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LABORATORY EVALUATIONS IN HIV-1–ASSOCIATED COGNITIVE/MOTOR COMPLEX

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The nervous system is invaded early in HIV-1 infection and subsequently is subject to a variety of neurologic problems, which can be classified into (1) primary HIV-1 CNS disease, in which HIV-1 is the sole etiologic factor; (2) opportunistic infections and tumors, which occur secondary to HIV-1–induced immunologic derangement; and (3) iatrogenic disease, which is caused by medical treatment of HIV-1 infection.

Primary HIV-1 neurologic disease remains a clinical diagnosis that is based on the presence of certain positive signs and symptoms, and on the exclusion of other known causes for neurologic disease, such as CNS opportunistic infections, tumors, and neurosyphilis.[117] The initial work-up typically is conducted by a neurologist or neuropsychiatrist, and these evaluations are covered by Dr. Stern elsewhere in this issue. Given the often subtle neurocognitive changes that may occur in asymptomatic or early symptomatic HIV-1 infection, a neuropsychological consult may be required and is detailed by Dr. Stern and Dr. Grant in their articles in this issue. A clinical neurologic and neuropsychological examination pro-

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guishes between different pathogens.[34, 35, 158] In a series of 56 AIDS patients who received a final diagnosis on the basis of either brain biopsy or postmortem brain examinations, a very high rate (up to 50%) of incorrect antemortem diagnoses was noted.[8] This issue is complicated further by the observation that many AIDS patients have multiple intracranial pathogens.[11]

CT and MR imaging studies also have established that primary CNS HIV-1 infection can be associated with characteristic imaging features. These include cortical atrophy, ventricular enlargement, and diffuse or patchy white matter abnormalities, particularly in periventricular areas.[34, 62, 77, 78, 111, 148, 157, 173] These findings are especially evident in more advanced HIV-1 disease, and occur most frequently in association with HIV-1–associated dementia.[52, 62, 77, 103, 116, 120] The presence of a "normal" scan, however, does not preclude active CNS HIV-1 disease. The neuroimaging abnormalities in patients with primary HIV-1 infection probably reflect the cumulative effects of long-term, on-going neuronal loss, astrogliosis, and demyelination that characterize HIV-1 encephalitis.

Studies that examined neuropathologic findings after imaging generally have reported good correlation between MR imaging abnormalities and pathologic changes such as cerebral atrophy and white matter changes.[34, 62, 77, 103, 173] Given the problems inherent in studies of MR imaging-pathologic relationships, particularly temporal delay of scan and pathology examinations, the generally good correlation for atrophy and diffuse white matter changes support the use of MR imaging gross features for detection and follow-up of disease. More subtle, but equally characteristic features of CNS HIV-1 infection, such as the presence of clusters of multinucleated giant cells, cannot be visualized on MR imaging or CT,[34, 77, 173] and indicate a relative lack of sensitivity to more subtle brain changes, particularly those likely to occur in HIV-1–associated minor cognitive/motor disorder.[173]

A number of recent imaging studies have included well-defined and appropriately matched HIV-1 seronegative control groups, systematic neurologic and neuropsychological work-ups,[40, 46, 108, 116, 131, 144] and quantitative MR imaging measures.[40, 144] These studies have indicated that MR imaging scans of subjects with early HIV-1 disease, with or without mild neuropsychological findings, are not significantly different from the MR imaging scans of controls. Quantitative MR imaging measures of atrophy[40, 144] or white matter abnormalities[116] are correlated positively with a more severe degree of HIV-1–associated cognitive/motor complex. Findings from neuroimaging studies, however, are not related invariably to clinical diagnosis.

Initial results from serial studies of MR imaging abnormalities have indicated that minor abnormalities seen in asymptomatic HIV-1 disease did not worsen over a 1- to 2-year period, nor were they associated with clinical progression.[175] In four patients with symptomatic HIV-1 neurologic disease, however, there were concurrent worsening (n = 3) or improvements (n = 1) in MR imaging, clinical, and neuropsychological testing. Likewise, isolated observations have indicated that MR imaging

abnormalities may improve with concurrent clinical improvements during treatment with zidovudine.[157]

Several studies have compared the utility of MR imaging to other standard laboratory measures used for the evaluation of HIV-1 neurologic disease.[37, 40, 46, 52, 108, 171] Neuropsychological,[40, 46] CSF,[37, 52, 171] and neurophysiologic findings[37, 108] appear to be more sensitive than MR imaging in detecting early effects of HIV-1 on the brain.

Single Photon Emission Tomography (SPECT)

Functional imaging is a new technology that has yet to be applied in large series or longitudinal studies in HIV-1 disease.[22] SPECT uses radionuclides that emit gamma waves along with CT to provide measures of regional cerebral blood flow (rCBF). No definitive data are available to indicate which radionuclide of the several used is most sensitive in HIV-1 disease, so these will not be differentiated here. Few studies have been published to date, and there has been a lack of standardization of methodology, and particularly of methods to quantitate rCBF, that makes direct comparison among studies difficult. The preliminary findings on small series, however, have been encouraging regarding the use of SPECT to identify potential early cases of HIV-1–related CNS disease. Studies using qualitative evaluation of SPECT scans have suggested that SPECT could be used to provide early detection of both primary[4, 113, 130, 131, 168, 211] and secondary[88, 167] HIV-1–related CNS disease. In primary HIV-1 neurologic disease, no consistent pattern of SPECT findings was reported, with cerebral asymmetries[113, 228] and multiple diffuse or focal uptake defects[4, 168, 211] evident, particularly in parietal, temporal, and frontal regions.[228] Masdeu and colleagues[131] reported high correlation (0.8) between global clinical neurologic ratings and retrospective ratings of SPECT scans in 32 patients with ADC.

Attempts to quantitate rCBF from SPECT scans have revealed specific regional SPECT abnormalities in the basal ganglia that are related to clinical severity.[110, 124, 188] As expected, the frequency and severity of SPECT abnormalities generally have been reported to be higher in more advanced disease, and in many instances have preceded MR imaging or CT findings.[4, 124, 130, 211, 220] SPECT abnormalities also have been found in some neurologically asymptomatic individuals,[188, 211, 220] although matched HIV-1 seronegative controls have yet to be evaluated.[220]

Positron Emission Tomography (PET)

PET scans involve the injection of radioactive tracers attached to specific ligands into the cerebral circulation. Depending on the ligand, PET imaging can measure cerebral metabolism, regional cerebral oxygen utilization, regional cerebral blood flow, or even myelin distribution. Only a few very preliminary studies in HIV-1 have been performed

using F^{18}-labeled fluorodeoxyglucose to image and quantitate regional cerebral metabolism. Regional metabolic asymmetries were reported in asymptomatic HIV-1–infected individuals, especially in prefrontal regions, in the absence of MR imaging abnormalities.[163] Patients with early HIV-1–associated cognitive/motor complex have been reported to show absolute[186] or relative hypermetabolism[222] in basal ganglia and thalamus, and perhaps frontal cortical regions.[186] More advanced neurologic disease has been associated with a more general decrease in cortical and subcortical metabolism,[21, 186] and the decrease is perhaps especially prominent in parietotemporal cortex.[21, 222]

A follow-up study with PET in asymptomatic cases showed no predictive value of initial metabolic asymmetries, but only seven cases of change in clinical status were reported.[163] Brunetti and colleagues[21] reported improvement of focal hypometabolic findings and generally increased glucose metabolic rates in four ADC patients after 2 months of treatment with zidovudine.

Although the small number of studies and total patients studied makes any conclusions very tentative, both SPECT and PET imaging appear to be more useful to establish dysfunction in early HIV-1 brain infection than MR imaging and CT. The PET and SPECT findings do strongly support subcortical changes in basal ganglia and perhaps thalamus as the earliest imaging findings in HIV-1 neurologic disease. The relative sensitivity of dynamic imaging compared with other nonimaging evaluation modalities (CSF, evoked potentials, and neuropsychological testing) has yet to be determined.

Magnetic Resonance Spectroscopy (MRS)

Another imaging technique recently used in HIV-1 disease is MRS, a technique that measures either water proton (^{1}H MRS) or phosphorus 31 (^{31}H MRS) resonance in vivo, although other elements can be measured.[106] MRS utilizes an MR imaging scanner with appropriate software to create spectra of target molecules. In research on HIV-1 disease, ^{1}H MRS has been used to produce spectra of primarily three molecules located in circumscribed areas targeted by the MR imaging scanner: N-acetylaspartate (NAA), an amino acid found in neuronal cell bodies and axons, and thus a putative marker of neuronal density; creatine (Cr); and choline (Cho). NAA/Cr and NAA/Cho ratios provide putative measures of neuronal density in the scanned regions. In the largest published study[141] to date of ^{1}H MRS (of only two found), both metabolic ratios were significantly reduced in 10 neuropsychologically impaired HIV-1 seropositive subjects compared with four asymptomatic HIV-1 seropositive and seven seronegative individuals. Four of ten impaired subjects (and 3 of 10 without MR imaging abnormalities) and 0 of 4 asymptomatic subjects had metabolic ratios below the range of the normal controls. In contrast, MR imaging showed sulcal and ventricular enlargement in only 2 of 10 impaired subjects and 1 of 4 asymptomatic subjects. In another

study,[2] cognitively impaired AIDS patients showed reduced metabolic ratios in areas of the parietal lobe that appeared normal on MR imaging.[139]

Using ^{31}H MRS, Bottomley et al[17] reported that absolute white matter phosphate concentrations, but not metabolic ratios, were reduced significantly in 12 AIDS subjects with mild to moderate HIV-1–associated cognitive/motor complex compared with 29 controls. Although the investigators showed that the metabolic differences remained after correction for atrophy, MR measures of atrophy also differentiated the AIDS subjects as well as the ^{31}H MRS. In contrast, Deicken et al[41] reported a significantly lower phosphate ratio in 17 HIV-1 seropositive men compared with six controls. Further, the phosphate ratio was correlated negatively with global neuropsychiatric ratings based on neurologic and neuropsychological testing; a lower ratio, indicating decreased brain cellular oxidative metabolism, was associated with higher rating scores (more severe neurologic disease).

Obviously, the results for MRS in HIV-1 disease are very preliminary, but indicate a potentially sensitive laboratory procedure for measuring global and localized in vivo cellular loss or dysfunction, as well as regional metabolic changes.

ELECTROPHYSIOLOGY

Electrophysiologic testing can be separated into a number of categories. The ongoing electrical activity recorded at the scalp is an electroencephalogram (EEG), which may be evaluated by inspection, as is the case in routine clinical EEGs, or it may be evaluated by computer, as in spectral analysis and topographic mapping. Event related potentials (ERPs) are averaged time-locked EEG signals in direct response to sensory stimulation, termed sensory evoked potentials (EPs), or the higher order processing of an external event, often termed *endogenous ERPs*. Sensory EPs provide information about the integrity of central conduction pathways from receptor, through subcortical relay nuclei, to primary and secondary sensory cortical projection regions, and, in some cases, the related association cortical areas. Endogenous ERPs provide information about neurocognitive processes associated with expectations of and decisions about the presence of specific events, or the occurrence of unexpected events. For both EPs and ERPs, the time from event onset to the peak of specific electrical potential components, termed a *component's latency*, is used as a measure of speed of conduction or speed of processing. Normative values are established in an appropriate reference population and abnormal latency values are defined in terms of two or three standard deviation points from the mean of the reference group stratified by age, gender, and sometimes by handedness. Multimodal ERP or EP studies refer to the evaluation of multiple sensory EPs and sometimes endogenous ERPs within the same study.

Electroencephalography (EEG)

Clinical EEG has been reported to be abnormal in diagnosed cases of HIV-1 dementia.[12, 56, 65, 86, 148, 193, 213] Abnormal EEGs also have been found in asymptomatic HIV-1–infected individuals in the absence of clinical findings,[26, 53, 65, 86, 108, 193] or concurrent with neuropsychological abnormalities.[184] In well-controlled studies, however, no differences were found in rate of clinical EEG abnormalities between HIV-1 seropositive and seronegative cases in the absence of CNS opportunistic infections or neoplasm.[16, 152] Tinuper and associates[213] also failed to find EEG abnormalities in 42 neurologically asymptomatic HIV-1–infected individuals regardless of symptomatic stage of infection, although 14 patients (33%) were considered to show a borderline EEG. In contrast, 15 of 28 (53%) patients with ADC showed an abnormal EEG.

Two studies that used computer-analyzed EEG demonstrated EEG power spectral abnormalities in neurologically asymptomatic HIV-1–infected individuals.[102, 161, 162] Parisi et al[162] reported computer-analyzed EEG abnormalities in 50 of 185 asymptomatic or lymphadenopathy only HIV-1–infected individuals. In most cases, the EEG findings occurred in the absence of neuropsychological (16 of 50) and CT abnormalities (12 of 50). Inclusion of intravenous drug users in the HIV seropositive group and an absence of matched seronegative controls make this study difficult to interpret regarding specificity of the EEG findings. Parisi and colleagues[161] also reported, however, that initial EEG abnormalities in 22 of 40 cases were predictive of subsequent development of HIV-1–related neurologic disease after periods up to 11 months, in contrast to only 2 of 37 without initial EEG abnormalities. Riedel and colleagues[184] reported concurrent neuropsychological and EEG abnormalities in about 20% of HIV-1 seropositive, but asymptomatic hemophiliacs, which increased to about 80% in AIDS patients. Increased EEG power was found in both symptomatic and asymptomatic HIV-1 seropositive individuals during a video-tracking task compared with seronegative controls.[84] The latter study is noteworthy in recording EEG power spectrum during a demanding behavioral task. Neither of the latter two studies, however, found computerized EEG findings to be more sensitive than behavioral testing for detecting abnormalities in HIV-1 disease. In addition, De Falco and associates[41] reported that EEG spectral changes were found in about 40% of 20 asymptomatic HIV-1 seropositive individuals, but these changes did not predict the occurrence of neurologic symptoms over a period of 6 to 16 months.

In the largest EEG study in asymptomatic HIV seropositive individuals to date, Nuwer and colleagues[152] reported no significant difference in either clinically or computer-analyzed EEG between HIV seronegative (n = 86) and seropositive (n = 114) gay men. They found that 22% of the seropositive men (13 of 59) and 26% of the seronegative men (10 of 39) with no neuropsychological abnormalities showed abnormal or borderline EEGs. The rates were higher in both groups (21 of 47 for seronegative men and 20 of 55 for seropositive men) when neuropsychological abnormalities were found, but the findings were unrelated to serostatus. Nuwer et al[152] concluded that the presence of an abnormal or borderline EEG in asymptomatic HIV disease was not related to serostatus.

One very recent study compared PET scan findings with EEG coherence measures in 15 AIDS patients, 9 of whom showed definite clinical evidence of mild to moderate dementia.[150] There were significant correlations between EEG coherence and regional hypermetabolism in thalamus and basal ganglia, which were interpreted as supporting the importance of subcortical brain dysfunction in mild to moderate AIDS dementia. The results of this study also suggest that EEG coherence measures may provide information comparable to that from F^{18} fluorodeoxyglucose PET scans regarding subcortical effects of HIV-1 infection. If confirmed, this would be a very significant finding given that the computerized EEG measure is much less invasive and costly, and much more readily accessible than PET.

Evoked Potentials (EP)

Bilateral brain stem auditory EP (BAEP) latency differences between components I and V, and III and V indicated significant increases in central conduction time in 35 neurologically asymptomatic HIV-1–infected individuals without CNS opportunistic infections or tumors, compared with 62 normal controls.[160] The 10 seropositive subjects in CDC stage IV had the longest conduction delays. Abnormal BAEPs were found in about 28% of the CDC group III cases and in 70% of the AIDS group. None of the seropositive cases had a history of alcohol consumption to confound the interpretation of prolonged conduction times. The results were interpreted as indicating white matter lesions in the upper brain stem auditory pathways between the superior olivary complex and inferior colliculus. Similar abnormal BAEP findings were reported in 0 of 18,[28] 3 of 16,[59] 3 of 15,[202] and 4 of 29[108] asymptomatic seropositive individuals, and 14 of 65,[59] 6 of 20,[87] and 8 of 17[38] individuals with ARC or AIDS. In general, the rate of BAEP abnormalities is low even in advanced HIV-1 disease, and this test does not appear useful by itself for early detection or prognosis of HIV-1 neurologic disease.

Cortical components of somatosensory EPs (SEPs) using median nerve stimulation have been found to be abnormal in 1 of 14,[59] 3 of 29,[108] and 8 of 18[28] asymptomatic HIV-1 seropositive men; 3 of 41 ARC patients[59]; and in 6 of 22,[59] 0 of 16,[38] and 0 of 43[202] AIDS cases. In the latter study,[38] significant group increases in latency were reported for SEPs measured at the T12 spinous process, which were attributed to central conduction delays and may have represented a subclinical marker of myelopathy. Tibial nerve SEP latencies also were found to be abnormal in 16 of 22[87] and 8 of 14[38] AIDS patients and were interpreted as subclinical signs of myelopathy. Tibial SEPs may provide early evidence of myelopathy, but neither tibiale nor median nerve SEP cortical components reliably indicate nerve conduction changes in the brain.[133]

Pattern reversal visual EPs (VEPs) were found to be abnormal in 1 of 15,[56] 5 of 18,[28] and 0 of 29[108] asymptomatic HIV-1 seropositive men; and in 5 of 17[38] and 16 of 65[59] symptomatic HIV-1 seropositive individuals. VEP as a separate test does not provide a sensitive measure of CNS abnormalities at any stage of HIV-1 disease.

Event-related Potentials (ERP)

The only endogenous ERP component examined in HIV-1 disease to date is the P300 component in target detection tasks. The sensitivity of P300 latency in detecting HIV-1–related CNS change has been equivocal. Given the relatively few studies available to date, the small number of subjects in some studies, and the large number of potential confounding variables, conflicting or equivocal results are not surprising.

Goodin and colleagues[73] reported statistically significant increases in the latencies of all four components (N1, P2, N2, and P3) of an auditory target detection task in 55 HIV-1 seropositive individuals without known CNS opportunistic infections or tumors. Seventy-eight percent (7 of 9) of clinically demented seropositive patients and 28% (13 of 46) of nondemented patients had at least one latency abnormality among the four ERP components. If only the results for P3 were considered for comparison with other studies, the detection frequency of an ERP abnormality would be 56% (5 of 9) for demented and 17% (8 of 46) for nondemented seropositive individuals, with similar findings for N2. The ERP results were considered to be substantially more sensitive in detecting HIV-1–related CNS abnormalities than concurrently evaluated clinical EEGs (1 of 54) and CT (3 of 4, but all 3 were demented) or MR imaging scans (5 of 10, and 3 of 5 were demented). One potential drawback of this study was the absence of matched HIV-1 seronegative controls. The control group was drawn from a different population than that for HIV-1 seropositive cases.

In the technically most sophisticated study of P300 in HIV-1 disease to date, Ollo and colleagues[156] reported reduced amplitudes and increased P300 latencies in nine symptomatic (7 AIDS, 2 ARC) HIV-1 seropositive individuals in both auditory and visual choice reaction time tasks compared with a control group of nine subjects matched for age, education, and reading ability. A group of nine asymptomatic subjects showed increased P300 latencies compared with normals only in the visual task. Earlier ERP components did not show the same pattern of findings. In contrast, there were no group differences in neuropsychological test performance. It appeared that P300 elicited in the visual task was more sensitive in detecting prolonged latencies in the asymptomatic seropositive group than the auditory task. In the auditory task one of nine (11%) asymptomatic patients and three of nine (33%) symptomatic patients had abnormal P300 latencies compared with the controls; whereas in the visual task, 44% asymptomatic patients and 63% symptomatic patients were abnormal on P300 latency. This is an important

study that needs both longitudinal follow-up and an expanded subject population.

Grotemeyer et al[82] found a P300 latency (but not amplitude) abnormality in 32% of 104 neurologically asymptomatic HIV-1–infected individuals. The rate of abnormality increased with Walter Reed stage; 20.5% of 73 at Walter Reed stages 2 and 3, to 64% of 22 at stages 5 and 6. Follow-up over 3 to 16 months indicated improved P300 latency in seven cases treated with zidovudine, and prolonged latency in seven untreated individuals. The source and possible cohort match of the control group were not given.

Two other studies that failed to find increased rates of P300 abnormalities in HIV-1–infected individuals on initial testing underscored the importance of a well-matched cohort of HIV-1 seronegative controls.[71, 133] Goodwin et al[71] examined 206 HIV-1–infected intravenous drug users and found no difference in latency or amplitude of P300 compared with seronegative intravenous drug users, but did find decreased amplitude and latency in the seropositive group compared with "normal" controls. McAllister and colleagues[133] did not find any P300 abnormalities, or other evidence of early CNS involvement, in 95 symptomatic and asymptomatic HIV-1 seropositive homosexual men compared with a cohort matched group of 32 seronegative controls.

In one of the few well-controlled longitudinal studies, Messenheimer and colleagues[140] reported significant P300 latency increases in both systemically asymptomatic and symptomatic HIV-1 seropositive subjects over periods of 6 months and 1 year in the absence of concurrent clinical changes. In contrast, P300 latency at baseline in 43 asymptomatic patients and 39 symptomatic subjects was not significantly different from that in 29 age-matched normal controls, and did not differ between the two seropositive groups. Latency of the N200 component (the negative wave immediately before P300) also was prolonged significantly in both seropositive groups, a finding consistent with Goodin and colleagues.[73] Interpretation of the longitudinal data from Messenheimer et al,[140] however, is problematic because the subset of 16 asymptomatic and 13 symptomatic individuals followed for 3 years had mean baseline latencies of P300 latencies below those of the normals and considerably below those of the full population of HIV-1 seropositive individuals. The significance of this difference and its relationship to the latency increases shown at 6 months and 1 year is not clear. These investigators concluded that P300 latency abnormality was neither sensitive nor specific in the HIV-1 seropositive population for measurement on a single occasion, like their baseline testing. In contrast, they stated that the latency increase through time may be an indicator of subclinical disease progression. If this was the case in their study, it would be especially significant as the subset of seropositive subjects who showed P300 latency increases over 1 year did not show comparable changes in neuropsychological test performance.

The data on P300 as an early marker for HIV-1 neurologic disease have to be considered equivocal at this point. Considerably more research is needed before ERP can be considered clinically useful for diagnosis, although a more likely role is in monitoring treatment. For diag-

nostic use, it must be determined whether abnormal ERP latencies precede neuropsychological and neurologic findings, and what the false-negative rate is in large populations.

A number of studies have included multiple EP procedures, termed *multimodality EPs*. An abnormality on any electrophysiologic test and measure is considered an abnormal CNS finding. In one study, pattern VEPs, median nerve SEPs, and BAEPs were evaluated in 18 systemically and neurologically asymptomatic HIV-1–infected individuals without a history of drug addiction, CNS opportunistic infection, or evidence of liver and kidney dysfunction.[28] At least one EP abnormality was found in 13 of 18 cases, and in 12 of 13, the abnormality was in a visual or somatosensory cortical EP component. Only 1 of 13 cases with abnormal EP findings had abnormal findings on the Wechsler Adult Intelligence Scale (WAIS) and none of the five cases with normal EPs had an abnormal finding on the WAIS. Repeat multimodal EP testing after 8 to 12 months showed no change in any subject. Similarly, Farnarier and colleagues[59] found at least one abnormality among VEP, SEP, and BAEP procedures in 6 of 16 asymptomatic, 21 of 42 ARC, and 14 of 23 AIDS individuals without neurologic signs or symptoms. Koralink et al[108] also reported that electrophysiologic testing (that included EEG and EP evaluations) was more sensitive than neurologic and neuropsychological testing in detecting CNS deficits. They detected at least one abnormality in 18 of 27 (67%) asymptomatic seropositive individuals compared with 3 of 30 (10%) in matched seronegative individuals. If these data on multimodality EP testing are confirmed in larger series and if the individuals with abnormalities go on to develop clinically evident HIV-1–associated cognitive and motor complex, use of an electrophysiologic testing battery that includes computerized EEG may provide very early diagnostic criteria for HIV-1 neurologic disease. Nuwer and colleagues[153] have criticized the study by Koralink et al on methodologic and statistical grounds, and have reported data to show that EEG is neither specific nor as sensitive as neuropsychological testing in detecting putative HIV-associated CNS abnormalities in asymptomatic HIV disease.[152]

CEREBROSPINAL FLUID (CSF) ANALYSES

CSF is a direct extension of the extracellular space of the cells comprising the central nervous system (CNS).[221] Solutes, such as IgG and albumin, found in the extracellular space of the CNS sink into the CSF. An examination of CSF constituents can be reflective of the content of the extracellular space of the CNS.[186] The volume of CSF in the average adult is about 150 mL, and this volume of fluid turns over about three times per day, making the CSF a very dynamic indicator of extracellular fluid changes. CSF analysis is an effective and established diagnostic tool as well as a measurement for monitoring treatment in most infectious and several immune pathologies of the CNS.[61]

Prior to a lumbar puncture to obtain CSF, an MR image or CT scan

should be conducted in patients with neurologic symptoms to rule out mass lesions with the potential to cause herniation. Further, because many HIV-infected individuals develop thrombocytopenia and other clotting disorders, the patient's coagulation status should be reviewed prior to a lumbar puncture.

Routine CSF studies include cell counts, total protein or albumin levels, glucose levels, VDRL and the appropriate cultures and serologies to identify opportunistic infections, and/or cytology to identify malignancy. There are a host of additional analyses that have been performed on CSF that yield information about immune activation and viral presence and quantity in order to follow the progression of HIV-1 disease.

At or about the time of primary infection, the majority of HIV-1 patients show evidence of HIV-1 penetration of the brain. In their large screening study of HIV-1 infection in the military, Marshall and colleagues[129] reported that 60% of the asymptomatic immunologically intact HIV-1–infected individuals demonstrated at least one CSF abnormality within 1 year, and more than 25% of these had three or four CSF abnormalities. Significant CSF abnormalities in asymptomatic HIV-1 seropositive individuals also have been reported in many other studies.[135, 136, 182, 199, 200] The most commonly noted CSF abnormalities and their putative relationship to HIV-1 neurologic disease are reviewed in this section. A more detailed review of the CSF in HIV-1 is presented elsewhere.[157]

Cytology

A total leukocyte (WBC) count of more than 5 cells per cubic millimeter is abnormal and has been found in 18% to 32% of asymptomatic HIV-1 seropositive individuals.[29, 129, 135, 200] Pleocytosis also may be present in an aseptic meningitis sometimes associated with primary infection.[29] In most HIV-1–infected individuals without CNS opportunistic infections or tumors, the WBC count is below 75 cells per cubic millimeter and is primarily lymphocytic.[129] Neither the frequency of finding an abnormal leukocyte count nor the absolute count, however, appears to be related to the severity of HIV-1 systematic or neurologic disease.[105, 200] Normal counts have been reported in patients with AIDS dementia complex,[51, 67, 105, 121, 136] with cryptococcal meningitis,[105] and neurosyphilis.[112] The presence of significantly elevated counts is probably indicative of a CNS opportunistic infection and should lead to a detailed search for the common CNS infections.

Although most studies report a predominance of small lymphocytes in HIV-1 CSF, monocytes, macrophages, plasma cells, and atypical lymphocytes also have been found. The presence of polymorphonuclear leukocytes in CSF of AIDS patients usually indicates a secondary infection, such as cytomegalovirus.[56] Flow cytometric quantitation of cell phenotypes in CSF suggests that the percentages of CD8, CD4, and other cells are highly correlated with those in peripheral blood[125]. In addition,

the proportion of $CD4^+$ lymphocytes showed a significant decrease in HIV-1 patients with dementia compared with those patients who were asymptomatic, which parallels the findings in peripheral blood.[125]

Total Protein, or Albumin

Elevated levels of CSF total protein have been reported in all stages of HIV-1 disease compared with controls.[117] McArthur et al,[137] however, reported significant elevations in demented compared with nondemented HIV-1 seropositive individuals, but no relationship to HIV-1 disease duration in the absence of dementia. An elevated CSF total protein reflects an increase in the leakage of albumin from blood across the endothelial tight junctions.

Albumin is synthesized only in the liver. Normal albumin concentration in the CSF is determined by concentration in the blood[181, 214] and by the natural leakiness of endothelial capillary tight junctions primarily located in the choroid plexus.[19] CSF albumin concentration is, thus, a useful index of intactness or leakage of the tight endothelial junctions to midsize protein molecules such as albumin and IgG.[181] Measures of leakage across the blood–brain barrier (BBB) are provided by the albumin index[212] and by a formula that calculates the trans-BBB albumin leakage rate.[219]

Mean CSF albumin levels in HIV-1–infected persons do not differ significantly from controls.[51, 128] The trans-BBB albumin leakage rate, however, was found abnormal (> 86 mg per day) in 25% of seropositive HIV-1 asymptomatic patients and 44% of AIDS patients.[200] There were statistically significant differences in albumin leakage rate between HIV-1 seropositive patients with and without neurologic disease.[200] The albumin index was found to be significantly elevated in HIV-1 seropositive individuals with dementia compared with those patients without dementia.[137]

Glucose

CSF glucose concentrations generally have been found to be within normal limits in HIV-1 disease.[83, 105, 118, 159] A low CSF glucose concentration suggests the presence of opportunistic infections or tumors.

Humoral Immunologic Markers

Two markers of humoral immunity have been reported extensively in the HIV-1 literature. These are indices that quantitate the amount of IgG synthesized in the brain, intrathecal IgG synthesis rate for either total or antigen specific IgG, and oligoclonal IgG bands. Both are available through commercial laboratories.

IgG is synthesized by only one cell type in the body, namely, the plasma cell.[147] In health, there are no plasma cells in the brain.[178] Normal IgG concentration in the CSF is determined by the concentration in the blood[181, 215] and by the natural permeability of endothelial capillary tight junctions primarily located in the choroid plexus.[19] When infection occurs in the brain, B lymphocytes are recruited into the CNS and mature there to plasma cells. The newly recruited plasma cells synthesize IgG. An abnormally elevated IgG concentration in the CSF also can be the result of an elevated blood IgG concentration in conjunction with breaks in the BBB endothelial tight junctions. If a correction of CSF IgG concentration for high serum IgG concentration and leakage of IgG across the BBB yields an excess of CSF IgG, then there exists intrathecal IgG synthesis.[218] Accordingly, intrathecal IgG synthesis calculations provide a measure of the presence and quantity of plasma cells secreting IgG inside the BBB, i.e., evidence of inflammation in the CNS. In HIV-1–infected individuals, the exact site(s) of this inflammation is unknown.

Several formulas to calculate intrathecal IgG synthesis rate are reported in the HIV-1 literature: (1) the IgG index,[212] (2) the Tourtellotte intrathecal IgG synthesis rate formula,[218] (3) IgG (loc),[181] and (4) intrathecal IgG synthesis.[191, 195] The first three calculations are used most commonly in clinical CSF immunology laboratories. Although there is continuing controversy regarding which formula is most valid and least affected by BBB damage,[115, 154, 216] the values from all four formulas are significantly highly correlated.[216, 217] The results of studies of abnormal intrathecal IgG synthesis are presented as if all formulas gave comparable results.

Intrathecal IgG synthesis in HIV-1 patients was first reported in ARC and AIDS patients[183] and later also in asymptomatic patients.[7, 32, 37, 51, 57, 66, 70, 76, 83, 122, 128, 129, 159, 182, 199, 200, 207, 224] In addition, the appearance of antibodies in CSF may precede their detection in blood.[51, 182, 185] Intrathecal IgG synthesis has been found to increase during the asymptomatic and early symptomatic stages of HIV-1 disease, but may decrease in the very late stages of infection.[51, 127, 200] The latter implies a failure of the immune system, rather than clearance of infection.

Studies using Tourtellotte's intrathecal IgG synthesis rate formula found evidence of intrathecal IgG synthesis in 22% to 88% of HIV-1–infected individuals.[7, 9, 15, 83, 127, 129, 182, 183, 200] There do not appear to be significant differences in the frequency of occurrence of intrathecal IgG synthesis between HIV-1–infected individuals with and without neurologic manifestations.[182, 200] In one study the mean IgG synthesis rate was found to be significantly higher in those with HIV-related neurologic dysfunction compared with those with no disease.[200] In another study, patients with HIV-1–associated dementia and mean CD4 counts less than 200 did not show significant differences in intrathecal IgG synthesis from HIV-1 seropositive individuals without dementia.[137]

An elevated IgG index has been found in 35% to 80% of HIV-infected individuals in all clinical stages.[7, 23, 37, 32, 51, 66, 83, 127, 129, 200, 207] Sönnenberg and colleagues[207] reported a strong relationship between the recov-

ery of HIV-1 from CSF and intrathecal IgG synthesis, suggesting that persistent HIV-1 antigenic stimulation may be an important factor in the genesis of intrathecal IgG synthesis. An inverse relationship also has been reported between the level of intrathecal synthesis of anti-HIV-1 IgG and peripheral blood $CD4^+$ counts.[224]

Studies that used other methods to detect intrathecal IgG synthesis have shown similar results to those for the IgG index and Tourtellotte equation.[2, 15, 55, 60, 122, 180, 225]

CSF oligoclonal IgG band detection is a very different way to detect intrathecal IgG synthesis. CSF IgG oligoclonal bands are clonally restricted IgG bands. The most reliable and sensitive technique to detect bands is isoelectric focusing (IEF) electrophoresis followed by immune fixation of heavy chain IgG antibodies and silver staining.[208] Other techniques for detecting IgG bands have been used in HIV-1 studies, but these generally are not as sensitive. A unique IgG band found in CSF and not in serum, or an IgG band more intense in CSF than in serum are both considered abnormal.[71, 208] The number of bands detected is technique specific, but within a given study, number of bands can provide a quantitative estimate of intrathecal IgG synthesis.

The presence of oligoclonal bands in CSF has been reported in all stages of HIV-1 infection, regardless of the presence or absence of neurologic disease.[7, 9, 23, 27, 32, 47, 66, 76, 80, 83, 121, 129, 182, 200, 201] In their comparison of CSF results with clinical disease status, Goswami et al[75] found no relationship between the presence of any antigen-specific oligoclonal band and systemic or neurologic disease status.[75]

In summary, intrathecal IgG synthesis begins shortly after infection and persists throughout all stages of HIV-1 disease, although levels may decrease in late AIDS. The presence of intrathecal IgG synthesis does not imply clinical neurologic disease because the frequency of intrathecal IgG synthesis is similar for both neurologically asymptomatic and symptomatic HIV-1 seropositive individuals. In addition, the very high frequency of occurrence of intrathecal IgG synthesis at all stages limits its usefulness as a predictor of future neurologic disease. Its usefulness for monitoring treatment efficacy awaits further study.

To date, most studies have measured total intrathecal IgG synthesis and have not accounted for its component antibody profile. HIV-1–specific synthesis appears to account for only about 10% of total intrathecal IgG synthesis,[182] but this percentage contribution may increase during the course of HIV-1 neurologic disease.[54]

Less is known about the CNS inflammatory response to other potential antigens and its contribution to total intrathecal IgG synthesis. For example, cytomegalovirus (CMV) and HIV-1 can co-infect brain cells.[149] Part of the total intrathecal IgG synthesis in AIDS is specific for CMV, herpes zoster (HZV), and herpes simplex (HSV).[122] Antibodies to these other viral agents can be found primarily in ARC and AIDS patients; although intrathecal antibody synthesis overall has been found to decline again in very late disease,[122] as might be expected by an increasingly compromised immune system. It is not clear whether the presence of these other antibodies is related to active co-infection, or to polyclonal

B-cell stimulation.[101] Additionally, the role of syphilis as a co-factor or as a solitary infection needs clarification.[13]

HIV-1 Detection and Isolation

HIV-1 isolation from CSF is possible in all clinical stages of infection.[30, 31, 33, 39, 96, 98, 182, 204, 205] It is possible to isolate HIV-1 from the CSF at the time of seroconversion[30] and during the aseptic meningitis associated with the HIV-1 seroconversion.[96] There is controversy, however, regarding both the maximum rate of recovery and which stage shows the highest rate of recovery. Low rates of recovery from CSF generally are reported in asymptomatic and immunologically normal patients.[203, 205] A high frequency of 75% to 80% in early symptomatic patients[30, 96] and a lower rate in AIDS patients[182] has been reported. There are also studies reporting no correlation between the frequency of HIV-1 isolation in CSF and clinical stage of systemic infection.[33, 39, 137, 204] No correlation has been reported between clinical neurologic status and the frequency of HIV-1 isolation.[30, 83, 137, 182, 204]

The probability of detecting free virus compared with virus in cells seems to increase with the progression of the disease. In the earlier stages of infection, free viruses are generally infrequently present in CSF, but virus can be isolated readily from cells. In the later stages of HIV-1 infection, free virus can be isolated readily in CSF.[204]

HIV-1 p24 antigen is a protein from a viral core, and is considered a reliable serum marker of active viral replication and systemic disease progression in HIV-1 seropositive patients.[5, 114, 123] Testing for p24 antigen is available through commercial laboratories. When matched samples of serum and CSF from the same HIV-1–infected patients are studied, it is possible to find HIV-1 antigen only in serum or only in CSF, or positive in both samples at the same time,[139] so that there is no strict correlation between CSF and serum levels of p24 antigen.[25] HIV-1 p24 antigen is rarely found in the CSF of neurologically normal and asymptomatic HIV-1–infected individuals,[57, 169] but it can be detected readily in symptomatic stages of HIV-1 infection.[25, 39, 200] Detection of HIV-1 p24 antigen is correlated with neurologic status[39, 169] and p24 antigen levels increase significantly in moderate to severe HIV-1–related neurologic disease.[200] Because the presence of p24 antigen is only occasionally detectable before neurologic deterioration, however, it is not a predictive marker for CNS involvement.[169] CSF HIV-1 p24 antigen levels have been reported to decrease following antiviral treatment, and, thus, could serve as a marker for treatment efficacy in reducing HIV-1 virus in CSF.[42] The decrease in p24 antigen, however, is not necessarily associated with clinical improvement.[42]

The usefulness of p24 antigen levels has been limited by the fact that much of the p24 is complexed with anti-p24 antibody and, thus, not

accessible by standard assays. A new assay for acid-dissociated p24 antigen may resolve this problem.[143]

The polymerase chain reaction (PCR) permits ultra-sensitive detection of viral RNA or DNA directly.[45, 72, 161, 176, 177, 198, 210] PCR has been proposed as potentially the most sensitive and specific method, not only to detect the presence of the virus, but also to quantitate viral load for HIV-1 and other viruses.[179] When compared with culturing and antigen assays, PCR is independent of masking by antibody neutralization and has a much higher sensitivity.

Recent papers have supported strongly the use of PCR to measure viral load in blood.[99, 100, 155, 191, 227] The level of HIV-1 infection in blood CD4+ cells is highly varied, but related to disease state, with the highest levels of infection found in subjects with more advanced HIV-1 disease.[99, 142, 167, 192] Michael and colleagues[142] also showed a correlation between blood levels of HIV-1 provirus and RNA on the one hand, and HIV-1 disease state on the other. These data indicate that, in the later stages of HIV-1 infection, the relative viral load increases substantially and may be the basis for the rapid decline of CD4+ cells seen in these patients.[191]

There have been only a few studies of PCR in CSF to date. Shaunak and colleagues[197] reported the presence of HIV-1 in CSF of 20 of 31 (64%) seropositive patients; 21 of 28 positive CSF PCR cases received a neurologic examination and were reported to be neurologically abnormal. The neurologically abnormal group, however, was composed of 10 patients with *Cryptococcus neoformans* meningitis, 2 with active CNS toxoplasmosis, and 1 with a CNS lymphoma. Twelve of the thirteen (92%) patients with *Cryptococcus*, toxoplasmosis, or lymphoma were found to be PCR positive for HIV. Sönnerberg and colleagues[205] performed PCR on 28 seropositive patients, 24 of whom showed no neurologic signs, and reported a PCR detection rate of 86% in the CSF.

In the only published paper dealing with viral load in CSF, Steuler et al[209] reported that HIV-1 proviral DNA was detected at a median value of 1 copy per 300 CSF cells (or 3.33/1000 cells) with a range from 1 per 20 (50/1000) to 1 per 2400 (0.42/1000) in 13 seropositive patients at varying stages of HIV-1 infection. The proviral load in CSF cells did not correlate with CDC disease stage. Their results provide some evidence that the level of HIV-1 provirus in the CSF cells may be higher per cell than that reported in peripheral blood. Seven of their thirteen patients, however, had a CNS opportunistic infection, and, thus, the results may not apply to HIV-1 CNS infection alone.

In a recent study, Schmid et al[189] used PCR to detect HIV-1 in 93 seropositive subjects without CNS opportunistic infections, tumors, or neurosyphilis; 67 of these had at least one CSF examination. HIV-1 provirus was detected in blood in 87 of 93 patients (94%) and in CSF in 63 of 67 patients (90%). There were no significant differences in detection rate in asymptomatic patients compared with those with ARC and AIDS, nor those with or without HIV-1–related neurologic disease. Viral load in blood was related significantly to disease stage. The median viral load in blood was 0.1 copies per 1000 CD4+ cells in seropositive asymptomatic patients, 1.4 in ARC, and 10.7 in AIDS ($P = 0.0281$). The viral load in seropositive patients was significantly greater in CSF than in blood; median 25 in CSF compared with 0.6 copies per 1000 CD4+ cells in blood ($P = 0.0001$). CSF viral load was greater in seropositive patients with than in those without HIV-1–related neurologic disease; median 43.5 compared with 17.6 copies per 1000 CD4+ cells ($P = 0.0614$), respectively.

Cytokines

Cytokines are soluble peptide mediators synthesized and secreted by activated immune cells (e.g., macrophages, lymphocytes, microglia, and monocytes) and, in some instances, by glial cells (astrocytes) and endothelial cells. Cytokines act on other cells of the immune and nervous systems to up- or down-regulate their functions.[11] Cytokines may have multiple, overlapping actions and some cytokines (e.g., interleukin-1 and tumor necrosis factor) have been found within neurons, implying that they also may function as neuromodulators.

The invasion of the CNS by HIV-1 causes immune activation and both proliferation and recruitment of immune cells in the CNS, which is accompanied by a rise in cytokine levels in brain and CSF. In some instances, elevated levels of cytokines have been implicated in the pathophysiology of HIV-1–induced CNS disease. Cytokines that have been reported to be elevated in the CSF and brains of HIV-1–infected individuals include gamma interferon, tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor-β.

Gamma interferon is produced by activated macrophages and T cells. In the brain, it induces class I and II major histocompatibility complex (MHC) antigen expression and is implicated in experimental autoimmune demyelination. Gamma interferon also induces the enzyme 2,3-indoleamine dioxygenase, which activates the kynurenine pathway of tryptophan metabolism, and is thereby implicated in the elevation of the neurotoxin quinolinic acid in HIV-1 CSF. Elevated levels of gamma interferon have been reported in CSF of HIV-1–infected individuals, but have not been associated specifically with primary HIV-1–related neurologic disease.[79]

TNF-α is synthesized by monocytes, macrophages, microglia, endothelial cells, and astrocytes. TNF-α also has been found in cell bodies of hypothalamic and brain stem neurons. Within the CNS, TNF-α facilitates the expression of class II (Ia) MHC molecules; increases the production of IL-6 and ACTH; and decreases the production of prolactin, thyroid-stimulating hormone, and growth hormone.[10] TNF-α has been implicated in the pathogenesis of astrocyte proliferation and autoimmune demyelination, both of which commonly are found in the brains of AIDS patients. TNF-α also up-regulates HIV-1 replication. Elevated levels of TNF in the CSF of adults with HIV-1–associated cognitive/motor complex have been reported,[81] but the relationship was not specific to primary HIV-1 neurologic disease. Elevated CSF TNF levels were associated with CNS

infectious processes in general.[81] Gallo et al,[69] however, failed to confirm the presence of TNF in HIV-1 CSF.

Interleukin-6 (IL-6) and IL-1β have been detected in CSF of HIV-1 patients.[67] IL-6 is secreted by monocytes, macrophages, endothelial cells, and T cells. It induces the production of acute-phase proteins, induces terminal differentiation of B cells into immunoglobulin producing cells, and co-stimulates the proliferation of T cells. The induction of B-cell differentiation promotes astrocyte growth (in conjunction with TNF). Although the cellular source of IL-6 detected in CSF is unknown, the significant association of IL-6 with intrathecal IgG synthesis[67] suggests that the presence of IL-6 in CSF in HIV-1 infection may contribute to the production of anti-HIV-1 antibodies and IgG synthesis. Gallo and colleagues[67] hypothesized that the correlation between the presence of soluble interleukin-2 receptor (sIL-2R) and IL-6 in HIV-1 seropositive patients might point to the intracerebral activation of some T-cell subsets invading the CNS.

IL-1 increases the production of other cytokines (e.g., IL-6 and TNF); induces fever; and induces proliferation of T cells, astrocytes, and endothelial cells. It also induces the ability of endothelial cells to bind T cells (i.e., enhances inflammation). Elevated levels of CSF IL-1 have been reported in HIV-1 patients both with and without neurologic complications.[67]

Findings of elevated levels of sIL-2R and macrophage colony stimulating factor also were reported in the CSF of HIV-1 patients.[68, 69] There were no significant correlations, however, between the elevated levels and intrathecal IgG synthesis or clinical status.

In summary, elevated levels of several cytokines have been reported in the serum, CSF, and brains of HIV-1–infected persons. These cytokines may play an important role in the pathogenesis of HIV-1 neurologic disease. As yet, no quantitative relationship has been established between levels of CSF cytokines and clinical neurologic disease, and measurement of CSF cytokines remains a research tool.

Neopterin and Beta-2-Microglobulin

Beta-2-microglobulin (β2m) is a peptide constituent of class I MHC structures on the surface of nucleated cells. Elevated levels of β2m are considered to reflect an activation of the cellular immune system or an increased cell membrane turnover.[3] Neopterin is a pteridine compound derived from guanosine triphosphate. It is produced by macrophages after stimulation with gamma interferon during activation of the cell-mediated immune response.[64, 101] β2m and neopterin are used as markers of immune activation. Neopterin levels in serum and CSF tend to parallel one another as do β2m levels.[165, 206]

Elevated levels of β2m and neopterin in blood have been found to correlate with clinical stage of HIV-1 infection[1, 58, 138] and CD4 counts.[137] The prognostic value of increased serum β2m levels in predicting progression of systemic HIV-1 disease is well documented.[11, 19, 58, 116] In addition, recent studies have demonstrated that neopterin and β2m can predict the future rate of decrease in $CD4^+$ T cells for at least 2 or 3 years.[97, 145]

Elevated levels of CSF neopterin have been associated with more advanced systemic disease[64, 79, 101, 206] and with the severity of HIV-1–related neurologic disease.[18, 50, 206] CSF neopterin levels were reported to decrease in conjunction with clinical improvement following zidovudine treatment.[18] CSF neopterin also is elevated in a wide variety of infectious neurologic diseases and in CNS opportunistic infections associated with HIV-1.[18, 79]

Both serum and CSF β2m were reported to be elevated significantly in HIV-1 seropositive individuals with HIV-1–associated dementia compared with those without dementia.[50, 132] Further, there was strong evidence for intrathecal β2m synthesis. A cut-off of 3.8 mg/l. for CSF β2m yielded a positive predictive value for HIV-1 dementia of 88% with a sensitivity of 44% and specificity of 90% compared with nondemented HIV-1 seropositive individuals.[132]

At present, both CSF β2m and neopterin are candidate predictors for the presence and perhaps severity of HIV-1–related neurologic disease. Both can be obtained from commercial laboratories. Both are, however, nonspecific markers and are only useful in conjunction with other procedures that rule out other CNS pathogens.

Myelin basic protein and anti-myelin basic protein antibodies also have been detected in HIV-1 CSF.[126, 132] Although myelin basic protein was not found in the CSF of asymptomatic HIV-1 seropositive individuals,[126] increased levels of CSF anti-myelin basic protein were detected in HIV-1 patients with severe dementia.[132] Myelin basic protein assays are commercially available.

Excitotoxic Metabolites

Quinolinic acid (QUIN) is an "excitotoxic" metabolite and an agonist of N-methyl D-aspartate (NMDA) excitatory amino acid receptors.[90, 91] The related metabolite, kynurenic acid (KYNA), is an antagonist of NMDA.[93] The increased concentration of the excitotoxin QUIN in brain and blood following immune stimulation is well documented in experimental animals.[92] In large concentrations, QUIN is a convulsant and a neurotoxin.[196] Increases in KYNA may reduce the neurotoxic effects of QUIN, whereas decreases in KYNA could enhance excitotoxic effects.[93] Human macrophages (and other cells) can convert L-tryptophan to QUIN.[95]

QUIN levels were found to be elevated significantly in HIV-1–infected individuals, with the highest values present in those with moderate to severe HIV-1–related neurologic disease.[89, 90, 91, 93, 94] In addition, significant correlations have been reported between increased CSF QUIN levels and the degree of neuropsychologic impairment in HIV-1–infected

individuals.[90] Although the increases in CSF and blood QUIN concentrations are not specific to HIV-1 infection,[91] the relationship between the CSF QUIN elevations and the neurologic complications of HIV-1 raise the possibility that QUIN might be acting as a contributory factor in the pathogenesis of HIV-1–related cognitive/motor complex. It also has been shown, however, that markedly increased concentrations of QUIN also may occur in the CSF of HIV-1 patients with opportunistic infections, neoplasm, and aseptic meningitis.[90] The latter finding may limit the usefulness of QUIN as a marker for HIV-1 primary neurologic disease to those cases in which other infections can be ruled out. At this time, the measurement of QUIN is a complex process that only can be performed in a few research centers.

SUMMARY

Laboratory tests can provide useful information about the presence and effects of HIV-1 in the CNS, but have thus far not yielded definitive diagnostic or prognostic markers of HIV-1–related cognitive and motor complex. The most clinically useful laboratory procedures are MR imaging and CSF examinations. The routine clinical use of MR imaging and CSF examinations, however, is still restricted to providing information for detecting and excluding secondary effects of HIV-1 infection. MR imaging and CT do not appear to be sensitive enough at current resolutions to provide early detection of HIV-1 CNS effects nor to follow disease progression. Several CSF variables are extremely promising as early markers of primary HIV-1 infection of the brain, and may provide preclinical indications for onset of treatment and for evaluation of treatment efficacy. These include CSF quinolinic acid levels, acid dissociated p24 antigen levels, neopterin or β2m, intrathecal IgG synthesis rate, and possibly quantitated PCR levels of HIV-1 viral load. Procedures such as nuclear magnetic resonance spectroscopy, SPECT, PET, computerized EEG, EP, and ERPs are all promising candidates for early detection or localization of HIV-1–related brain dysfunction, but at this time all must still be considered primarily research tools. Before any of these procedures can provide reliable diagnostic and prognostic information about primary HIV-1 neurologic disease, currently on-going longitudinal evaluations of large numbers of asymptomatic HIV-1–infected individuals as they progress to neurologically symptomatic disease must be completed.

There is currently no laboratory marker in blood or CSF that definitively predicts the risk for HIV-1–associated cognitive/motor complex. HIV-1–associated cognitive/motor complex remains a clinical diagnosis, which is made on the basis of positive neurologic signs and symptoms and abnormal neuropsychological findings after other causes of neurologic disease are excluded. Laboratory measures, such as the electrophysiologic methods and some CSF variables, are likely to remain adjuncts to the diagnosis because, with few exceptions, they provide data that are nonspecific as to etiopathogenesis. Dynamic imaging, electrophysiologic

methods, and CSF indices provide presumptive evidence for the presence of HIV-1–associated CNS damage, and with clinical and neuropsychological evidence, could be used to establish a new definition of primary HIV-1–associated CNS disease along the lines used in establishing a diagnosis of multiple sclerosis.[170]

The use of the other laboratory procedures, particularly CSF measures of viral load, immune activation and neuronal toxins,[151] and functional imaging, are providing valuable insights into potential etiologic mechanisms for HIV-1–associated cognitive/motor complex. We also expect, however, that one or more of the procedures reviewed in this article will become diagnostic and prognostic markers that will help to provide objective measures of treatment efficacy in the next few years.

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