



Clinical Science Workshop 4

Peripheral nervous system

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65

Peripheral neuropathy in FIV infection: evidence of axonal injury

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Background: HIV-associated distal sensory peripheral neuropathy is a growing problem because of longer survival times and intense antiretroviral usage. Feline immunodeficiency virus (FIV) is a lentivirus that causes neurological disease and immunosuppression in domestic cats.

Objective: To determine the extent of peripheral nervous system disease in animals infected with the infectious FIV molecular clone, FIV-Ch, which contains the full FIV-V1CSF env-encoding region in a laboratory-adapted FIV background vector. **Methods:** Neonatal cats were infected with live FIV-Ch (n=9) or heat-inactivated (n=8) virus, followed by weekly measurements of weight and neurobehavioral performance. At weeks 8 and 12 post-infection (PI), animals underwent necropsy and we harvested blood, sural and sciatic nerves, lumbar-sacral spinal cord and hind limb footpads for morphological, FACS and PCR analysis.

Results: FIV-Ch infected animals showed reduced CD4 and CD8 T-lymphocyte levels in blood at 12 weeks PI, together with diminished neurobehavioral performance ($p < 0.01$). Morphological studies of sural nerve revealed reduced fiber areas in 12-week FIV-infected animals ($33.0 \pm 1.6 \text{ mm}^2$) compared to age-matched control animals ($42.6 \pm 2.1 \text{ mm}^2$) ($p < 0.05$), which was accompanied by reduced myelin sheath thickness ($p < 0.05$). Immunocytochemical studies of foot pads displayed reduced intraepidermal fiber density of FIV-infected animals at 12 weeks PI ($5.7 \pm 1.6 \text{ mm}^2$) compared to control animals ($15.7 \pm 5.4 \text{ mm}^2$) ($p < 0.01$). PCR studies of sciatic nerves and lumbar-sacral spinal cord indicated that provirus was detectable in both tissues among all infected animals at 12 weeks but not in controls. Viral RNA was found in both nerve and spinal cord of FIV-infected animals with concomitant detection of TNF- α mRNA.

Conclusions: FIV infection results in the rapid onset of peripheral neuropathy that is defined by axonal loss and reduced intraepidermal innervation with detection of viral genome in peripheral nerves, resembling HIV-associated neuropathy. These results suggest that peripheral neuropathy may be common among lentiviral infections and is associated with immune suppression.

66

Macrocytosis in HIV associated vacuolar myelopathy

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Objective: To evaluate whether a macrocytic anemia is associated with HIV vacuolar myelopathy. **Introduction:** A macrocytic anemia is often seen with B12 deficiency and is due to abnormal methylation in the red corpuscle. There is evidence suggesting that there is a hypomethylated state in the patient with vacuolar myelopathy. Transmethylation abnormality is thought to cause vacuolar myelopathy (VM). If so, the metabolic abnormality most likely is a systemic phenomenon and may lead to other signs of abnormal methylation such as a macrocytic anemia. We hypothesize that patients with vacuolar myelopathy may have a macrocytic anemia.

Methods: 50 male patients with documented HIV infection and presumed diagnosis of HIV associated vacuolar myelopathy concurrently enrolled in a Methionine treatment study for HIV myelopathy. Control patients were HIV-positive patients without myelopathy who were matched by CD4 count and concomitant medications that can cause anemia. Hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), serum folate and vitamin B12, CD4 count and plasma HIV-1 RNA samples were collected at the time of the clinical evaluation. HIV-1 RNA was measured in each sample using PCR Amplicor Monitor Test (Roche Diagnostics, Indianapolis, IN). Anemia is defined by Hgb level less than 14g/dl with Hct level less than 41% in men.

Results: In the myelopathy group there were 48 men and 2 women. The women were excluded as they naturally would have a lower Hemoglobin. The 48 subjects had a CD4 count of 253 (SD \pm 196.6). There were 32 male control subjects with a mean CD4 count of 373 (SD \pm 277.3) MCV for the Myelopathy patients was 106.6 (SD = \pm 11.8) was significantly higher than for the control group MCV 100.3 (SD \pm 12.0) with a p-value of .005. There was no significant difference between Hemoglobin or Hematocrit for the two groups.

Conclusion: Patient with VM have an elevated MCV which suggests that the transmethylation abnormality that is seen in their CSF may be a systemic metabolic abnormality. This suggests that a systemic transmethylation abnormality is present in HIV vacuolar myelopathy.

67

HIV-1 associated necrotising arteritis peripheral neuropathy—clinical, laboratory features and the response to treatment

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Introduction: HIV associated necrotising arteritis (NA) has only been reported anecdotally. This report describes the largest case series to date.

Objectives: to ascertain the prevalence, the clinical, laboratory including pathological features and treatment responses of HIV associated necrotising arteritis.

Methods: This retrospective study was carried out at a secondary referral centre with a specialist interest in HIV and peripheral nerve disorders (L'hopital Kremlin Bicetre). The records of all patients between 1986 and 1996 with HIV infection, a symptomatic neuropathy and evidence of NA on nerve and/or muscle biopsy were reviewed.

Results: 294 patients with HIV infection and peripheral neuropathy underwent biopsy. Twelve patients fulfilled the criteria giving a prevalence of 4% at a specialist centre. A mononeuritis affecting the common peroneal nerve was present in nine patients and a symmetrical sensorimotor neuropathy was present in three. Systemic features were present in two patients. The CD4 count ranged from 71–1000 cells/mm³. Nerve conduction test abnormalities were evident in all. On biopsy, both epi and perineurial were involved. Most biopsies revealed an endoneurial inflammatory infiltrate with mononuclear cells. Seven out of eight patients responded to corticosteroids with no relapse at the end of treatment.

Conclusion: This study confirms that NA in HIV is rare. NA may occur at all stages of HIV infection. The clinical presentation is similar to non HIV cases of NA. Pathologically, endoneurial vessel involvement is more common with a mononuclear rather than a polymorphonuclear infiltrate. NA in HIV is responsive to treatment with corticosteroids.

68

ddI entry into the CNS and the effect of other nucleoside anti-retroviral drugs

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The accumulation of anti-HIV drugs into the brain and CSF is of importance if HIV infecting the CNS is to be treated. Drug movement into the CNS is restricted by the presence of the blood-brain barrier (BBB) and blood-CSF barrier (choroid plexus). The objective of this study was to examine the passage of the nucleoside reverse transcriptase inhibitor (NRTI), 2'3'-dideoxyinosine (ddI), across the CNS barriers and the subsequent accumulation in the brain and CSF.

An *in situ* brain perfusion technique was utilised whereby an artificial plasma containing [3H]ddI (2.3 nM) and [14C]mannitol (1.1 microM) (a vascular space marker) were perfused through the carotid arteries into the CNS of the anaesthetised guinea-pig (J. Neurochem. 2002: 80, 392–404). Following perfusion periods of up to 30 mins the brain and CSF were sampled. Accumulation of [3H]ddI and [14C]mannitol into the CNS was expressed as a ratio of levels in the artificial plasma.

Results: indicated that ddI was able to accumulate in the CNS: after 30 mins, brain and CSF levels of [3H]ddI (corrected for mannitol) reached 1.9 ± 0.2 ml/100 g and 4.0 ± 0.7 ml/100 g, respectively. Perfusions in the presence of 100 microM unlabelled ddI resulted in significantly reduced levels of [3H]ddI in the brain ($p < 0.05$, Student t-test) but not CSF. Additional self-inhibition studies revealed that [3H]ddI transport into the brain was partly saturable ($K_m = 20.1 \pm 6.7$ microM, $V_{max} = 6.5 \pm 0.9$ pmol/min/g) and partly a result of diffusion ($K_d = 0.22 \pm 0.09$ microl/min/g). Cross competition studies implicated the involvement of a BBB nucleoside transporter in the passage of ddI into the brain.

Additionally, preliminary results indicate that when ddI is used in combination with AZT, D4T or 3TC there is no significant effect on ddI distribution into the brain and CSF. However, there is evidence that ddI does interact with AZT at the choroid plexus. Further studies are underway to explore whether use of ddI and AZT in combination could result in sub-optimal drug concentrations in the mammalian choroid plexus.

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