Journal of NeuroVirology (1996) 2, 5–6

HIV infection of the nervous system: pathogenetic mechanisms

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HIV-1 neuropathogenesis is still incompletely understood but many important aspects of this process have been identified in recent years. In broad terms HIV-1 neuropathogenesis can be divided into three important components. These are: 1. virus entry/virus localization in the nervous system; 2. the role of viral proteins and/or cellular products in neural tissue damage; and 3. the mechanism(s) of neuronal dysfunction/damage/death.

Many neuropathological studies have identified a discrepancy between the number of HIV-1 infected cells in the brain, and the presence of dementia on pre-mortem examination. Other investigators have provided data that virus localization does correlate, to some degree, with neocortical damage to the dendritic arbour, and with pre-mortem dementia. There is a fairly broad consensus that HIV-1 is necessary, probably not sufficient to account for the neuronal injury that ultimately underlies HIV associated dementia. The major cell type harbouring productive HIV-1 infection in the nervous system is the perivascular macrophage. There still exist some controversy as to whether these are blood derived macrophages, or secondarily infected resident brain microglia. Less attention has been given to date to the trafficking of HIV infected T-lymphocytes. Recently HIV-1 infection of brain astrocytes restricted to the expression of regulatory gene products has been described in both children and adults. It has been postulated, but not proven, that restricted infection of astrocytes causes astrocyte dysfunction and may contribute to neuronal injury or to disruption of the blood-brain barrier (BBB).

Numerous studies of the CSF and of postmortem tissues have demonstrated that a state of chronic inflammation/immune activation exists in the nervous system during the later stages of HIV-1 infection. This appears to be associated with disruption of BBB integrity. Less is known about early changes in brain during HIV-1 infection, although disruption of the BBB may be an early event. BBB damage may be responsible for the white matter pallor described in HIV-1 infection and this damage could result in further entry into the nervous system of toxic viral or cellular products, or additional HIV-1 infected cells.

There is good evidence that HIV infected macrophages produce excessive amounts of pro-inflammatory cytokines, including tumour necrosis factor alpha, and platelet activating factor, and that these products, are directly toxic to human neurons *in vitro*. In addition the HIV-1 envelope glycoprotein, gp 120 may further stimulate the release of toxic factors from brain macrophages. Other HIV-1 proteins tat and nef have been implicated as direct neuronal toxins.

One or more of these 'indirect mechanism' ultimately results in neuronal injury or death. *In vitro* studies have shown that the toxic effects of the candidate toxins of both viral and cellular origin can be antagonized by blocking NMDA (or AMPA) glutamate receptors. This as well as the type of damage in the dendritic arbour, point to an excitotoxic mechanism of neuronal damage/death. It has been postulated that (weak) excitotoxicity, leads to oxidative stress in neurons, and ultimately to apoptosis. In fact neuronal apoptosis has recently been described in the brains of both children and adults with HIV-1 infection.

Further studies are necessary to understand: the trafficking of HIV-1 infected cells into (and out of) the nervous system, the mechanism of BBB injury, and the role of viral and cellular products in neuronal injury and death.

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