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Plenary session 9

Neuropsychology & neuropharmacology of AIDS/Diagnostic imaging

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HIV dynamics in cerebrospinal fluid (CSF) after antiretroviral therapy initiation and interruption

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Background: Characterizing CNS viral dynamics may benefit the rational design of treatments for HIV in the brain. Viral dynamics are determined by the kinetics of antiretroviral drug influx/efflux, the turnover rate of infected cells and local immune responses.

Objective: To define the parameters of HIV viral load decline and rebound following the initiation or interruption of highly active antiretroviral therapy (HAART), and to compare these with concomitant plasma dynamics.

Methods: We sampled CSF and plasma at multiple time points after changes in HAART. CSF and plasma viral loads were measured by using RT-PCR, and general linear models and nonparametric regression were employed to describe viral dynamics.

Results: After HAART initiation, viral load decline in plasma typically preceded CSF. CSF decline was often slower than in plasma, particularly among subjects with advanced HIV disease or dementia. After structured treatment interruption (STI), plasma viral load rebound preceded CSF; however, the growth rate in CSF approximated that in plasma. CSF viral load rebound was frequently followed by a transient, striking CSF pleocytosis. A steady state was reached in both fluids 2-3 months after STI.

Conclusions: HIV dynamics in CSF and plasma differ in ways that reveal the kinetics of drug distribution to CNS tissues, the contributing cellular sources of HIV RNA, and local immune responses. The lag of CSF dynamics behind plasma after starting or stopping HAART is consistent with slow drug influx to, and efflux from CNS tissues. The diminished slope of decline in CSF compared to plasma among AIDS patients suggests that a longer-lived cell population contributes substantially to CSF viral load. The rapid rate of rise of CSF HIV RNA during STI is consistent with a local source of replication-competent cells with short half-lives. The pleocytosis that develops in CSF after viral rebound may represent recruitment of activated lymphocytes intrathecally in response to rises in viral antigen production. Eventually, CSF viral loads reach a steady state reminiscent of the viral 'set-point' seen in plasma.

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Psychiatric complications of HIV infection

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HIV infection is associated with psychiatric complications. They include cognitive impairment, affective disorders and psychosis. The cognitive impairment starts as a simple forgetfulness, resulting in difficulties to perform tasks of every day life and leads to a florid dementia. Cognitive deficits have been reported in the early stage of the infection. Similarly, cognitive impairment was observed in the SIV/macaque model of HIV infection using various behavioural tests. In addition a marked reduction of choline acetyltransferase (ChAT) in the hippocampus was observed. ChAT is the enzyme responsible for the synthesis of acetylcholine and serves as a biochemical marker for cognition. Other psychiatric complications include affective disorders, such as depression and mania and psychosis. Accordingly, antidepressants and neuroleptics are often advocated to HIV-infected patients. The high vulnerability of infected patients to develop parkinsonism following anti-psychotic treatment implies an impairment of the dopaminergic system. Based on the pharmacotherapy of psychiatric complications of HIV-infected patients as well as neurochemical data of SIV-infected rhesus monkeys, we discuss how psychiatric complications may arise and alarm clinicians for the potential danger of the symptomatic psychiatric treatments in HIV-infected patients.

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Diagnostic MR spectroscopy in HIV-patients

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Proton localized magnetic resonance spectroscopy (MRS) is a method of non invasive human neurochemistry based on the magnetic resonance phenomenon. This exploration of brain metabolism, performed without any injection, detects neuronal, glial, and membrane markers. MRS of the brain does not purport to be a metabolic "biopsy," but unique applications for brain MRS are (1) quantitating the oxidative state of the brain and defining neuronal suffering, (2) assessing and mapping neuron damage, (3) evaluating membrane alterations and demyelination, (4) characterizing glial activation

or gliosis, (5) identifying macrophagic invasion and/or hypoxia, (6) detecting modification in the metabolism of macromolecules (lipids, proteins), (7) pinpointing anomalies in the metabolism of glial and neuronal aminoacids.

Brain MRS can be performed routinely after conventional MRI, without moving the patient, as a valuable metabolic and functional complement to the anatomical evaluation of the cerebral status of HIV-positive patients. For these patients, brain MRS plays a major role 1) in the early diagnosis of HIV-related encephalopathy, 2) in the differential diagnosis of HIV-related encephalopathy versus psychiatric symptoms or occurring in AIDS people, 3) in the differential diagnosis of HIV-related encephalopathy versus other brain lesions related to AIDS, and 4) in the follow-up of patient response to therapy. In these indications MRS is frequently more reliable than neuropsychological testing and more sensitive than MRI.

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Neuroimaging in HIV-related brain diseases

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Patients infected with HIV may present with opportunistic infections or HIV dementia. In the era of potent antiretroviral therapy, the incidence of certain opportunistic infections, such as cerebral toxoplasmosis, has declined significantly but the prevalence of HIV dementia may increase since many HIV patients are surviving longer. A variety of physiological MR imaging techniques may improve clinical diagnoses or assessments of opportunistic infections. Several advanced neuroimaging techniques (magnetic resonance spectroscopy, perfusion MRI, functional MRI, etc.) have been shown to assess the severity of HIV-associated brain injury, and some techniques can detect brain injury even during the asymptomatic stages. In addition, quantitative measurements with these techniques may serve as surrogate markers to monitor treatment effects. Other neuroimaging techniques may evaluate neuropathological mechanisms associated with HIV dementia. Dynamic T1-mapping with MRI could be used to quantify the leakage of a contrast agent, such as gadolinium, across the blood brain barrier (BBB), thus allowing the evaluation of BBB integrity; the breakage of BBB has long been postulated to be a point of entry for HIV-infected macrophages into the CNS. Carbon-11 labeled radioactive tracers that bind to dopamine transporters and receptors can be used to assess possible dopaminergic dysfunction in those with HIV dementia. Preliminary findings from these studies will be presented and discussed.

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