Hypothesis on the pathogenesis of vacuum myelopathy, dementia, and peripheral neuropathy in AIDS

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Abstract
Certain aspects of the clinical syndrome of dementia, cerebral atrophy, predominantly sensory neuropathy, and vacuum myelopathy in AIDS resemble those seen in vitamin B12 deficiency. Pathologically, there are similarities not only in the changes in the spinal cord, but also in the brain and peripheral nerves. The pathogenesis of vacuum myelopathy may be secondary to a combination of immune mediated myelin and oligodendrocyte injury, and simultaneous impairment of repair mechanisms due to a deficiency of S-adenosylmethionine (SAM). Products derived from macrophages may interfere directly with the methyl transfer cycle through the generation of reactive oxygen intermediates and reactions involving nitric oxide and peroxynitrite which may limit the supply of methionine for conversion to SAM, both by direct interaction as well as through inhibition of methionine synthase. Macrophage activation with secretion of cytokines and other biologically reactive substances within the nervous system is sustained in the late stages of HIV infection by the general effects of immune depletion, including loss of T cells (with concomitant reduction of macrophage regulatory molecules) and recurrent opportunistic infections, and may be further augmented by the local presence of the virus itself (or its surface glycoprotein gp120). This would account for the common, but not exclusive, occurrence of vacuum myelopathy in AIDS. The ability of the virus and its products to stimulate macrophage and microglial activation may also explain the association between severity of vacuum myelopathy and the presence of HIV encephalitis. A similar mechanism may underlie the pathogenesis of dementia, cerebral atrophy, and peripheral neuropathy. Local factors or differential susceptibility between the central and peripheral nervous system may determine whether myelotoxic or neurotoxic processes predominate; the prominence of myelin involvement in the spinal cord, and axonal involvement peripherally may reflect both ends of this range, with the brain manifesting a more equal balance of both processes. Publications support an indirect relation between HIV and the pathogenesis of vacuum myelopathy, peripheral neuropathy, and dementia. The role of products and cytokines derived from macrophages or microglia has been emphasized by some, and defective methylation due to a deficiency of S-adenosylmethionine (SAM) by others, with some suggesting that the two may be linked.

We propose that concomitant SAM depletion and cytokine or oxygen mediated toxicity underlie myelin and neuronal damage in AIDS. The SAM depletion may occur as a result of (a) reduced SAM production secondary to inhibition of methionine availability due to reduced methionine production caused by inhibition of methionine synthase by macrophage derived nitric oxide (NO), and oxidation of methionine by peroxynitrite, and (b) increased consumption of SAM in repair mechanisms triggered by the toxic effects of cytokines and oxygen radicals on myelin or membranes.

This model suggests a direct link between macrophage activation and SAM depletion in AIDS and explains the neuroanatomical lesions in vacuum myelopathy, which is pathologically indistinguishable from subacute combined degeneration of the cord (SACD). A similar clinicopathological syndrome of dementia, vacuum myelopathy, peripheral neuropathy, and SAM depletion is seen in vitamin B12 deficiency.

The proposed pathogenesis is discussed in the following order: vacuum myelopathy, dementia, and peripheral neuropathy. Figure 1 shows a summary of the pathogenetic cascade. Figure 2 shows the relation of methionine, vitamin B12, and folate with SAM production and the association of the single carbon transfer pathway with glutathione metabolism.

Vacuolar myelopathy
(A) ACTIVATION OF MACROPHAGES, MONOCYTES, OR MICROGLIA
The secretion of immunoactive or toxic substances by activated macrophages and microglia contributes to CNS immunopathology in AIDS. Factors which may contribute to macrophage activation within the CNS in AIDS (figure 1) include: (a) decreased production of macrophage regulatory lymphokines interleukin-4 (IL-4) and IL-10; (b) recurrent infections; (c) increasing viral load and interaction of gp120 with macrophages leading to cytokine interleukin 1 (IL-1) and arachidonic acid metabolite production; (d)
secretion of tumour necrosis factor-α (TNFα) (also stimulated by IL-1). TNFα upregulates the transcription of integrated HIV, leading to a positive feedback cycle of TNFα production, HIV replication, and macrophage activation (fig 1).

In vacuolar myelopathy, macrophages may be attracted to specific areas of cord by degenerating myelin (see section (c) on SAM depletion). If HIV by itself does not cause the changes found in vacuolar myelopathy, but when present within macrophages, augments their capacity to secrete myelotoxic substances, several conflicting findings may be clarified; for instance, the apparent association between the presence of HIV infected macrophages and the severity of vacular change, the occurrence of vacuolar myelopathy in the absence of detectable HIV in the cord, the lack of correlation between the presence of coincidental HIV myelitis and the severity of vacuolar change, and the frequent coexistence of HIV encephalitis (HIVE) and vacuolar myelopathy in AIDS.

Astrogliosis in the brain in dementia and in cords with and without vacuolar myelopathy is common in AIDS. Macrophage-astroglial interactions are an important source of immunopathology. Coactivation of astrocytes by TNFα results in the secretion of other cytokines such as IL-6 and granulocyte-macrophage colony stimulating factor (GM-CSF), which activate macrophages and microglia and which act synergistically with TNFα to induce HIV-1 expression in macrophages.

(b) OLIGODENDROCYTE AND MYELIN INJURY AND VACUOLATION

The main pathological insult in vacuolar myelopathy is to myelin; axonal degeneration occurs secondarily in severe cases. Tumour necrosis factor-α may play a major part in oligodendrocyte and myelin injury in vacuolar myelopathy and in the CNS in AIDS. It is produced by activated macrophages, microglia, astrocytes, and endothelial cells and causes myelin vacuolation of mouse spinal cord oligodendrocytes in vitro. The presence of TNFα within macrophages and microglia in the lateral and posterior columns even in mild, presumably early, vacuolar myelopathy is consistent with its direct role in the pathogenesis of myelin vacuolation in vacuolar myelopathy.

The viral surface glycoprotein gp120 may bind to oligodendroglia, and to peripheral myelin associated glycoprotein. Infected macrophages expressing gp120 may similarly bind to, and damage, such glycoproteins on oligodendrocytes and central myelin. Alternatively, gp120 bound to myelin glycoproteins may be ingested by scavenging macrophages attracted by damaged myelin. Macrophages may act as antigen presenting cells, thus further enhancing the immune reaction, in conjunction with TNFα mediated upregulation of MHC class II antigen expression (fig 1). Oligodendrocytes in transgenic mice with a vacuolar myelopathy express HIV-1 proteins.

The generation of reactive oxygen intermediates and other reactive species—such as NO and peroxynitrite—by activated macrophages and microglia may damage myelin and membranes. Nitric oxide production is stimulated by many substances including TNFα, interferon-γ (IFNγ), lipopolysaccharide, IL-1, interactions with astroglial cells, and perhaps arachidonic acid. Peroxynitrite, a powerful oxidant formed by combination of NO with the superoxide free radical, can attack a wide range of biological targets including thiols, lipids, methionine,
**Pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS**

**Figure 2** The single carbon (methyl) transfer pathway. Relation with B12 and glutathione metabolism. (Modified from Surtees 1993, Bottiglieri et al 1994, and Castagna et al 1995.)

- **Methionine adenosyltransferase**
  - S-adenosylhomocysteine
  - Methionine synthase
  - Homocysteine
  - B12
  - Methyl B12
  - 5-Methyl THF
  - THF
  - 5,10 Methylene THF reductase
  - THF = tetrahydrofolate
  - SAM = S-adenosylmethionine
  - GSH = glutathione
  - Cystathionine
  - Cysteine
  - GSH
  - Cysteiny1 glycine

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The mechanisms for SAM depletion and the links with the products of activated macrophages and microglia in HIV disease will be outlined. A possible explanation for the observations made on the concentrations of various components of the methyl transfer cycle in these patients, some of whom had myelopathy, will also be suggested.

SAM is the mammalian “universal” methyl group donor in the brain, and is responsible for the biological methylations that modify proteins (including myelin basic protein), nucleic acids, fatty acids, porphyrins, phospholipids, polysaccharides, and biogenic amines such as catecholamines. A SAM deficiency is critical to the development of demyelination in cobalamin (vitamin B12) deficiency. It may also be essential to the pathogenesis of vacuolar myelopathy.

Comparisons of CSF concentrations of the components of the methyl transfer pathway in HIV seropositive patients with neurological disease and HIV seronegative controls show decreased SAM. In HIV + patients, SAM deficiency occurs when methionine synthase, acting on homocysteine, is inhibited by B12 or folate deficiency or 5-methyltetrahydrofolate induced by macrophage secreted neopterin has been suggested, but there is no evidence of folate deficiency in patients with HIV with neurological complications (including myelopathy).

The supply of methionine is determined by the activity of the vitamin B12 dependent methionine synthase, acting on homocysteine (fig 2). The diet is unlikely to be an adequate source, as the neurological consequences of SAM deficiency occur when methionine synthase is inhibited by B12 or folate deficiency or nitrous oxide misuse.

Vitamin B12 deficiency may exacerbate SAM deficiency in some patients, but it cannot be the primary cause. Firstly, most patients with vacuolar myelopathy do not have B12 deficiency. Secondly, although B12 deficiency is common in AIDS, those shown to be SAM deficient were B12 and folate replete.

Limitation in the bioavailability of methionine may relate to the production of NO and peroxynitrite by activated macrophages and microglia. Peroxynitrite oxidises methionine to ethylene or methionine sulfoxide. This powerful oxidant may be generated in the vicinity of activated macrophages which are capable of secreting NO and superoxide simultaneously, and is likely to cause local reduction in methionine concentrations.

Bovine heart cytochrome c oxidase catalyses the reduction of NO to nitrous oxide in...
anaerobic conditions,\(^{45}\) raising the further possibility that NO derived from macrophages gives rise to nitrous oxide in vivo with consequent methionine synthase inhibition and neurological sequelae—such as SACD—as seen in nitrous oxide misuse.\(^{42} 43\) Also, NO itself may cause a rapid dose dependent inhibition of methionine synthase.\(^{40, 47}\) Reduced CNS concentrations of glutathione in patients with HIV may further contribute to impairment of methionine synthase activity.\(^{47}\)

Methionine synthase inhibition in isolation normally causes a rise in homocysteine concentrations, but this was not found.\(^1\) Homocysteine concentrations may be kept within normal limits by several mechanisms. Firstly, with the production of oxygen radicals by macrophages in AIDS, homocysteine may be consumed by the trans-sulphuration pathway to replenish falling concentrations of the antioxidant glutathione, which was found to be low in these patients (fig 2).\(^7\) Secondly, the kinetics of the enzyme SAH hydroxase (fig 2) favour the formation of SAH, the reaction in vivo being normally driven in the opposite direction (of homocysteine) only by the rapid removal of homocysteine and adenine.\(^{15}\) Normal or rising homocysteine concentrations would therefore be expected to favour the conversion of homocysteine to SAH. This may also account for the high concentrations of SAH and low methyla-
tion ratio.\(^7\)

Thus, in AIDS, macrophage derived products in the CNS may lead to increased consumption of SAM, and simultaneously limit its production. Where SAM deficiency is sustained chronically, this may lead to the clinical and pathological changes of vascular myelopathy. Such a link between macrophage activation and SAM metabolism may account for the high incidence of vascular myelopathy in AIDS, as well as its occurrence in immuno-
suppressed HIV seronegative people.\(^{46}\)

**Dementia and cerebral atrophy**

The brains of patients with AIDS with dementia or cerebral atrophy show varying degrees of demyelination, neuronal loss, gliosis, microglial activation, multinucleated giant cells, and detectable HIV antigen or RNA.\(^{46, 50}\) Probable mechanisms responsible for the non-specific neuropathological changes are as follows: (a) the gliosis results from astrocyte proliferation in response to TNFα;\(^{14}\) (b) the myelin pallor may be due to SAM deficiency or the produc-
tion of TNFα or other cytokines and oxygen radicals;\(^{11, 15}\) and (c) the neuronal loss may be due to local production of neurotoxins such as quinolinic acid,\(^{41}\) arachidonic acid metabolites,\(^{10}\) free radicals, and NO.\(^{26}\) NO, produced by certain types of neurons\(^{36}\) as well as macrophages, microglia, and astrocytes, may also mediate the neurotoxicity of gp120.\(^{25}\)

The presence and degree of dementia and/or cerebral atrophy cannot be correlated specifically with any one neuropathological feature.\(^{15, 50}\) Several explanations could be forwarded. Firstly, the neurological features may be the product of variably contributing factors, in each person (fig 1). Gliosis, myelin pallor, or neuronal loss may be more prominent in some patients, whereas in others multinucleated giant cells and microglial nodules may predominate if the level of productive viral infection is high. The degree of SAM de-
ciency may contribute to the extent of demyeli-
nation. In B12 deficiency, demyelination may vary from small, often perivascular, foci to dis-
semination over wide areas of the corona radiata, sometimes accompanied by diffuse gliosis,\(^{48}\) closely resembling descriptions in AIDS.\(^{57}\)

Secondly, impairment of neurotransmitter function (as in SAM deficiency), which may contribute to AIDS dementia, is not detectable by routine histopathological techniques. The SAM dependent enzymatic methylation of phospholipids plays an important part in the transduction of receptor mediated signals through cellular membranes. Catecholamine neurotransmitters interacting with cell surface receptors initiate a cascade of biochemical and physical changes in local domains of the membrane leading to increased phospholipid meth-
ylation and mobility of receptors.\(^{33, 34}\) Concentra-
tions of SAM in the CSF also seem to influence brain monoamine metabolism.\(^{35, 36}\)

**Peripheral neuropathy**

A distal symmetric predominantly sensory axonal neuropathy (DSPN) of unknown aetiology is common in AIDS. Some authors distin-
guish between the painful and non-painful subgroups,\(^{66}\) whereas others do not.\(^{69}\) In HIV disease, as in HIV seronegative people, both painful and non-painful distal neuropathies are heterogeneous entities. A proportion of the painful subgroup may be caused by cytomegalo-
lovirus (CMV)\(^{60, 62, 63}\); other causes include vasculitis,\(^{44}\) drugs,\(^{65}\) inflammatory processes,\(^{66}\) nutritional defects in iron, and diabetes. However, in most patients with DSPN, no cause is found. Macrophage mediated immunopathol-
ogy, together with SAM depletion, may be important factors in the pathophysiology of DSPN in AIDS. The mechanism of macro-
phage recruitment in peripheral neuropathy may be similar to that described for vascular myelopathy.

Vitamin B12 deficiency may present as a painful, or non-painful neuropathy.\(^{67, 68}\) There is no correlation between serum B12 concentra-
tions and the presence of distal sensory peripheral neuropathy in AIDS.\(^{68}\) As described in vascular myelopathy, SAM deficiency can occur with normal serum concentrations of B12 and folate and may contribute to the pathophysiology of DSPN.\(^{69}\)

Wallerian-like degeneration of myelinated and unmyelinated fibres, and distal axonal degeneration involving both the peripheral and central branches occur in DSPN.\(^{63, 65, 70}\) Axonal atrophy seems to be found in painful but not in non-painful peripheral neuropathy.\(^\) The path-
ology of peripheral neuropathy in B12 deficiency is poorly documented but a similar reduction in numbers of myelin sheaths and axons, with degeneration in the centrally directed posterior root fibres, has been
Pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS

described. In B12 deficiency in monkeys, both Wallerian type axonal and myelin degeneration were seen in the peripheral nerves. Macrophages expressing TNFα within degenerating nerve fibres seem to be activated to a greater extent, and present in higher density for a given degree of Wallerian-like degeneration in AIDS, compared with seronegative controls with neuropathy. Cytokines secreted by activated macrophages may account for the damage to unmyelinated and myelinated fibres.

Clinical implications

Supplementation with SAM has been used clinically in the treatment of various disorders including depression and osteoarthritis. Concentrations of SAM in the CSF can be measured. However, SAM supplementation early in HIV infection is incorrect, SAM supplementation early in HIV infection would exacerbate the infection of the spinal cord. Correlates directly with extent of disease. Cytokine expression. Human immunodeficiency virus type 1 proteins under the regulation of Vitamin B12 deficiency virus type 1 proteases under the regulation of the J Neuroimmunol 1989;36:349–44.


