In this regard, the mucosa of the foreskin would appear a particularly effective pathway series of mechanisms strongly conducive to persistent self-amplification in establishment and progression of the HIV-1 infection. On the other hand, high urethral concentrations of HIV-1 specific IgA may possibly contribute to seroconversion subsequent to HIV-1 exposure[15].

An inbuilt system of antigen presentation to cyclically preconditioned groups of repeatedly stimulated lymphocytes and macrophages would relate to an established HIV-1 infection destined to persistent systemic progression. Also, in patients on HAART, the incidence of autoimmune disease in HIV-infected individuals is on the rise.

HIV-1 encephalitis that is transformed to ADIS dementia largely in terms of amplified increase in HIV-1 infectivity: Macrophage tropism for HIV-1 might perhaps contribute towards HIV-1 encephalitis that inherently comprises various principal pathways of spread within the central nervous system.

Such spread would not only be infiltrative in nature but particularly be based on amplified systems of production of increasingly infectious forms of the virus[16]. In this sense, a real transformation in modes of infectivity by the HIV-1 might relate particularly to a shift in modes of involvement initially of the macrophage and subsequently of the neuronal cell populations of the brain. In this sense, macrophage infectivity would in various ways create a series of microenvironmental conditions permitting not only enhanced transmissibility of the virus to other regions of the CNS but a particularly amplified infectivity that primarily enhances HIV-1 replication and integration within the infected cells.

This would be associated with an immune dysfunction that possibly includes autoimmune reactivity, possibly via molecular mimicry mechanisms.

In this sense, initially slow replication of HIV-1 within neurons would subsequently implicate a predominant replicative infectivity of neurons in terms only of a large CNS load of the virus but especially of a greatly enhanced distribution of repeated cyclical infections of cells in the presence of increased levels of monocyte chemoattractant protein and of other chemokines and cytokines in the brain.

Systems of recycling of repeated neuronal infection by cmv or HIV-1 in promoting widespread cortical neuronal cell loss: A system of primarily evolutionary dimensions would attest to a full set of attributes culminating in virally associated neuronal death in terms of participating roles of an active infection both as virion replication and production, on the one hand, and of a full sequence of consequent events of such viral replication, on the other[17]. This is significant especially since HIV eradication from the body has not been demonstrated with HAART[18].

In terms particularly of a viral replication cycling somehow inducing persistence of the viral infection affecting several types of cells as seen in the CMV-infected brain, one might also realize how microglial infection is itself a constituent part of the integral immune response. Microglial activation, for example, follows drug abuse and would contribute to premature neurodegeneration in ADIS encephalitis[19].

Indeed, it would appear that persistent viral replication within microglia would not only prove a primary source of persistence of the infection in viral encephalitis but actually promote transformation of a low-grade viral infection of neurons to widespread neuronal cell loss. In terms not only of CMV encephalitis but especially in terms of whole pathways of widespread neuronal death as seen in ADIS patients, one might perhaps recognize amplified systems of accelerated progression in cortical neuronal death dependent especially on cerebral blood supply.

Recycling blood-borne cytokines and chemokines would promote transformation of low grade to high grade activity of viral infection of the neurons as amplified repetitive reinfection evolves both quantitatively and probably also qualitatively. Low blood CD8+ T lymphocytes associated with a high circulating monocyte count predict progressive HIV-1 associated encephalopathy in children[20].

Various pathways of transformation of the neuronal HIV-1 infection might evolve as a viral replication utilizing neuronal components towards quantitative progression and also in particular as acquired attributes for increased viral spread to neuronal groups further afield.

Widespread neuronal cell loss as seen in CMV and

ADIS encephalitis would prove dependent on essential recycling of viral replication and distribution in the CNS derived from pathophysiologic attributes of a rich cerebral blood flow and of also important participation by the innate rather than simply adaptive immune response.

Mitochondrial DNA mutations at the basis of neuronal injury in ADIS dementia based on amplified transcription initiated by tat gene: A synergistic system of proinflammation might perhaps serve to induce neuronal injury in terms of toxic stress injury. But it is significant, presumably, to recognize effective oxidative bursts of released free radicals as constitutively damaging to such high energy organelles as membrane-bound mitochondria[21].

Strict proinflammatory stimulants as constituted by Nuclear Factor kappa Beta and AP-1 and CREB might perhaps involve essential dynamics of a DNA binding to promoter regions that would promote in various ways multiple pathways of amplification based primarily on attributes of transcription events themselves.

Synergistic effects resulting especially from concurrent action of TAT gene (of the HIV-1 genome) with methamphetamine toxic action would promote the execution of various amplified effects of a proinflammatory type based perhaps on TAT gene transcriptional dynamics. TAT gene transcriptional action in promoting NF-kappa Beta and of AP-1, would in various ways contribute to much of the attributes of a phenomenon of oxidative bursts that is particularly prone to subsequent amplified effect.

Mucosal delivery of HIV TAT protein may induce neutralizing antibody production, cytotoxic T lymphocytes and mucosal IgA[22].

In terms of an amplified series of dynamically induced oxidative burst activity, neuronal injury in ADIS patients might correlate analogously with systems of mitochondrial DNA mutation characterizing ragged red myofibers and neuronal infarcts in terms clinically of seizure activity and of loss of consciousness, as seen in and as typified by hereditary disorders of mitochondrial myopathy and of repeated cerebrovascular ischemic events of a familial type.

Developmental neuronal determinants of selective vulnerability: Selective vulnerability of neurons might refer in various ways to a summation phenomenon directed principally to how injured neuronal subsets would progress in terms of integrative systems of recoverability.

One might speak of a selective neurotropism essentially evolving in terms of a variably graded susceptibility not only to cellular injury but especially as a systemic progression of such cellular injury.

A Th1 polarized immune response appears important in developing a systemic immunity to HIV, as would be afforded by DNA vaccination[23].

Indeed, conceptual considerations regarding specific cellular subsets in terms of selective vulnerability might arise and evolve largely as a systemic participation of various tissue and organ systems in determining dynamics of established progression of cellular involvement in inflammation, ischemia and neoplastic transformation as seen in ADIS patients.

The continued use of HAART and systemic anti-CMV therapy would tend to reduce mortality considerably in addition to beneficial effects of prevention of Pneumocystis carinii and Mycobacterium avium intracellulare infection [24].

In such terms a responsiveness on the part of various tissue and organ systems of participation would evolve as integral reflections of how various specific cellular or neuronal subsets not only respond to either reversible or permanent injury, but especially also of fundamental developmental determination of evolving selective vulnerability within vicious cycles of neuronal injury progression.

Concurrently and interactively induced neuronal and lymphocytic depletion in ADIS-type immunosuppression: ADIS might perhaps fundamentally constitute a series of interactive systems of potentiation of an immunosuppression that somehow determines basic characterization of the CNS in terms especially of an immune participation as successive opportunistic infections develop and subsequently progress

Indeed, one might perhaps account for aspects of an ADIS phenomenon that would implicate even conventional phases of a viral infection such as viral particle entry into cells and of subsequent viral integration in terms of a reactivity determining and predetermining establishment of subsequent immunosuppression in ADIS patients. Also, a subset of blood and mucosal HIV-1 specific cytotoxic T lymphocytes may traffic between anatomically distinct compartments and participate in the induction of adaptive immunity to HIV[25].

It would be in terms of a reactive immunosuppression that evolves not only in terms of successive episodes of opportunistic infection in any one patient but especially in terms of how neuronal involvement would provide a series of actively suppressive effects influencing lymphocytic proliferation and reactivity. In this regard, also, DNA vaccines in humans remain suboptimal, and

strategies require to be developed to facilitate expression of the vaccine in vivo [26].

One would envisage reactively induced immunosuppression in the ADIS patient as a form of HIV-1 infection that transforms not only the infected T helper lymphocytes but also dynamic interactions between neuronal and lymphocytic subsets, leading subsequently to depletion of both constituent cell types.

An integral neuronal/lymphocytic subtype phenomenon in ADIS: The apparently immune privileged status of the CNS would help to better delineate systems of immune suppression evolving particularly in terms of interactive action in further enhancing immune reactivity or nonreactivity. This would relate to a need for the establishment of both mucosal and systemic immunity to the HIV-1 once exposure to this virus occurs[27].

Indeed, CNS components of an integral immune reactivity type might encompass peculiar attributes of an immune response and of immune surveillance as a basic pathway mechanism leading to cellular transformation of primarily developmental proliferative events.

The homing lymphocyte would perhaps help account for fundamental dynamics of a proliferating neoplastic cell pool that intrinsically infiltrates and metastasizes via vessels in terms of a series of trophic phenomena of potentially characterized type. Indeed, active HIV-1 infection of CNS neurons would consequently involve lymphocytic subpopulations in lymph nodes that would reflect CNS immunosuppression arising and evolving as an integral neuronal/lymphocytic phenomenon.

Migratory homing lymphocytes to CNS targeted by HIV-1 proliferation and by immunosuppressive action of the ADIS process: The particularly prominent manifestations of CNS involvement in ADIS patients might evolve not simply in terms of an active HIV infection of the neuronal subpopulations but especially in terms of an active participation of multiple inter-related systems of neural influence towards cyclical immune reactivity and nonreactivity in such infected ADIS patients. In terms especially of immunosuppression arising directly from stress-induced influences, on the immune/lymphocytic systems in particular, one might speak of central nervous system interactions with reactive immune pathways towards establishment of repetitive cycles of opportunistic infection. For example, one might perhaps explain how a Primary CNS Lymphoma would evolve in the strict spatial context of the brain or spinal cord that is totally excluded from active participation by systemic proliferative events involving especially lymphocytes and the immune response.

In a sense, active HIV-1 infection might primarily determine a systemic involvement that targets the central nervous system with subsequent consequential participation of migrating lymphocytes and various homing mechanistic pathways that would promote a potentiality for transforming and amplifying progression of HIV-1 infection mainly via participation of the resident microglial population in the brain.

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