HIV-1 Infection of the Nervous System Comes of Age

By Karl Goodkin, MD, PhD, FAPA

Early in the acquired immunodeficiency syndrome (AIDS) epidemic, human immunodeficiency virus type 1 (HIV-1) infection of the nervous system was largely confined to the central nervous system (CNS). Originally, the concept of a dementia due to HIV-1 was challenged—thought to be better attributed to a complicating infection, such as cytomegalovirus encephalopathy. However, studies investigating pathology in the brains of infants and children infected with HIV-1 provided evidence that the dementia is actually caused by HIV-1 itself.

In the lead article of this issue, Paul Shapshak, PhD, and colleagues thoroughly examine the importance of the load of HIV-1 in the brain. Unlike research focusing on the periphery, research on the CNS has been predominantly focused on indirect mechanisms of cell death and inflammatory mediators. Shapshak et al discuss the possibility that independent clustering and evolution of virus occurs normally across brain regions over time, as well as the importance of strain variation related to neurovirulence. In addition, the attention given to the molecular epidemiology of the virus incorporates a novel aspect of work. Cytokines and chemokines, which have been the predominant mechanistic focus of research, are also thoroughly considered.

From the early stages of the epidemic, the issue that the dementia was a diagnosis of exclusion was highly clinically relevant (Mauricio Concha, MD, MHS, and Alejandro Rabinstein, MD). Toxoplasmosis frequently caused lesions in the brain and CNS lymphoma was already the second most common mass lesion in these patients. Cryptococcal meningitis was also a frequent cause of morbidity and mortality. In addition, less common fungal infections in the CNS are discussed—histoplasmosis, coccidioidomycosis, mucormycosis, blastomycosis, Candida, and aspergillosis. Over time, it became clear that neurosyphilis was frequently overlooked, could be asymptomatic, and may appear despite a negative serological test for syphilis—heralding the return of syphilis as the “great masquerader.” In addition, tuberculosis increased in incidence and made a continued climb as the AIDS epidemic grew. As a result, tuberculous meningitis became an important entity to screen as well. Other less common bacterial infections of the CNS are also discussed—Mycobacterium avium complex (which is much more common in the periphery), listeriosis, and nocardiosis. Progressive multifocal leukencephalopathy stood out as an opportunistic viral infection that struck fear into patients and seemed hopeless to treat.

In addition, other viral encephalopathies are discussed—cytomegalovirus, herpes simplex virus, and varicella zoster virus. With this plethora of conditions to screen, it became incumbent upon neuropsychiatrists as well as neurologists to familiarize themselves with these conditions.

Nutrition has been studied as a cofactor of HIV-1 clinical disease progression systemically, as well as specifically in neuroAIDS conditions. Since the beginning of the epidemic, the patients have been interested in nutritional intervention for longevity and treatment of symptoms and illnesses associated with HIV-1 infection. Teri Baldecwicz, PhD, and colleagues present an excellent review of the data regarding how nutritional deficiencies may contribute to the cognitive dysfunction, neurologic abnormalities, mood disturbances, and immune dysregulation associated with HIV-1 infection. Of relevance to peripheral neuropathy to be covered in the next issue, pyridoxine and cobalamin are addressed, along with their effects on other outcomes, such as mood. S-adenosyl methionine and folate are discussed in conjunction with cobalamin in terms of 1-carbon fragment metabolism. Oxidative stress is a physiopathological mechanism of major interest for several illnesses in the field of neuroAIDS (relevant to deficiencies in vitamins A and E, as well as selenium). In addition, zinc has a clinically relevant role as an immunostimulant as well as other roles in neuroAIDS conditions. The recent interest in polyunsaturated fatty acids and lipids in HIV-1 infection is approached from the perspective of neuroAIDS therein as well. Finally, this article ends with a consideration of nutritional issues in special populations—children and substance users. Overall, this article is one of the most comprehensive, up-to-date presentations available on nutritional relationships in neuroAIDS conditions.

In summary, this first issue of two issues on neuroAIDS is focused on the virological mechanisms of HIV-1–associated dementia, on a review of complications of HIV-1 in the CNS, and on a comprehensive and current review of nutritional relationships with a mechanistic focus. These foci make this issue important reading for any neurologist or neuropsychiatrist seeing HIV-1 infected patients.
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Absence seizures (petit mal) do not appear to be controlled by carbamazepine. The most frequently reported adverse events (particularly during the initial phases of therapy) are dizziness, drowsiness, unsteadiness, nausea, and vomiting. Adverse events can be minimized by initiating therapy at the lowest possible effective dose.

**INDICATIONS AND USAGE**

Carbatrol® (carbamazepine extended-release capsules) is Indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant is based on clinical investigations performed in adults and from postmarketing experience. The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be started at a low dosage and increased gradually.

**PRECAUTIONS**

Geriatric Use

Geriatric use of carbamazepine has been safely managed, with a modest increase in incidence of adverse effects occurring in older patients and a modest increase in the severity of those adverse effects observed. Because there is no information on the use of carbamazepine in children under 16 years of age, it is recommended that this drug be used with caution in children. Use of this drug should be individualized.

**Concentration of Drug in milk**

Concentrations of carbamazepine and its epoxide metabolite are transferred to breast milk. The concentration of carbamazepine in breast milk is approximately 20% of that found in maternal plasma. In a newborn infant of a patient with an average concentration of carbamazepine in plasma of 3.0 mg/mL, the maximum concentration of carbamazepine in plasma was 0.6 mg/mL. The safety and effectiveness of carbamazepine for use in women who are breastfeeding are unknown. Because effective contraception is necessary during therapy with carbamazepine, it is recommended that women who breastfeed while they are receiving treatment should use another method of contraception.

**Pregnancy Category D (See WARNINGS) Lab Data**

Lab data should be performed. Lab data should be performed because of the potential for serious adverse reactions in nursing infants from carbamazepine, particularly drowsiness, dizziness, ataxia, confusion, and sedation.

**WARNING**

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in the diet in doses of 2500 mg/kg/day (mg/kg/day on a mg/m² basis), and the drug is accumulated in the milk of lactating rats at levels approximately 50% of the plasma level. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, it is recommended that women who breastfeed while they are receiving treatment should use another method of contraception.

**Reproduction Studies**

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**WARNINGS**

**Epilepsy**

Before prescribing Carbatrol, the physician should be thoroughly familiar with the details of the full prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

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