

HIV-RELATED CNS DISORDERS

- **CNS Disorders:** HIV invades the brain (CNS) early, may have subtle or profound effects on the patient, and is often a diagnosis of exclusion.
- **HIV Disease by Stage - 4 Categories:** acute, asymptomatic, early symptomatic, late symptomatic. (1) **Acute HIV infection:** affects 50%-70% within 3-6 weeks; sudden onset; flu-like syndrome; possible neurological signs/sxs (e.g., HA, photophobia, possible peripheral neuropathy or myelopathy, etc). Sxs resolve spontaneously. Psychotic symptoms may occur this early, but r/o previous psych hx. (2) **Asymptomatic infection:** HIV enters CNS soon after infection ("neuropathic" virus); labs may be normal; brief cognitive screen for *subcortical* dysfunction may be helpful, but generally, most show no manifestations of neuropsychiatric (N-P) impairment. (Remember, the MMSE is more sensitive to *cortical* dysfunction than *subcortical* dysfunction, therefore, it is *not* an adequate screening tool.) If positive on a brief cognitive screen, then refer for formal N-P evaluation. (3) **Early symptomatic infection:** positive result on neuropsychologic (N-P) testing requires clinical correlation; if evaluation reveals a deficit, consider dx. of HIV-associated Minor Cognitive Motor Disorder (MCMD). (4) **Late symptomatic infection:** significant N-P impairment here. If associated functional impairment is mild, consider MCMD; if moderate or severe, consider HIV-associated dementia (HAD). **HAD risk factors:** pt.'s age, CD4 <100; HIV RNA (viral load) high, low Hct/Hgb (anemia), IDU, HAART resistance, CNS opportunistic infections (OI's), delirium, wasting, female gender. Remember, both MCMD & HAD are dx's of exclusion! **Always r/o treatable brain disorders first.**
- **Comprehensive Evaluation:** 4 components: (1) *general medical w/u*; (2) *psychiatric w/u*; (3) *cognitive screening w/u*; (4) *functional status assessment*.
- **(1) General Medical Work-up:** comprehensive hx; review of prescribed, OTC, herbal supplements, and "street" drug usage; detailed neurocognitive hx (helpful if hx can be provided by family member, spouse, partner, etc.); full PE; thorough neurological exam (including timed gait, i.e., incoordination, ataxia); mental status exam (MSE); bedside HIV Dementia Rating Scale; appropriate N-P test batteries *(see below). Also, complete metabolic w/u, possibly including ABG's; evaluation for psychoneurotoxicity (including therapeutic serum levels where indicated); lumbar puncture (LP). **LP's:** may help dx: cryptococcal meningitis (India ink stains, fungal cultures); neurosyphilis (CSF VDRL, fluorescent treponemal antibody test, CSF protein/chemistry profile, polymerase chain reaction [PCR]; TB (acid fast stain, AFB cultures); cytomegalovirus (CMV); Epstein-Barr virus (EPV); JC virus; tumor-CSF cytology; etc.
- **-About Neuroimaging:** **CT, computerized tomography,** is useful for seeking toxo., PML, CNS lymphoma. **"High resolution" CT** differentiates lesions from surrounding edema; discriminates between lesions in close proximity; locates lesions for biopsy; detects small cortical lesions with spatial resolution. **MRI, magnetic resonance imaging,** is a structural imaging technique; more sensitive than regular CT for demyelinating lesions. **PET, positron emission tomography,** functional imaging which displays cerebral glucose utilization and blood flow. **MRS, magnetic resonance spectroscopy,** images metabolite concentration for markers of CNS cellular dysfunction. **SPECT, single photon emitted computed tomography,** determines local changes in cerebral blood flow.
- **-About Metabolic Studies:** evaluation for hypoxemia (PCP pneumonia); anemia (drug-induced, chronic disease); uremia; hepatic encephalopathy (monitor serum ammonia levels); serum vitamin B12 levels; thyroid function tests (TSH); hepatitis B, C; CMV hepatitis; mycobacterium avium intracellulare (MAI); dehydration (chronic diarrhea from cryptosporidiosis); hyponatremia due to sodium depletion (associated with seizures); hypokalemia; psychoneurotoxicity & substances of abuse (ETOH, cocaine, THC, opioids, stimulants, sedative-hypnotics, hallucinogens, nitrite inhalers). **Iatrogenic sources** (some antiretrovirals, gancyclovir, pentamidine, dapsone, amphotericin B, metronidazole, steroids, interferon, acyclovir, foscarnet, interleukin, protease inhibitors, efavirenz.

FAST FACTS

CLINICAL
REFERENCE
SERIES

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- **(2) Psychiatric Work-up:** recognize the limits of clinical evaluation vs. a full psychosocial or N-P test battery. Collateral history helpful. R/o: delirium, major depressive disorder/other depressive spectrum d/o's; manic/hypomanic states; psychotic d/o's; personality d/o's; ETOH & substance use d/o's; personality d/o's; disorders secondary to a general medical condition. (see "Mood, Anxiety, Psychotic and Substance Use Disorders")
- **(3) Cognitive Screening Work-up:** use the **HIV Dementia Rating Scale**, useful in detecting *subcortical* dysfunction. Comprised of 4 items: antisaccadic eye movement error task; timed alphabet; verbal memory; copying a cube. Impaired cognitive function is monitored for notation, using a score < or = to "10". **The Mini-Mental Status Exam (MMSE)** is more sensitive to *cortical* function deficits such as those seen in Alzheimer's, however, you can *suspect* cognitive-motor disorder if a higher MMSE cut-off, such as ~26 out of 30, is found. **Other tests:** Trails Making Test A & B; Figure Visual Scanning Task (correlates with other early N-P deficits; California Verbal Learning Test (delayed verbal memory test); WAIS-R (Digit Symbol Task), Halstead-Reitan Battery, etc. **N-P domains for examination:** attention, information processing speed, verbal memory, visual memory, visuospatial/constructive skills, abstraction, language processes.
- **(4) Functional Status Assessment:** Need to differentiate MCMD from HAD. If functional impairments are *mild*, dx likely MCMD; if *moderate or severe*, dx HAD (key distinguishing factor between MCMD and HAD is severity of functional impairments). **Useful objective instruments:** Karnofsky Performance Scale (brief clinical rating of general life function; scale 0-100; DSM Axis V Global Assessment Functioning (GAF) (clinical rating of current adaptive mental health functioning; scale 0-100); DSM Social and Occupational Functioning Assessment Scale (mental status functioning); Sickness Impact Profile (self-administered & sensitive to cognitive-motor impairment); Direct Assessment of Functional Status (clinical rating scale developed for Alzheimer's pt.'s; looks at ability to maintain daily living); Cognitive Difficulties Scale; AAN staging of HAD (stage 0.5 = subclinical; stage 1 = mild; stage 2 = moderate; stage 3 = severe; stage 4 = end-stage).

CNS Diagnoses Secondary to Immunosuppression:

Most common non-viral OI's: (by decreasing frequency of occurrence) ..

toxoplasmosis	most common cause of CNS mass lesion in individuals with HIV/AIDS; focal sxs-70%; HA-45%; lethargy/confusions-40%; seizures-40%; fever-35% Tx's: pyrimethamine, sulfadiazine, trimethoprim/sulfamethoxazole, dapsone
cryptococcus	fever; HA; malaise; <i>can present with 1st time Mania</i> ; stiff neck & photophobia-30%; focal signs rare. Tx's: fluconazole, amphotericin-B
TB	frequent complication of HIV; TB found in CSF; clinical or radiological evidence of extra-meningeal TB-65%; abnormal CT of head-70%. Tx: mortality-35%; INH, rifampin, pyrazinamide, ethambutol
atypical TB	(mostly MAI); CNS infection uncommon. Tx: azithromycin, clarithromycin, ethambutol, clofazimine, rifabutin
candida	infrequent in CNS; microabscesses in brain at autopsy. Tx: amphotericin-B
aspergillus	uncommon. Tx: mortality extremely high; amphotericin-B, itraconazole of limited value
coccidioides	uncommon in CNS, but for those in the southwestern U.S. ("cocci belt"), a common <i>re-activation</i> infection; shortness of breath; diffuse pulmonary infiltrates. Tx: amphotericin B, fluconazole, itraconazole
listeria	low incidence in HIV. Tx: IV penicillin, ampicillin
neurosyphilis	infrequent, but occurs earlier than in non-HIV pt.'s; acute syphilitic meningitis; polyradiculopathy; cranial nerve dysfunction; ophthalmic syphilis; general paresis less common presentation. Tx: penicillin G, chloramphenicol, ceftriaxone

Most common viral OIs

cytomegalovirus	(CMV); most common brain co-infection; slow, progressive MSE changes; focal or diffuse motor weakness; seizures; frontal lobe dysfunction; may present with altered sensorium Tx: acyclovir
PML	(progressive multifocal leukoencephalopathy); caused by JC virus; slow onset/single focus; MSE changes; limb weakness; ataxia; visual disturbance; dysarthria; sensory abnormalities. Tx: usually pt. dies within 6 months
varicella-zoster	a reactivation of chicken pox; cranial nerve palsies; HA; auditory hallucinations; dermatomal zoster (shingles). Tx: acyclovir, famciclovir

Most common neoplasms

CNS lymphoma	primary; focal neurological signs & sx's; confusion, lethargy, memory->50%; hemiparesis, aphasia->40%; seizures-15%; infrequently HA alone. Tx: rapidly fatal if untreated; whole brain radiation; chemotherapy (intrathecal cytosine arabinoside)
CNS lymphoma	secondary to extension from periphery
Kaposi's sarcoma	(KS); red to purple macular, papular or nodular lesions; symmetrical presentation along Langer's lines; also in mouth, and internally; focal cerebral lesions of brain mets. Tx: local & systemic tx's are palliative; radiation, chemotherapy
cervical cancer	90% are squamous cell, associated with human papilloma virus (HPV); metastases not common. Tx: surgery, radiation
anorectal cancer	95% are adenocarcinoma; metastases not common. Tx: wide surgical resection; 5-fluorouracil
leukemia	found with co-infection with HTLV-1. Tx: as for other leukemias

Cerebrovascular disorders

CVA	uncommon
hemorrhage	most common cause is thrombocytopenia
vasculitis	several types reported

Primary HIV CNS Disorders: (Minor Cognitive Motor Disorder, HIV-Associated Dementia, delirium, aseptic meningitis, vacuolar myelopathy, psychiatric d/o's due to a medical condition) **(See other sections for cognitive testing, differentials and treatment options.)**

MCMD: 2 or more of the following for >1 month: impaired attention, concentration or memory; mental slowing; slowed movements; incoordination; personality change/lability. Sx's must be *verified* by N-P testing/neuro exam
Look for: interruption of smooth ocular pursuit; slowing or inaccuracy of saccades; "frontal release" signs; slowing of rapidly alternating movements; ataxia. Mild, if any, impairments of *functional status*. No evidence of another etiology. A dx of MCMD is made if there are virtually *no significant functional impairments*, but there are significant N-P findings.

HAD: a *subcortical* dementia with preserved *cortical* function; often *misdiagnosed* as **Depression** if in *early HAD* (i.e., lethargy, apathy, social withdrawal, isolation, etc), or **Psychosis** if in *late HAD* (prominent sx's, severe language dysfunction, seizures, mutism, incontinence, etc). Abnormality in 2 or more of the following: attention,

concentration, abstraction, memory/learning, speed of information processing, visuospatial skills, speech/language. At least 1 of the following present: abnormality in motor function; decline in motivation or emotional control; absence of delirium; no evidence of another etiology. A dx of HAD is made if functional impairment is moderate to severe, i.e., significant decrements in social/occupational function are required for dx.

Delirium: *Medical Emergency!* *most common* N-P dx in hospitalized/critically ill HIV pt.'s (~65% in late stage AIDS); often underdiagnosed. Associated with increased morbidity/mortality. Hypo- & hyperactive subtypes may occur. May predispose to HAD and vice versa (see "*Risk Factors*" above). Full neurodiagnostic work-up is required (see above) which may uncover a number of general medical etiologies, several of which are reversible with appropriate treatment. Rule out medication side effects/interactions and alcohol/substance intoxication/withdrawal as potential underlying causes. Important to reverse as soon as possible to prevent further deterioration. Treatment choice is dependent on etiology (see above) – find underlying cause(s) and treat ASAP. Atypical neuroleptics and low-dose haloperidol for short term use may be utilized to control behaviors.

Aseptic meningitis: is most frequent type seen; may be with or without fever, HA, meningeal signs (e.g. nuchal rigidity.) Absence of signs increases with degree of immunosuppression. More malignant form may include cranial nerve involvement; long tract signs.

Vacuolar myelopathy: (>25%) affects dorsolateral columns with spastic gait, hyper-reflexia, urinary and fecal incontinence. B12 deficiency may be a predisposing co-factor.

Mood, Psychotic, or Anxiety d/o's due to a medical condition: may be due to the (1) primary effect of HIV on the brain; (2) may be secondary to medications used to treat them, or (3) multiple other medical problems (OI's). (See also "Mood, Psychotic, and Anxiety Disorders")

Peripheral nervous system disorders: chronic distal sensory polyneuropathy; chronic inflammatory demyelinating polyneuropathy, autonomic nervous system disorder.

Non-Pharmacologic Interventions: cognitive skills training/rehabilitation; issues for caregivers of HAD and other AIDS pt.'s (pt. care includes restitution of lost functions, adaptation and compensation, environmental engineering); local care-giver support groups.

Pharmacologic Interventions:

Antiretroviral Medications (Check for new additions)

1. NRTI's = nucleoside reverse transcriptase inhibitors:
abacavir [ABC]; (Ziagen); didanosine [ddI] (Videx); stavudine [d4T] (Zerit); zalcitabine [ddC] (Hivid); lamivudine [3TC] (Epivir); zidovudine [AZT] (Retrovir); lodenidine [FddA]

2. NtRTI's = nucleotide reverse transcriptase inhibitors:
tenofovir; adefovir (Preveon) – removed

3. NNRTI's = non-nucleoside reverse transcriptase inhibitors:
delavirdine (Rescriptor); efavirenz (Sustiva); nevirapine (Viramune); emavirine

4. PI's = protease inhibitors:
amprenavir (Agenerase); indinavir (Crixivan); nelfinavir (Viracept); ritonavir (Norvir); saquinavir (Invirase); tipranavir; atazanavir

5. Entry inhibitors [(a) receptor blockers or (b) fusion inhibitors]
enfuvirtide (Fuzeon)

6. Integrase inhibitors
pentafuside

Immunostimulants and Inflammatory Response Modulators

Peptide T inhibits binding of gp120 to CD4 receptor; appears to reverse as well as prevent

impairment; downregulates production of TNF-a; those with CD4's of 200-500 may have cognitive improvements

TNF-alpha blockers (pentoxifyline, thalidomide) decrease blood viscosity, suppress expression of TNF-a respectively

calcium channel blockers (nimodipine) shown cognitive improvements when added to a regimen with AZT
n-methyl D-aspartate receptor blockers (memantine) block quinolinic acid (a known convulsant that facilitates calcium influx) at excitatory amino acid receptors

antioxidants associated with suppression of HIV-1 replication in monocytes. macrophages

vitamins/minerals: E, B6, B12, zinc, appear to be especially useful

nerve growth factor - ?

lazaroids "scavengers" of oxidative free radicals and inhibitors of lipid peroxidation

Neurotransmitter Manipulation

psychostimulants: (methylphenidate – see "Mood Disorders") for early HAD psychomotor slowing and attention deficits. For late HAD, psychostimulants may be toxic. Watch for side effects; caution when there is a history of *seizures, hypertension, substance abuse, mania, or psychosis*; beware of potential abuse issues.

SSRI's and other AD's: (see "Mood Disorders" for medications & dosing)

dopamine precursors (carbidopa)

MAO type B inhibitors (selegiline)