Neurologic Complications in HIV-Infected Children and Adolescents

I. Introduction

Prior to the introduction of highly active antiretroviral therapy (HAART) in 1996, the rates of neurologic dysfunction in children with symptomatic HIV infection were estimated to range from 30% to 50% for progressive encephalopathy and close to 90% for static encephalopathy. Since the advent of HAART, the rates of progressive encephalopathy found in clinical practice are much lower (approximately 5% to 10%). Because of early treatment and ongoing clinical monitoring, neurological symptoms are identified early and therefore tend to be less severe.

Neurologic dysfunction in the setting of pediatric HIV infection is believed to be caused by an active and primary infection of the brain by HIV. Infection is persistent and probably occurs shortly after birth. In children with perinatal infection, clinical signs of neurologic dysfunction may appear as early as 2 months of age and as late as 5 years of age or older.

The natural history of HIV encephalopathy in the era of HAART is not known. Previous longitudinal studies suggest three distinct neurologic and developmental courses:

1) Rapid progression
2) Steady, subacute progression
3) Static neurologic deficits

Other factors, such as in utero exposure to drugs, also may have an effect on neurologic function.

As children with HIV infection reach adolescence, they may retain sequelae of early neurologic insults. In addition, HIV-infected adolescents, whether perinatally or behaviorally infected, are at risk for the same neurologic complications seen in adults with HIV. As some children and adolescents who have not responded to HAART become older and more severely immune compromised, complications, such as opportunistic infections and intracranial tumors, may become more prevalent.

Children with HIV infection can develop neurologic illness in the same manner as non-infected children. Many children at risk for HIV infection are also at risk for developmental delays and neurological deficits because of co-morbidities commonly seen in the HIV-exposed population.

II. Baseline Neurologic Evaluation

Recommendations:

At routine visits, the primary care physician should be particularly vigilant for the appearance of the following conditions:

• Developmental delay or loss of previously acquired milestones
• Microcephaly/deceleration in head growth
• Abnormal tone and reflexes (especially clonus and cross adductor reflex)
• Focal findings
• Speech and language delay
A baseline neurological consultation should be obtained for all children with developmental delay or neurological signs and symptoms (e.g., focal weakness, seizures, altered mental status or microcephaly) and for any HIV-infected child with a high viral load (>100,000 copies/mL) at baseline.

The neurologic specialist should discuss correlation and interpretation of neurologic examination and diagnostic studies with the primary care physician.

A routine ophthalmologic evaluation, including a yearly retinal examination, should be performed in all HIV-infected children. Clinicians should be aware that HIV-infected children with significant immune suppression are at risk for ocular infections, including CMV retinitis, toxoplasmosis, and herpes infections.

The necessity and timing of further evaluations should be determined by the following:

- Severity of neurologic involvement at the time of initial assessment
- Value of repeated neurologic examinations in terms of available therapeutic intervention and prognostic measures
- Appearance of new neurologic symptoms

Children with well-controlled HIV disease and isolated developmental delays without other neurologic findings should be reassessed 3 months after detection of the delay. If there is no change in neurologic examination and development is proceeding, follow-up should occur according to routine neurological care practice.

The purposes of a neurologic evaluation are as follows:

- Identification and documentation of abnormal neurologic findings
- Identification of non-HIV-related neurologic illness
- Categorization, when possible, of the neurologic course the patient seems to be following (rapidly progressive, subacute, or static)

The frequency of neurological reassessments for patients with developmental delays will vary according to status of HIV disease and neurodevelopmental status.

III. SPECIFIC COMPLICATIONS

A. HIV Encephalopathy

RECOMMENDATION:

HIV should be considered in any child with progressive neurological deterioration who has not been previously tested for HIV or who might have it despite a previous negative test.

In the era of neonatal HIV screening programs, HIV encephalopathy is rarely the initial mode of HIV presentation in infected children in the United States.

1. Presentation

Progressive encephalopathy usually occurs in children with documented HIV infection and symptomatic disease. Progressive neurologic dysfunction associated with HIV resembles a white matter neurodegenerative disorder. Most commonly, evidence of underlying HIV progression, such as immunologic compromise, coincides with onset of symptoms of encephalopathy, but because of possible compartmentalization of HIV in the central nervous system (CNS) (i.e., a sequestered reservoir of actively replicating HIV in the CNS), HIV encephalopathy may occasionally occur in well-controlled, otherwise asymptomatic HIV-infected individuals. Regardless of mode of presentation, HIV encephalopathy rarely, if ever, exhibits focal neurologic signs.
2. Diagnosis

a. Clinical Signs Associated With Progressive HIV Encephalopathy

• Impaired brain growth. In children <2 years of age, impaired brain growth manifests as deceleration of head growth or acquired microcephaly. In older children, it manifests as cerebral atrophy on neuroimaging (see Radiological Findings Associated With Progressive HIV Encephalopathy described below).

• Progressive bilateral pyramidal tract signs. These include bilateral tone abnormalities and onset of pathologic reflexes (hyperreflexia and clonus), chiefly affecting the legs. Progressive motor dysfunction may result in a spastic diparesis, which, if severe, may interfere with ambulation. If left untreated, motor deficits may progress to a spastic quadriparesis with pseudobulbar palsy. However, with effective ARV therapy, this outcome is seldom encountered. Hypotonia with pyramidal tract involvement is described early in the course of encephalopathy in young children. Ataxia and parkinsonian rigidity are uncommon signs and are seen only in very advanced CNS disease.

• Developmental delay, loss of motor milestones, or cognitive impairments. In young children, HIV encephalopathy may manifest as stagnation in development or loss of developmental milestones. Older children and adolescents may develop HIV dementia indistinguishable from that described in adults (for more information on HIV dementia in adults, refer to Mental Health Care for People With HIV Infection). Cognitive impairments are almost always detected but may be subtle. It is therefore useful to have baseline psychometric data obtained when the child’s HIV disease is well controlled to enable detection of a decline in mental or motor performance. HIV dementia may occur with or without motor signs or psychiatric manifestations, such as psychosis.

b. Laboratory Evaluations

• Cerebrospinal fluid. Cerebrospinal fluid (CSF) parameters in children with HIV-1 infection are usually normal and, thus, are usually not assessed unless an opportunistic infection is suspected. In the absence of opportunistic infections, CSF abnormalities are non-specific and reveal a predominantly lymphocytic pleocytosis and elevated protein levels that are rarely >100 mg/dL. CSF viral load is not routinely obtained for diagnostic purposes. Its utility is limited because of a significant overlap in CSF viral load among children with and without encephalopathy; however, levels above 10^6 copies/mm^3 have been more strongly associated with HIV dementia.

c. Radiological Findings Associated With Progressive HIV Encephalopathy

Diffuse cerebral atrophy manifested as enlargement of subarachnoid space and ventricles is the most common neuroimaging finding. Foci of demyelination also may be seen, usually in the centrum semiovale or parieto-occipital white matter. Frontal lobe or basal ganglia enhancement and calcifications are late manifestations and occur primarily in symptomatic infants. Because of its greater sensitivity in detecting demyelination, MRI is the preferred brain imaging modality. However, because radiographic findings may lag behind the clinical symptoms, MRI can be normal early in the course of HIV encephalopathy. CT scan, in addition to MRI, may be of use in settings of advanced disease to detect calcification.
3. Treatment

**RECOMMENDATIONS:**

HIV encephalopathy should be treated with the same ARV agents used to treat symptomatic HIV disease, with the goal of achieving low to undetectable viral load and reversal of immune suppression.

HIV-infected children with neurologic impairments and developmental delays should be referred to early intervention programs.

With effective response to HAART (decreased viral load and restoration of immune function), arrest of HIV encephalopathy and gradual resolution of the neurological signs and symptoms usually follow. Clinical trials are assessing the efficacy of combination therapy comprised of reverse transcriptase and protease inhibitors. The use of HAART has resulted in decreased morbidity and mortality and diminished progression to AIDS.

**B. Infections of the Central Nervous System**

**RECOMMENDATIONS:**

A pediatric HIV Specialist should be consulted whenever a central nervous system infection is suspected.

Various etiologic agents should be excluded via lumbar puncture and CSF testing, unless contraindicated (see Table 1).

The true prevalence of CNS infections (HIV-related and opportunistic) in HIV-infected children is not known, but it is thought that such infections are much less frequent in children than in adults. The neurologic impairment most frequently observed in children is due to HIV infection of the CNS rather than to opportunistic infection or CNS tumors. However, several distinct infections in immunosuppressed children with neurologic dysfunction should be considered (see Table 1).

<table>
<thead>
<tr>
<th><strong>Table 1</strong></th>
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<tr>
<td><strong>Laboratory Evaluations for Children with Acute CNS Manifestations</strong></td>
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**Blood**
- Complete blood count (CBC)
- Blood culture
- Electrolytes

**Toxicology screen**
- Toxoplasmosis serum antibody
- Cryptococcal antigen and culture

**Lumbar puncture (unless contraindicated)**
- opening pressure
- gram stain
- cell count
- protein
- glucose

- bacterial culture
- cryptococcal antigen and culture
- PCR for EBV, CMV, VZV and HSV
- viral, fungal and mycobacterial cultures
- VDRL

1. *Cryptococcus neoformans*

In the pre-HAART era, cryptococcosis was relatively common in adults with AIDS but uncommon in children with AIDS (7% vs. 1%, respectively).4

a. **Presentation**

Symptoms of intracranial cryptococcosis may include headache, fever, meningesmus, focal findings, or subtle neurologic dysfunction. Localized extraneural lesions may also occur in the liver, lungs, lymph nodes, and elsewhere.
b. Diagnosis

**RECOMMENDATIONS:**

Isolation of *Cryptococcus neoformans* by culture, serum, and CSF cryptococcal antigen test, or histologic examination of tissue specimens should be performed to obtain a definitive diagnosis.

Cryptococcal meningitis should be considered in any HIV-infected patient who has new neurologic findings and should be excluded by lumbar puncture. CSF antigen testing is a useful test for diagnosis and for following response to therapy. Detection of cryptococcal capsular polysaccharide (cryptococcal antigen) correlates well with culture results, although several cultures may be needed to confirm the diagnosis. Serum antigen may be tested if CSF is not available.

c. Treatment

**RECOMMENDATIONS:**

Treatment for cryptococcosis should be initiated if the organism is identified by stain or by increased levels of cryptococcal antigen (see Table 2). Waiting for culture results is not advisable before initiating therapy because it may take days or weeks to grow.

Cryptococcal meningitis should be treated with amphotericin B (with or without flucytosine) or fluconazole depending on severity of disease and immune suppression (see Table 2 for dosing).

Therapeutic lumbar punctures should be used to control symptoms of increased intracranial pressure secondary to communicating hydrocephalus caused by cryptococcal meningitis.

Because HIV-infected patients cannot be cured of cryptococcosis, most patients should be maintained on lifelong chronic therapy.

<table>
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<th>TABLE 2</th>
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<tr>
<td><strong>STANDARD AND ALTERNATIVE DRUG REGIMENS FOR TREATMENT OF CRYPTOCOCCOSIS</strong></td>
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**Standard Regimen**

Amphotericin B intravenously (0.7-1.0 mg/kg per day of the standard preparation or liposomal amphotericin 3-5 mg/kg per day) in one daily dose for 2 weeks or until clinically stable

\[ \text{with or without} \]

5-fluorocytosine (100-150 mg/kg per day po), divided into four daily doses for 2 weeks or until clinically stable,

\[ \text{then} \]

Fluconazole (10-20 mg/kg IV or PO for 1 day up to 800 mg, then 5-10 mg/kg per day up to 400 mg indefinitely)

**Alternative Regimens**

For very mild disease:

Fluconazole alone for 6-10 weeks

**For very severe disease or in severely immune deficient children:**

Amphotericin B + 5-fluorocytosine for 6 weeks prior to beginning fluconazole suppression
Some experts may consider discontinuation of chronic maintenance therapy reasonable when the adolescent patient has successfully completed a course of initial therapy and remains asymptomatic with an increase in CD4 count for >6 months following HAART. However, there are not sufficient data in the pediatric population to recommend discontinuation of lifelong therapy at this time.

In extremely refractory cases, intrathecal amphotericin has been used. These are anecdotal reports, however, and safety, efficacy, and dosing recommendations for it have not been established.

The choice of which regimen to use will depend on the severity of cryptococcal disease and especially the severity of immune deficiency. The standard regimen is amphotericin B intravenously (0.7-1.0 mg/kg per day of the standard preparation or liposomal amphotericin 3-5 mg/kg per day). Those with severe cases or severe immune deficiency should be treated with amphotericin B and 5-fluorocytosine. Children with milder cases may respond to fluconazole alone.

Altered mental status, headaches, or cranial nerve palsies may indicate the development of symptomatic communicating increased intracranial pressure (ICP), which has been associated with poor outcome, such as blindness and death). These symptoms warrant (after documenting no mass lesion by CT or MRI at the time of diagnosis) obtaining a therapeutic lumbar puncture to decrease ICP. Opening pressure should be documented at the time of diagnosis. Normal opening pressure is <200 mm H2O in infants and children and <110 mm H2O in neonates. If ICP is normal for age, the child should be treated medically, and lumbar puncture should be repeated at 2 weeks to document sterility based on culture, not antigen.

If opening pressure is elevated but not more than twice normal, at the time of diagnostic lumbar puncture, the clinician should draw off enough fluid to decrease the pressure to the normal range. If the opening pressure is elevated to more than twice normal (400 mm H2O in a child; 220 mm H2O in an infant), the physician should draw off enough fluid to reduce the pressure in half. Increased pressures may persist despite sterilization of the CSF. Repeated lumbar punctures may be necessary as often as once a day to keep the pressure stable. In some cases, long-term drainage, such as a ventriculoperitoneal shunt, may be necessary.

d. Clinical and Laboratory Monitoring

RECOMMENDATIONS:

The neurologic status of patients with cryptococcosis should be monitored daily. Lumbar puncture should be repeated within 1 week (sooner if clinically indicated), and cryptococcal antigen level should be monitored. Antigen level should decrease with successful therapy. Opening pressure should be measured at each lumbar puncture.

For patients receiving amphotericin B, complete blood count and tests for electrolytes, BUN, creatinine, and liver function should be performed at least once weekly to monitor for toxicities and more frequently at the beginning of therapy (see Table 3).

For patients receiving 5-fluorocytosine, complete blood count, platelet count, creatinine, and serum liver enzyme levels should be obtained. Serum drug levels should be monitored, if available (see Table 2).

A patient with cryptococcosis may be discharged from the hospital when neurologic status, especially intracranial pressure, is stable and adequate arrangements have been made for therapy at home.
After successful therapy for cryptococcal meningitis, the patient should be maintained on lifelong suppressive therapy. Suppressive therapy regimens include daily oral fluconazole or weekly intravenous amphotericin.

### TABLE 3

<table>
<thead>
<tr>
<th>Major Toxicities That May Occur During or After Therapy for Cryptococcosis</th>
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<tr>
<td><strong>Toxicities from Fluconazole</strong></td>
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<tr>
<td>- Liver dysfunction</td>
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<tr>
<td>- Rash</td>
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2. **Toxoplasma gondii**

CNS toxoplasmosis is relatively common in adults with AIDS but uncommon in children with AIDS because it is usually a reactivation of previous infection, and primary toxoplasmosis is uncommon in children.

#### a. Presentation

Clinical presentation of cerebral toxoplasmosis is variable and may include fever, focal neurologic findings of recent onset, generalized or focal seizures, or subtle cognitive changes. Radiographic imaging of the brain usually reveals one or more ring-enhancing mass lesions. Although these lesions are characteristic of toxoplasmosis, they are not pathognomonic.

#### b. Diagnosis

**Recommendations:**

If *Toxoplasma* serology is positive, a child should be treated empirically with pyrimethamine/sulfa for 2 weeks before considering more invasive diagnostic procedures.

If *Toxoplasma* serology is negative or if CSF EBV PCR is positive, invasive diagnostic procedures, such as a brain biopsy, should be considered to determine the diagnosis. A positive CSF EBV PCR indicates the likelihood of CNS lymphoma.

If a favorable response to empiric treatment is documented, CNS toxoplasmosis is the presumptive diagnosis. In cases in which no improvement is documented, further invasive diagnostic procedures may be indicated to exclude other opportunistic infections, brain abscess, or tumor.

Toxoplasmosis serology has 90% to 95% sensitivity. A negative IgG serology makes toxoplasmosis unlikely but does not entirely exclude the diagnosis.
c. Treatment

RECOMMENDATION:

Toxoplasma encephalitis should be treated with one of the regimens listed in Table 4 for 4 to 6 weeks.

Neurosurgical consultation for re-evaluation of toxoplasmosis should be obtained when the patient fails to improve with empiric therapy and further invasive diagnostic procedures are contemplated.

As the risk of relapse is quite high, treatment for toxoplasmosis is usually maintained for life (see Table 4).

<table>
<thead>
<tr>
<th>TABLE 4</th>
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<tbody>
<tr>
<td><strong>STANDARD AND ALTERNATIVE DRUG REGIMENS FOR TREATMENT OF TOXOPLASMOsis</strong></td>
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<tr>
<td><strong>Standard Regimen</strong></td>
</tr>
<tr>
<td>Sulfadiazine 120-200 mg/kg/day divided into four doses</td>
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<tr>
<td>and</td>
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<tr>
<td>Pyrimethamine [loading dosage of 2 mg/kg per day (max, 100 mg) divided into two doses for 3 days, followed by maintenance dosage of 1 mg/kg per day (max, 25 mg), delivered orally].</td>
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<tr>
<td>and</td>
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<tr>
<td>Folinic acid (1 to 2 mg per day in infants and 5 to 10 mg every 3 days in older children, delivered orally) for patients receiving pyrimethamine</td>
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<tr>
<td><strong>Alternative Regimen</strong></td>
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<tr>
<td>Clindamycin (40 to 60 mg/kg/day IV divided into 4 doses) plus pyrimethamine plus folinic acid</td>
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</table>

* The effectiveness of the alternative regimen is unproven in pediatric patients. Acceptable reasons for using the alternative regimen are patient participation in a research protocol and patient inability to tolerate or failure to respond to the standard therapeutic regimen.

As the risk of relapse is quite high, treatment is usually maintained for life. However, no relapse was found in adults not receiving anti-toxoplasmosis prophylaxis who had immune function restoration as a result of HAART. Discontinuation of treatment may be considered in adolescent patients whose signs and symptoms of toxoplasmosis have resolved and who have a sustained (>6 months) increase in their CD4 counts following HAART.

Some experts may consider discontinuation of chronic maintenance therapy in children reasonable when the patient has successfully completed a course of initial therapy and remains asymptomatic with an increase in CD4 count for >6 months following HAART. However, there are not sufficient data in the pediatric population to recommend discontinuation at this time.

d. Laboratory Monitoring

RECOMMENDATION:

Close monitoring of patients receiving treatment for toxoplasmosis, including CBC and serum liver enzymes, is required to detect adverse drug reactions (see Table 5).
3. **Herpes Viruses**

Herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) are all fairly common causes of nervous system disease in children with HIV. Although all three may present with encephalitis, each has other characteristic presentations.

PCR of CSF may be used to diagnose HSV, VZV, or CMV infection of the CNS. This methodology may also be helpful in determining the severity of the involvement and the efficacy of treatment. When PCR is not available, viral culture can be used, although, in the case of CMV, it may not be particularly expedient. Pathognomonic lesions can help establish a diagnosis.

### a. Herpes Simplex Virus

#### i. Presentation

Herpes simplex virus (HSV) can cause encephalitis, most commonly in neonates. Herpes encephalitis can occur with or without the common skin, eyes, and mouth (SEM) manifestations. Neonatal herpes infections, if untreated, have a high mortality rate and commonly lead to long-term neurologic sequelae.

After the neonatal period, HSV encephalitis can occur with primary or secondary infection. Alterations in personality and consciousness, convulsions, and focal neurologic dysfunction can be the presenting signs, and the course is often fulminant and rapidly fatal.

#### ii. Diagnosis

Pleocytosis is common, with both lymphocytes and erythrocytes present in the CSF. Radiographic imaging and electroencephalogram (EEG) are often helpful in localizing lesions in HSV encephalitis.

#### iii. Treatment

**RECOMMENDATION:**

HSV encephalitis should be treated with acyclovir. Beyond the neonatal period, the dosage is 30 mg/kg/day IV divided into three doses administered every 8 hours for 14 to 21 days. The neonatal dose is 60 mg/kg/day IV divided into three doses administered every 8 hours for 14 to 21 days.

### b. Varicella Zoster Virus

#### i. Presentation

Varicella zoster virus CNS complications may be acute or recurrent. Encephalomyelitis, dermatomal radiculopathies associated with shingles, zoster ophthalmicus with retinal necrosis, and cranial nerve abnormalities are reported to be associated with VZV in patients with advanced AIDS. In adults, 70% of cases of neurological complications have shingles and/or acute retinal necrosis.

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**TABLE 5**

<table>
<thead>
<tr>
<th>Toxicities from Pyrimethamine</th>
<th>Toxicities from Sulfonamides</th>
<th>Toxicities from Clindamycin</th>
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</thead>
<tbody>
<tr>
<td>• Bone marrow suppression</td>
<td>• Rashes</td>
<td>• Colitis</td>
</tr>
<tr>
<td>• Acts as a folic acid antagonist</td>
<td>• Hematuria</td>
<td>• Rashes</td>
</tr>
<tr>
<td></td>
<td>• Crystalluria</td>
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<tr>
<td></td>
<td>• Bone marrow suppression</td>
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ii. Diagnosis

Examination of CSF shows prominent pleocytosis (mean CSF white blood cell count, 126 cells/mm³) with elevated protein (mean CSF protein, 2.3 g/L). Diagnosis is increasingly made by CSF PCR rather than by culture or tissue examination. CSF PCR is invaluable in diagnosing CNS herpes virus infection, with sensitivity ranging from 70% to 90% and specificity >90%. Radiographic imaging and EEG are often helpful in localizing lesions in varicella encephalitis.

iii. Treatment

**RECOMMENDATION:**

Acyclovir at 1500 mg/m²/day IV divided into three doses administered every 8 hours for 7 to 10 days (or 30 mg/kg/day divided q8h) should be used to treat VZV infection.

c. Cytomegalovirus

i. Presentation

Although HAART has notably decreased the incidence of CMV disease, CMV infections are common and severe complications of HIV infection. The virus often involves the nervous system, causing retinitis, encephalitis, polyradiculoneuropathy and cranial or peripheral neuropathies.

CMV retinitis is a leading cause of blindness in persons with AIDS. Symptoms such as loss of visual acuity, blurred vision, and visual field defects may be particularly difficult to detect in children. Ophthalmologic examination usually shows characteristic retinal lesions.

CMV meningoencephalitis may present with seizures, focal findings, and altered mental status. MRI reveals foci of demyelination that are similar to that seen in primary HIV encephalopathy.

In the pre-HAART era, numerous patients with rapid progression of delirium and dementia had CMV neurologic disease detected on autopsy. CMV polyradiculopathy may present with an ascending weakness. Clinical signs and symptoms are often overlooked in a very sick, non-verbal child.

ii. Treatment

**RECOMMENDATIONS:**

CMV infection may be treated with intravenous ganciclovir (10 mg/kg per day divided into two doses every 12 hours), and maintenance therapy is needed until immune restoration occurs.

For ganciclovir-resistant retinitis, foscarnet should be used (limited data in pediatrics).

Routine retinal examinations should be performed every 6 months in children with severe immunosuppression.

CMV is susceptible to various antivirals, including ganciclovir, foscarnet, and cidofovir. However, CMV infections of the nervous system, particularly encephalitis, respond poorly to standard treatments. The combination of ganciclovir plus foscarnet is currently under evaluation in clinical trials.
4. JC Virus

Progressive multifocal leukoencephalopathy (PML) is a chronic demyelinating disorder that results from infection with JC virus, which is a papova virus. It occurs in approximately 4% to 6% of adults with AIDS but is exceedingly rare in children.

a. Presentation

PML manifests with dementia and focal abnormalities. Lesions are commonly located in the parieto-occipital or frontal region, affecting both periventricular and subcortical white matter but may occur anywhere in the brain.7

b. Diagnosis

On MRI, images appear as areas of increased signal without mass effect on T2. Lesions rarely enhance with contrast and may be difficult to distinguish radiographically from HIV demyelination. CSF PCR for JC virus is highly sensitive in diagnosing PML. Quantitative levels in CSF may be of prognostic value, with lower levels associated with longer survival.8

c. Treatment

RECOMMENDATION:

Clinicians should recommend HAART for patients with PML.

In the pre-HAART era, PML had a poor prognosis. Approximately 90% of adults with PML died within 10 months; mean survival was 4 months. There are now a number of anecdotal reports of increased survival in patients with PML who are receiving HAART. Progression of PML may stabilize and even revert radiographically with HAART. Specific anti-JC virus therapy has been unsuccessful, even if given intrathecally.9

5. Bacterial Meningitis

a. Presentation

Various bacteria may cause meningitis in HIV-infected children. These patients may have nuchal rigidity, fever, headache, and focal or generalized signs of neurologic dysfunction. The encapsulated organisms, Streptococcus pneumoniae and Haemophilus influenzae type b, are of special importance in causing such CNS infections.

b. Diagnosis

RECOMMENDATION:

Definitive diagnosis of bacterial meningitis is made by isolating and identifying the organism from CSF or blood culture. Lumbar puncture is needed to make a correct diagnosis.

A presumptive diagnosis can only be made in cases in which the patient has a consistent clinical presentation and the patient is awaiting lumbar puncture or lumbar puncture is contraindicated.

c. Treatment

RECOMMENDATION:

Antimicrobial therapy directed at the most common etiological agents (i.e., S pneumoniae, H influenzae) should be used to treat bacterial meningitis. Both vancomycin and ceftriaxone at meningitic doses should be used in the empiric treatment of community-acquired bacterial meningitis. Antibiotic choice may be modified once an organism is identified and antimicrobial sensitivities are available. Duration of therapy is usually 10 to 14 days.
Corticosteroids may be used in conjunction with antibiotics for initial therapy of *H. influenzae* type b meningitis. Some authorities believe that corticosteroids have a beneficial effect on prevention of hearing loss in patients with *H. influenzae* type b meningitis. The benefit of steroid use in meningitis caused by other organisms is unproven.

d. Clinical and Laboratory Monitoring

**RECOMMENDATIONS:**

- Neurologic status of patients with bacterial meningitis should be monitored daily.
- If diagnosis is in doubt, lumbar puncture should be repeated to diagnose bacterial meningitis and to document sterility.
- Hearing tests (audiogram, auditory evoked responses) should be performed in patients with bacterial meningitis before discharge and at 6-month follow-up visit after discharge.
- Patients with bacterial meningitis may be discharged from the hospital when neurologic status is stable and adequate arrangements have been made for follow-up.

6. Syphilis (*Treponema pallidum*)

a. Presentation

The course of *T. pallidum* infection may be altered by HIV infection. Pediatric patients either present with infection acquired perinatally (congenital syphilis) or with new acquisition of infection. Adolescent patients may present with the typical manifestations noted in adults. Clinical symptoms are protean.

b. Diagnosis

**RECOMMENDATIONS:**

- Neurosyphilis should be considered in the differential diagnosis of neurologic dysfunction in an HIV-infected patient, regardless of serologic evidence.
- Definitive diagnosis can be made by positive non-treponemal (VDRL, RPR) and fluorescent treponemal antibody-absorption (FTA-ABS) tests; however, a VDRL may be negative if the infection is early. The organism may be identified by dark-field microscopy from lesions.
- A CSF examination (opening pressure, cell count, total protein, glucose, and VDRL) is strongly recommended for all children and adolescents co-infected with HIV and syphilis.
- Clinicians should perform a CSF examination in all infants with congenital syphilis born to mothers with HIV co-infection.
- Diagnosis is usually established by serological diagnosis (non-treponemal and treponemal tests) or by identification of the organism by dark-field microscopy. In the adult population, cases of *T. pallidum* infection have been reported even when the results of these tests were negative. The frequency of this rare occurrence is not known.
- A presumptive diagnosis can be made when clinical presentations are consistent with congenital syphilis, primary syphilis (genital, oral, or rectal chancres), secondary syphilis (characteristic rash), or neurosyphilis (may or may not be symptomatic). CSF may or may not have pleocytosis, high protein, and a positive non-treponemal test (VDRL).
When neurosyphilis is suspected, a CSF examination is required. Pleocytosis, high protein, and a positive nontreponemal test may or may not be present. If these findings are present, the diagnosis is more secure.

c. Treatment

**Recommendation:**

Treatment of syphilis should be guided by the following factors: 1) the stage of syphilis, 2) whether it is congenital, 3) whether it is neurosyphilis, and 4) whether the patient is pregnant. For specific treatment and monitoring recommendations for syphilis, clinicians should refer to the Centers for Disease Control and Prevention’s guidelines (http://www.cdc.gov/std/treatment/).

7. Mycobacteria

*Mycobacterium tuberculosis* (MTB) and atypical mycobacteria may cause CNS infection.

a. Presentation

Patients may present with granulomatous meningitis, occasionally accompanied by progressive cranial neuropathies, or with focal clinical signs resulting from mass lesions (i.e., tuberculoma).

b. Diagnosis

**Recommendations:**

A presumptive diagnosis should be made if the patient presents with consistent clinical findings and has a positive purified protein derivative (PPD) test. Patients with HIV and severe immune suppression may be anergic.

Because AFB smear and culture of the CSF are not very sensitive diagnostic tools, a strong effort should be made to obtain as much as 10 mL of CSF to increase the yield.

CT scan or MRI with contrast will demonstrate mass lesions; severe basilar meningitis may show subarachnoid enhancement at the base of the brain. Lumbar puncture may reveal high protein, low glucose, and lymphocytic pleocytosis. PCR for identification of mycobacteria in the CSF is being studied.

Definitive diagnosis of mass lesions can only be made by tissue diagnosis.

c. Treatment

**Recommendation:**

Treatment of MTB CNS infection should begin immediately upon recognition of a positive smear or if other causes of meningitis are unlikely. Culture may be negative or may take several weeks to grow, and treatment should not be delayed.

Symptomatic tuberculous meningitis is invariably due to MTB. In advanced HIV disease, *Mycobacterium avium* complex is a common neuropathological finding but has little, if any, clinical impact. Suspected mycobacterium meningitis is due to MTB, unless proven otherwise.

For complete discussion of therapy of tuberculosis and atypical mycobacteria, refer to the *Pulmonary Manifestations* chapter, which will be available in 2004.
C. Primary CNS Lymphoma

Primary CNS lymphoma is the most common cause of focal neurologic deficit in HIV-infected children with HIV infection, accounting for approximately 4% to 6% of focal, mass lesions in autopsy series.

a. Presentation

Primary CNS lymphoma in AIDS is always of a high-grade B-cell type. Common changes in mental status include confusion, lethargy, and memory loss. Seizures are reported in approximately one-third of patients. Increased intracranial pressure may occur as a late effect.

b. Diagnosis

RECOMMENDATIONS:

CNS lymphoma should be suspected in the presence of focal neurologic deficits, seizures, or changes in mental status and when the CT scan or MRI reveals a mass lesion.

Children with lymphoma detected outside the CNS should be vigorously assessed for possible intracranial involvement.

Lumbar puncture for Epstein-Barr virus PCR and cytology (assuming no evidence of mass effect on neuroimaging studies), and functional neuroimaging (SPECT scan) are non-invasive methods by which to diagnose lymphoma. A pediatric oncologist should be consulted.

In HIV-infected children, a brain biopsy may be necessary to confirm diagnosis of lymphoma.

On a CT scan, CNS lymphoma lesions appear isodense or hypodense with ill-defined borders and scant edema. They are enhanced homogeneously with contrast. Such masses show a high signal on dual echo (T2) MRI and are enhanced with gadolinium. Lymphoma lesions are often multifocal and may be ring-enhancing, making it difficult to differentiate both clinically and radiographically from Toxoplasma brain abscess. Neurocysticercosis may also present with ring-enhancing lesions and should be considered in the differential diagnosis when the patient has recently been in a country where the parasite is endemic (e.g., Mexico), or when the patient's immune function makes CNS lymphoma or toxoplasmosis unlikely.

Non-invasive methods by which to diagnose lymphoma include Epstein-Barr virus PCR and functional neuroimaging. Identification of Epstein-Barr virus in CSF by nested DNA-PCR is a sensitive (80%) and highly specific (97%) method by which to diagnose B-cell CNS lymphoma in patients with AIDS. CSF PCR assays for toxoplasmosis may also provide important information in the evaluation of CNS mass lesions. Functional neuroimaging capitalizes on differences in vascularity between lymphoma and toxoplasmosis to enhance diagnostic accuracy over conventional neuroimaging (MRI).

CNS lymphoma lesions are highly vascular, resulting in focal increases in cerebral blood flow on single-photon emission computed tomography (SPECT), whereas the opposite is found with toxoplasmosis brain abscesses, which have necrotic centers and low vascularity.

In adult patients with AIDS, the four-fold greater frequency of toxoplasmosis compared with lymphoma often merits empirical treatment with anti-Toxoplasma agents for 2 weeks. The absence of a response to treatment would then warrant performing a diagnostic brain biopsy. In children, the infrequency of toxoplasmosis argues against empirical treatment for toxoplasmosis; diagnosis usually requires a brain biopsy, especially if the child is young and Toxoplasma serology is negative.
c. Treatment

**Recommendation:**

CNS irradiation and oral prednisone are treatments for lymphoma and may prolong survival.

Success of treatment for lymphoma is disappointing, and, despite intervention, prognosis is poor; however, HAART has seemed to improve the prognosis in several cases.

D. Antiretroviral Toxicities

**Recommendations:**

Suspected ARV-related neurologic disease in an HIV-infected child should be fully assessed and managed according to accepted pediatric neurology standards.

A child exposed to ARV drugs who develops seizures and psychomotor regression should be evaluated to exclude mitochondrial dysfunction by obtaining arterial and CSF lactate and pyruvate. Diagnostic confirmation requires muscle biopsy for immunohistochemistry and respiratory chain complex measures.

Several studies in France have identified a few cases of neurologic disease of varying severity in children who were exposed to ARV drugs in utero. Long-term follow-up studies of such children are ongoing to determine whether this is attributable to ARV-related mitochondrial toxicity. No similar cases have been reported in studies from the United States or other countries.

1. ARV-Associated Peripheral Neuropathy

   Historically, peripheral neuropathy has been one of the more common side effects of ARV therapy, in particular nucleoside reverse transcriptase inhibitors (NRTIs). It is believed to be a mitochondrial toxicity and is most commonly seen in patients receiving didanosine and zalcitabine. Occurrence of this toxicity seems to have decreased during the HAART era, presumably because of lower doses of didanosine when used as part of HAART and because of a decrease in the use of zalcitabine.

   a. Presentation

   The most common symptoms of polyneuropathy are painful dysesthesia, characterized as a burning or aching sensation, primarily in the soles of the feet. Contact sensitivity and hyperpathia may be so severe that ambulation is affected. Occasionally areflexia, depressed reflexes, and intrinsic foot muscle weakness may be noted.

   b. Diagnosis

   In patients receiving didanosine, zalcitabine, or stavudine, peripheral neuropathy is usually assumed to be medication-related. Diagnosis is made when symptoms regress spontaneously or when they disappear in response to a change in ARV medication.

   c. Treatment

   **Recommendations:**

   ARV-related neuropathy is often self-limited, and in mild cases should be treated with pain medications.

   When ARV-related neuropathy is severe, the medication should be discontinued and replaced with another drug.

   ARV-related neuropathic symptoms usually revert after cessation of the medication. Occasionally symptoms may continue to worsen or take up to 100 days to resolve.
E. HIV-Related Neuropathy/Myopathy/Myelopathy

1. HIV Polyneuropathy

Peripheral nerve involvement in HIV-infected children can be of several types and may occur in as many as one third of HIV-infected children. The more common type is a sensory distal neuropathy, which usually occurs in older children with advanced HIV disease.

   a. Presentation
   
   HIV-related acute inflammatory demyelinating polyneuropathy is relatively rare in perinatally infected children. The clinical presentation is the same as that seen with Guillain-Barré syndrome.

   b. Diagnosis

   **Recommendation:**

   Clinical evaluation for HIV polyneuropathy (presumed to be unrelated to ARV therapy) should include an electromyogram, nerve conduction studies, lumbar puncture, and, depending on severity and type of neuropathy, a nerve biopsy.

   Sensory distal neuropathy is indistinguishable from the sensory neuropathy seen as a side effect of ARV treatment with didanosine, zalcitabine, or stavudine. Because of lower doses of didanosine (90-150 mg/m² q12h) used in current regimens, the infrequent use of zalcitabine, and the less frequent occurrence with stavudine, most sensory neuropathies are currently due to advanced HIV disease rather than to ARV exposure.

   Nerve conduction tests may be normal with isolated sensory neuropathies. Demyelinating neuropathies typically result in elevated protein without pleocytosis, but CSF may be normal early in the course of the illness.

   c. Treatment

   **Recommendation:**

   When warranted, treatment of demyelinating polyneuropathies is the same as that for inflammatory demyelinating polyneuropathies. Treatment should be given in consultation with a neurologist. Plasmapheresis and intravenous immunoglobulin are both efficacious for treating acute demyelinating polyneuropathies.

   HIV-related neuropathy may improve with heightened control of HIV replication. Neuropathic pain may respond to palliative treatment with gabapentin, carbamazepine, or amitriptyline.

2. HIV Myopathy

Inflammatory myopathy (polymyositis) is rare in HIV-infected children. In adults, toxic mitochondrial myopathy induced by NRTIs has been described, related to duration but not to dosage of zidovudine. It usually accompanies an inflammatory myopathy.

   a. Presentation

   Clinical findings include proximal muscle weakness, myalgias, and increase in serum creatine kinase.

   b. Diagnosis

   **Recommendation:**

   Diagnosis of HIV myopathy is made by clinical observations and evidence of myopathic changes on electromyogram. Mitochondrial myopathy can be diagnosed by muscle biopsy and respiratory chain assays.
c. Treatment

**RECOMMENDATION:**

Discontinuation of a specific NRTI and its replacement with another ARV agent should be considered in patients with myopathy. Prednisone should be considered in patients with myopathy.

3. HIV Myelopathy

Spinal cord involvement is commonly noted in autopsies of adults with HIV infection but is rare among children with HIV infection.

a. Presentation

Spinal cord pathology of affected children may show demyelinating changes of the corticospinal tracts and vacuolar changes or myelitis attributable to HIV-1 or other viruses (e.g., cytomegalovirus).¹⁴

b. Diagnosis

**RECOMMENDATIONS:**

HIV myelopathy should be suspected in an HIV-infected child when spastic paraparesis (bilateral lower extremity hypertonia) without cognitive decline is the predominant neurologic finding.

MRI of the brain should be performed to exclude bilateral cerebral involvement mimicking spinal compromise.

Magnetic resonance of the spine is usually normal but occasionally may show a high signal intensity on T2 consistent with demyelination. Abnormalities in CSF, when present, are nonspecific (see Section A: HIV Encephalopathy). Myelopathy may be suspected clinically, but definitive diagnosis cannot be made without a brain biopsy, which is rarely performed in the absence of specific additional treatment options.

c. Treatment

HIV myelopathy should be treated with the same ARV agents used to treat symptomatic HIV disease, with the goal of achieving low to undetectable viral load levels on PCR testing and reversal of immune suppression.

 Arrest of HIV myelopathy and gradual resolution of the neurological signs and symptoms are usually achieved with effective response to HAART (decreased viral load and immune function restoration).

F. Seizures

**RECOMMENDATIONS:**

As in non-HIV-infected children, electroencephalogram testing, in addition to an MRI scan and lumbar puncture, should be performed if indicated in the setting of seizures.

Simple febrile seizures (single, brief, generalized tonic-clonic seizure) with a clear source of infection do not warrant a lumbar puncture or electroencephalogram. A lumbar puncture to exclude meningitis or encephalitis should be performed in children with complex febrile seizures, or when there is any question about their mental status, neurological examination, or source of infection.

Patients with unprovoked afebrile seizures should be referred to a neurologist for seizure management.
G. Stroke

HIV infection produces inflammation of cerebral vessels, thereby increasing risk of stroke. In HIV-infected children, the incidence of clinically overt strokes in one pre-HAART autopsy series was approximately 1.3% per year. More than 50% of strokes were hemorrhagic and occurred in patients with thrombocytopenia (especially immune thrombocytopenic purpura) and CNS neoplasia. Currently, strokes are more frequently seen among children with advanced HIV disease or HIV encephalopathy. Non-hemorrhagic strokes and subarachnoid hemorrhage (SAH) were associated with arteriopathy affecting the large vessels of the circle of Willis or the medium to large meningocerebral arteries.

a. Presentation

Clinical signs in patients experiencing stroke include focal clinical signs, seizures, and changes in mental status. HIV-related strokes may be clinically silent, especially among children with advanced HIV encephalopathy.

b. Diagnosis

**RECOMMENDATIONS:**

Strokes should be suspected with the onset of focal clinical signs, seizures, or changes in mental status. When a patient presents with these signs and symptoms, the clinician should consult with a pediatric neurologist.

MRI with diffusion weighted imaging is the most sensitive imaging technique available to identify strokes. An angiogram or angio-MRI may assist in determining the extent of vascular compromise.

Possible cause(s) for stroke (e.g., coagulopathy, neoplasia) should be identified, as well as whether the stroke is hemorrhagic or ischemic.

If subarachnoid hemorrhage occurs without obvious precipitating factors (i.e., trauma, neoplasia, coagulopathy), the rupture of an aneurysm should be suspected, and imaging tests should be obtained (angio-MRI, angiogram).

A neurosurgical consult should be obtained if intraparenchymal hemorrhage, especially with mass effect, or an aneurysm is found.

Hemorrhage is easily identified on a CT scan; however, in cases of ischemic, non-hemorrhagic (bland) strokes, CT images may be normal in the first 24 hours and may need to be repeated. The CT scan should be followed by an MRI with diffusion weighted imaging, which, if negative, excludes cerebral infarction.

c. Treatment

**RECOMMENDATIONS:**

Subarachnoid hemorrhage should be managed by the consulting neurologist and neurosurgeon.

There is no specific drug treatment for HIV-related ischemic strokes. A rehabilitation medicine specialist should be consulted early in the course of a stroke.

All patients with subarachnoid hemorrhage should be monitored in intensive care, and neurological examination should be performed frequently with attention directed to changes in mental status.

Increased intracranial pressure should be treated as necessary.
REFERENCES


