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HIV and Neurological Diseases

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Neurological manifestations are the initial symptoms of HIV infection in about 10 to 20% of patients. HIV enters the brain as early as two days after infection, and persists throughout the course of the disease. About 60% of those with advanced AIDS will have clinically evident Neurological dysfunction. Autopsy studies have demonstrated pathological abnormities of the nervous system in 75 to 90% of cases.

All levels of the nervous system may be involved and the degree of involvement is independent of the CD4 cell level, *follow to Tables*

Table 1, Neurological involvement in HIV infection

HIV related	OI related
• Acute aseptic meningitis • Chronic meningitis • HIV encephalopathy (AIDS dementia) • Vacuolar myelopathy • Peripheral neuropathy • Myopathy	• Cryptococcal meningitis • Cerebral toxoplasmosis • CMV retinitis and encephalitis • Progressive multifocal leukoencephalopathy (PML) • Primary CNS lymphoma • TB • Syphilis

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Table 2, Neurological syndromes and opportunistic infection in AIDS (Aetiological Diagnoses)

Syndrome	Clinical features	Aetiology
Meningitis	Headache, fever, nausea, vomining, Altered consciousness	Cryptococcosis, syphilis, listeriosis, tuberculosis
Focal cerebral lesions	Headache, focal signs, convulsions	Toxoplasmosis, progressive multifocal leukoencephalopathy (PML), syphilis, cytomegalovirus
Encephalitis	Cognitive impairment, psychiatric, features, altered consciousness	Cytomegalovirus, herpes simplex, toxoplasmosis
Myelitis	Sensory disturbances, paraparesis, sphincter disturbance	Cytomegalovirus, herpes simplex, varicella zoster, syphilis, toxoplasmosis

Table 3, Conditions of the neurological system

Aetiology	Presenting signs and symptoms	Diagnostic (Laboratory, X-ray, etc)	Management and Treatment	Unique Features, Caveats
Toxoplasma gondii (toxoplasmosis)	*Clinical symptoms may evolve in less than 2 weeks* • Headache (Severe, Localized) • Fever • Confusion • Myalgia • Arthralgia • Focal neurogical defects such as seizures • Hemiparesis • Hemiplegia, • Crebellar, • Tremor, • Cranial nerve • Palsies, • Hemisensory	Available at CT scan or MRI Toxoplasma lgG titre In a resource-constrained setting: diagnosis based on clinical symptoms CT scan or MRI findings: multiple ring lesions in the cerebral hemispheres An HIV infected individual presenting with typical symptoms	Treatment for acute phase >6 weeks Pyrimethamine 100-200 mg loading dose, than 50-100 mg/day PO + folinic (or folic) acid 10 mg/day Po + sulfadiazine 1-2 g qid (Dexamethasone 4 mg PO or IV q 6 h for mass effect) OR	Usually occurs when CD4 count <100 cells/mm^3 Clinical response in 1 week and MRI response expected in 2 weeks Check blood picture regularly as the relatively high doses of drugs can lead to toxicities. Leucopenia,

	loss, • Visual problems or blindness, • Personality changes and cognitive disorders	and normal cerebrospinal fluid (CSF) findings should be given treatment for toxoplasmosis. CSF values Protein: 10-150/ml WBC: 0-40 (monocytes) Blood: full blood count (FBC)	TMP/SMX 5/25 mg/kg daily OR Clindamycin (600 mg tid) + Pyrimethamine 100 mg daily loading does Followed by 50 mg daily + folinic acid 10 mg daily ***Maintenance*** Preferred regimen: Suppressive therapy required after a patient has had toxoplasmosis Pyrimethamine 25-75 mg PO qid + folinic acid 10 mg qid + sulfadiazine 0.501.0 g PO qid (50% of acute dose) Give dapsone PO 100 mg once daily or clindamycin IV (or oral) 600 mg qid pr atovaquine 750 mg PO qid Eptoin 50-100 mg bid or tid or tegretol 100-200 mg bid or	ombocytopenia and rash are common. Folinic acid reduces the risk of yelosuppresion During treatment, advise patients to maintain a high fluid intake and urine output. Secondary prophylaxia may be discontinued if free of toxoplasma encephalitis; and sustained CD4 + T lymphocyte count of > 200 cells/mm^3 for >6 months of ART

			tid (to be started only if the patient has convulsions)	
Mycobacterial infection –M Tuberculosis (TB meningitis)	• Gradual onset of headache and consciousness • Low-grade evening fever Night sweats • Weight loss • Neck stiffness and positive Kernig sigh • Cranial nerve palsies from exudate around base of the brain	Lumbar puncture CSF microspcopy CSF may be cloudy		CD4<350 cells/mm^3 Up to 10% of AIDS patient who present with TB show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne. Always exclude cryptococcal meningitis by CFS microscopy (India ink stain)
Strept Pheumoniae, Neisseria, meningitides (meningitis)	• Fever • Headache • Stiff neck • Photophobia • Vomiting • Malaise • Irritability • Drowsiness • Coma • Symptoms tend to present within 1 week of infection. • May be preceded by a prodromal respiratory illness or score	CFS examination Full blood count Common finding; CFS shows increased pressure, cell count 100-10000/mm3 and decreased glucose <40 mg/dl or <50% of the simultaneous glucose blood level Gram stained smear of a spun sediment of CSF can reveal the	Penicillin (24 million units daily in divided doses every 2 to 3 hours) OR ampicillin (12 g daily in divided doses every 2-3 hours) OR chloramphenicol (4-6 g IV/day) Treatment should be	Often encountered during late stages of HIV disease. Prompt diagnosis and aggressive management and treatment ensure a quick recovery.

	throat	aetiological agent	continued for 10-14 days. Crystalline penicillin 2-3 mega units and chloramphenicol 500-700/750 mg 6 hourly for 10-14 days	
***Cryptococcus neoformans* (cryptococcal meningitis)**	• Presentation usually nonspecific at onset, which may be true for > 1 month • Protracted headache and fever may be the only signs • Nausea, vomiting and stiff neck may be absent and focal neurological signs uncommon. • Extraneural symptoms include skin lesions, pneumonitis, pleural effusion and retinitis • Fever, malaise and nuchal pain signify a worse prognosis, and nausea, vomiting and altered mental status occur in the terminal stages	CSF values: Protein 30-150 mg/dl WBC: 0-100 (monocytes) Glucose decreased: 50-70 mg/dl Culture positive: 95-100% India ink positive: 60-80% Crypt Ag nearly 100% sensitive and specific India ink staining of spinal fluid Test spinal fluid and/or serum for cryptococcal antigen	Preferred regimen: Amphotericin B 0.7 mg/kg/day IV + flucy-tosine 100 mg/kg/day POx 14 days, followed by fluconazole 400 mg/day x 8-10 weeks Finally, maintenance therapy with fluconazole 200 mg/day for life Alternate regimen: Amphotericin B 0.7 mg/ kg/day IV + flucytosine 100 mg/kg/day POx 14 days followed by itraconazole 200 mg bid for 8 weeks Fluconazole 400 mg/day PO x 8 weeks,followed by 200 mg once daily Itraconazole	If untreated, it is slowly progressive and ultimately fatal. It occurs most often in patients with a CD4 count <100 cells/mm^3 Headache is secondary to fungal accumulation, so the headache increases gradually overtime, goes away and then comes back and is harder to get rid of. Then it becomes continuous, and this is what the patient reports Repeated LP might be indicated as adjunctive therapy among

			200 mg PO tid x 3 days, then 200 mg PO bid x 8 weeks after initial treatment with amphotericin Fluconazole 400 mg/day PO + flucytosine 100 mg/ kg/day PO	patients with increased intracranial pressure Discontinuation of antifungal therapy can be considered among patients who remain asymptomatic, with CD4+T-lymphocyte count>100-200 cells/mm3 for >6 months
Cytomegalovirus (CMV)	• Fever ± delirium, lethargy, disorientation, malaise. Headache most common • Stiff neck, photophobia, cranial nerve deficits less common • No focal • Neurological deficits • Gastrointestinal symptoms: diarrhoea, colitis, oesophageal ulceration appear in 12-15% of patients • Respiratory symptoms, i.e. pneumonitis, present in -1%	Retinal exam to check for changes Consult an ophthalmologist. CMV retinitis, characterized by creamy yellow white, haemorrhagic, full- thickness retinal opacification, which can cause visual loss and lead to blindness if untreated; patient may be asymptomatic or complain of floaters, diminished acuity or visual field defects. Retinal detachment if disease is extensive UGI endoscopy when indicated	Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21 days; ganciclovir 5 mg/kg IV bid x 14-21 days, then valganciclovir 900 mg PO qid Patients without immune recovery will need to be on maintenance therapy lifelong for retinitis Extraocular: ganciclovir and/or foscarnet	Evolution <2 weeks CD4 count <100 cells/mm^3 Although any part of the retina may be involved, there is a predilection for the posterior pole; involvement of the optic nerve head and macular region is common Treatment is very expensive and usually not available. CMV management needs special care.

				Therefore, early referral is essential
Progressive multifocal leukoenceph-alopathy (PML)	• Afebrile, alert, no headache • Progressively impaired speech, vision, motor function • Cranial nerve deficits and cortical blindness • Cognition affected relatively late	CT brain scan may be normal or remarkable for areas of diminished density or demyelination (deterioration of the covering of the nerve) PCR of CSF for detection of the James Canyon (JC) virus JC virus PCR positive in about 60% of cases Differential diagnosis: Toxoplasmosis, primary CNS lymphoma Definitive diagnosis is by brain biopsy (if available)	There is no treatment for this illness ART can improve symptoms and prolong life	An end-stage complication of HIV, caused by the JC virus PML is rare in the general community, but relatively common in HIV infection (affecting 4% of all AIDS patients). Routine testing for HIV should be considered for any patient with PML. Evolution: weeks to months Usually occurs when CD4 count <100 cells/ mm^3
Primary CNS lymphoma	• Disease • progresses slowly over a few weeks • Afebrile; headache • Focal and multifocal neurological deficits (confusion, hemiplegia, seizures) • Mental status change (60%,	CT scan/MRI Location: preventricular in one or more sites Prominent oedema, irregular and solid on enhancement CSF: Normal—30-50% Protein—10-150/ml WBC—0-100 (monocytes) Cytology positive	There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative Corticosteroids can also help some patients	Primary CNS lymphoma is rare in the general community, but affects about 2% of AIDS patients Survival after diagnosis is usually limited (a few months only).

	personality or behavioural • Seizures (15%)	in <5% Suspect when toxoplasma IgG is negative or there is failure to respond to empirical treatment for toxoplasmosis		Typical end-stage complication of HIV disease Evolution: 2-8 weeks Usually occurs when CD4 count <100 cells/ mm^3
AIDS dementia complex (ADC) HIV-associated dementia [HAD]	• In up to 10% of patients, it is the first manifestation of HIV disease. • Afebrile; general lethargy • Triad of cognitive, motor and behavioural dysfunction • Early: • concentration and memory deficits, • inattention, motor incoordination, ataxia, depression, emotional lability • Late: global dementia, paraplegia, mutism The frequency in all patients is 10-15%	Neuropsychological tests show subcortical dementia Mini-mental examinations not very sensitive	Possible benefit from antiretroviral regimens with agents that penetrate the CNS (AZT, d4T, ABC, nevirapine) Benefit of AZT at higher dose for mild or moderately severe cases is established; monitor therapy with neurocognitive tests Anecdotal experience indicates response to ART, if started early Sedation for those who are agitated and aggressive—use smaller	Prevalence increases with improvement in general management of various Ols because patients live long enough to develop severe immune suppression. Patients present with a demeanour similar to Parkinson disease and may even be misdiagnosed as such

			doses initially to avoid oversedation Close monitoring: to prevent self-harm to ensure adequate nutrition to diagnose and treat Ols early	

Aseptic meningitis

It may occur as one of the manifestations of acute HIV syndrome. The onset may be several weeks after the other manifestations of the acute HIV syndrome. There may be retro-orbital pain, confusion, irritability, polyneuropathy, polyradiculopathy, facial palsy and weakness. Seizures and Guillain-Barre syndrome may occur. HIV can be demonstrated and cultured in the CSF but not in the blood. Treatment is supportive.

Acute bacterial meningitis

Acute bacterial meningitis occurs with equal frequency in HIV-infected and -uninfected persons. Common organisms include S. *pneumoniae, H. influenzae* and *N. meningitides. Jhe* symptoms and signs include fever, headache, stiff neck, photophobia, vomiting, malaise, irritability, drowsiness and coma. Symptoms tend to present within one week of infection, and may be preceded by a prodromal respiratory illness or sore throat. On examination, the CSF shows increased pressure, a high cell count (100-10 000/mm^3), increased protein (>100 mg/dl) and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level). A Gram-stained smear of spun sediment of the CSF may reveal the aetiological agent. A full blood count should also be done. Where available, CT scan or MRI may be performed to evaluate focal neurological deficits. Specific treatment depends on the aetiological agent.

CRYPTOCOCCAL MENINGITIS

It is caused by *Cryptococcus neoformans* var *neoformans.* It is the most common fungal meningitis in AIDS and affects about 10%.The majority of cases are seen when the CD4+ counts are <50 cells/mm^3. It commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise and headache. Classical symptoms and signs such as neck stiffness or photophobia occurs only in one-fourth to one-third of AIDS patients. Some patients may present with encephalopathic symptoms such as lethargy, altered mentation, personality changes and memory loss. Some patients have disseminated disease without concurrent meningitis. Approximately half of them have pulmonary involvement. Skin lesions may be seen.

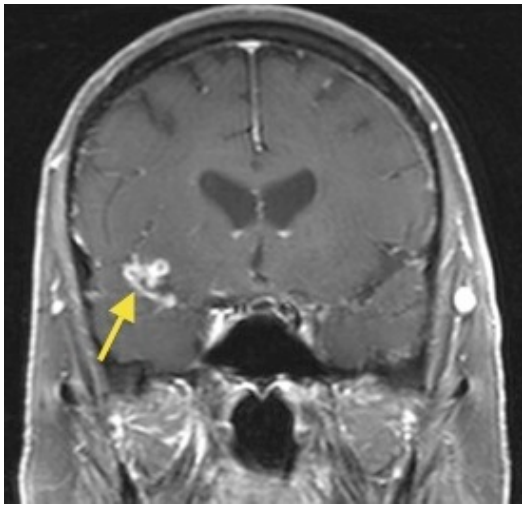


Figure 1; MR angiography of large vessel stenosis after cryptococcal meningitis

DIAGNOSIS

Analysis of the CSF usually shows mildly raised protein, normal or slightly low glucose, with an increased white cell count (5-100 cells: predominantly mononuclear lymphocytes).The opening pressure of the CSF is elevated. India ink staining demonstrates the organism. Culture of the CSF grows *Cryptococcus.* Up to 75% of those with HIV-associated cryptococcal meningitis have positive fungal blood cultures. Serum cryptococcal antigen might be useful in making an initial diagnosis.

Diagnosis is said to be *confirmed when Cryptococcus* is identified in the CSF or CNS tissue by positive culture or histopathology.

Diagnosis is said to be probable in the presence of:

- Compatible clinical syndrome that includes fever and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/or focal deficits.
- Positive serum cryptococcal antigen
- Specific antifungal therapy initiated or recommended.
- Diagnosis is considered *possible* when:
    - There is a compatible clinical syndrome that includes fever and one or more of the following signs or symptoms of meningitis: headache, altered mental status, stiff neck and/or photophobia, seizures and/ or focal deficits, and
    - Specific antifungal therapy initiated or recommended.

TREATMENT

Untreated, cryptococcal meningitis is fatal. The recommended initial treatment for acute disease is amphotericin B for 2 weeks, followed by fluconazole alone for an additional 8 weeks. This approach has a mortality of <10% and a mycological response of 70%. If new symptoms or

clinical findings occur after 2 weeks of treatment, a repeat LP should be performed. Serial measurement of CSF cryptococcal antigen might be useful but require repeated LPs and is not routinely recommended. Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances.

Lipid formulations of amphotericin B are fairly effective in doses of 4 mg/kg daily. However, under the national programme, non-lipid formulations of amphotericin B are provided. Combination therapy with fluconazole (400-800 mg/daily) and flucytosine is also effective for treating AIDS-associated cryptococcal meningitis but the latter is not available in India.

Primary therapy

Acute - Induction: Amphotericin B (0.7 mg/kg/d) ± 5- flucytosine 25 mg/kg qid x 14 days
Consolidation: Fluconazole 400 mg/day for 8-10 weeks or until the CSF is sterile.

Maintenance: Fluconazole 200 mg/day lifelong (stop when the CD4+ count is >200 cells/mm^3 for 3 months)

Lumbar puncture: Repeated LPs are needed if the CSF opening pressure is >250 mmH_2O.The initial LP should reduce the opening pressure by 50%. Daily LPs are needed to maintain the opening pressure at <200 mm CSF. LP may be stopped once the opening pressure has been normal for several consecutive days. CSF shunting should be considered when daily LPs are no longer tolerated or when the signs and symptoms of cerebral oedema are not relieved. Acetazolamide has no role in reducing the intracranial pressure.

Maintenance therapy

Without maintenance therapy, relapse occurs in 50-60% of patients within 6 months. Maintenance therapy is given with fluconazole at a dose of 200 mg daily lifelong or until the CD4+ count remains above 200 cells/ mm^3 for 3-6 months in a patient on HAART. Alternative therapy is possible with amphotericin B, voriconazole, and high-dose fluconazole + terbinafin.
Fluconazole has drug interactions with nevirapine used in HAART and leads to hepatotoxicity in 25% of patients receiving both drugs. This combination has to be used with caution and with regular monitoring of liver function tests.

Failure of therapy

With maintenance therapy, relapses are uncommon and usually related to noncompliance. Rarely, drug resistance and drug interactions which lower fluconazole levels may be responsible. Monitoring serum cryptococcal antigen titres is not useful in predicting relapse.

CEREBRAL TOXOPLASMOSIS

It is caused by the protozoon *Toxoplasma gondii*. Although *T. gondii* usually causes encephalitis, it also causes disease in various organs including the eyes and lungs. Infection is acquired by

contact with cats or birds, and eating undercooked meat, especially pork, lamb or venison. Encephalitis occurs from reactivation of latent cysts, and is most common among HIV-positive people with CD4 counts <50 cells/mm^3. Anti-*Toxoplasma* antibodies are not protective and only indicate prior infection.

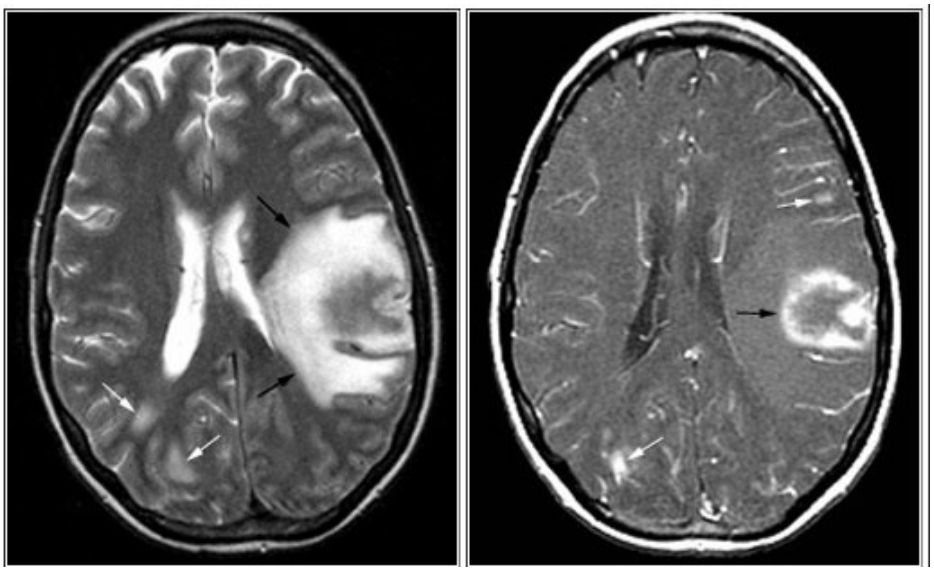


Figure 2, (Left) Axial T2-Weighted image shows a left temporal lobe mass with surrounding edema (black arrows) other small lesions are seen in right parietal lobe (white arrows)
Figure 3, (Right) Axial contrast T1-weighted image shows nodular and irregular ring enhancement (black arrows), small enhancing lesions are seen in bilateral cerebral hemispheres (white arrows)

CLINICAL FEATURES

Symptoms include headache, fever, confusion, progressive focal neurological deficits, seizures, abnormal behaviour, motor weakness and coma.

DIAGNOSIS

Serum IgG and IgM *anti-Toxoplasma* antibodies can be estimated, but do not indicate active disease. Polymerase chain reaction (PCR) tests have high specificity but low sensitivity. CT or MRI scans showing focal lesions may be helpful in making a diagnosis, although differentiation from other CNS diseases such as lymphoma may be difficult. Newer imaging devices such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) scans may be more helpful, although more expensive. Stereotactic CT-guided brain biopsy is reserved for patients who fail to respond to therapy.

TREATMENT

If CNS toxoplasmosis is suspected, treatment should precede confirmation of diagnosis. Brain biopsy is required only if the patient does not respond to treatment. Biopsy may be required to diagnose toxoplasmosis of other tissues such as the lungs.

A combination of pyrimethamine, sulfadiazine and leucovorin is the recommended initial regimen. Pyrimethamine is started orally at a dose of 100-200 mg daily, followed by a lower dose. It penetrates the brain parenchyma even if there is no inflammation. Leucovorin contains folate, and decreases the haematological side-effects of pyrimethamine. Sulfadiazine is given orally four times a day at a dose of 4-8 g/day. Clindamycin or TMP-SMX can be used in case sulfadiazine is not available.

Other combnations used include: atovaquone + sulfadiazine; atovaquone + pyrimethamine + leucovorin; azithromycin + pyrimethamine + leucovorin. Dapsone, 5-fluorouracil, clarithromycin, and minocycline have all been used with in various permutations and combinations.

Initially, high doses of these medications are given for 4-6 weeks followed by lower doses as maintenance therapy to prevent recurrence. Maintenance therapy can be discontinued in an asymptomatic patient on HAART with a CD4 count >200 cells/mm^3 for at least 6 months. It has to be restarted if the CD4 count falls or the MRI/CT shows persistent cerebral mass lesions.

Corticosteroids such as dexamethasone may help control inflammation of the brain in patients with focal neurological symptoms. However, they need to be used carefully, given that corticosteroids may precipitate other Ols. Anticonvulsants should be administered only if there is a history of seizures and should not be used prophylactically.

ADVERSE EVENTS

Pyrimethamine can cause rash, nausea and bone marrow suppression. Sulfadiazine and TMP-SMX can cause rash, fever, leucopenia, hepatitis, nausea, vomiting, diarrhoea, crystalluria, hepatotoxicity and *Clostridium difficile* colitis. Drug interactions between anticonvulsants and ART may necessitate adjustment of dosages.

PREVENTION

The best way to prevent toxoplasmosis is to avoid contact with *T. gondii*. Meats such as pork, lamb or venison should be well cooked. Precautions should be followed while handling cats and birds.

Daily TMP-SMX is the most effective regimen to prevent toxoplasmosis. For patients who are allergic, dapsone + pyrimethamine + folic acid once a week is a good alternative.

AIDS DEMENTIA COMPLEX (ADC)

ADC or HIV-associated dementia (HAD) is different from other 01s in that the disease is caused by the HIV itself, which enters the brain as early as two days after infection. HIV can then damage the nerve cells in the brain. ADC is more likely with CD4 counts <200 cells/mm^3.

Between 20% and 35% of all HIV-positive people eventually develop ADC at CD4 counts of 100-200 cells/mm^3.

There is acquired and slowly progressive cognitive decline, motor and behavioural changes, and non-focal or diffuse CNS signs. Signs of early dementia include: trouble learning new things, difficulty remembering things that happened in the past, changes in behaviour, confusion and depression. Advanced dementia produces abnormalities of speech, balance, vision, gait, and loss of bladder control. It can also lead to mania (exaggerated feeling of well-being) or psychosis (loss of contact with reality).

DIAGNOSIS

ADC is a *diagnosis of exclusion.* The CSF findings are non-specific and CT/MRI shows only cerebral atrophy and ventricular dilatation. Several AIDS-related diseases such as toxoplasmosis, lymphoma and PML can cause symptoms similar to those of ADC.

TREATMENT

HAART is the most effective treatment and ARV regimens should include agents that penetrate the CNS (AZT, d4T, ABC, nevirapine). Even though HAART can treat the underlying cause, it may not effectively treat the symptoms, and may actually worsen them in some cases. Additional supportive treatment strategies may be needed in some cases. Sedation is required for those who are agitated and aggressive, with smaller initial doses to avoid over sedation. Close monitoring to prevent self-harm, adequate nutrition, early diagnosis and treatment of other Ols, and psychological support for caregivers are important accessories to therapy.

PRIMARY CNS LYMPHOMA

Primary CNS lymphoma is rare in the general community, but affects about 2% of HIV/AIDS patients. Survival after diagnosis is usually limited to a few months only. It is a typical end-stage complication of HIV disease. The disease evolves over 2-8 weeks. It usually occurs when the CD4 count is <100 cells/mm^3.

Disease progression occurs over a few weeks. Patients are afebrile, with headache and focal neurological deficits (confusion, hemiplegia, seizures). They may present with mental status changes (60%), and personality or behavioural changes. Seizures occur in 15%.

DIAGNOSIS

CT scan/MRI shows periventricular irregular lesions which appear solid on enhancement in one or more sites. There is prominent oedema. Lymphoma is suspected when the *Toxoplasma* IgG is negative or there is failure to respond to empirical treatment for toxoplasmosis. Neuropsychological tests show subcortical dementia. Mini-mental status examinations are not very sensitive. CSF analysis is normal in 30-50% of patients. The CSF cytology is positive for malignant cells in <5% of patients.

TREATMENT

There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative. Corticosteroids can also help some patients.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML results from multifocal demyelination caused by the James Canyon (JC) virus. It is a neurological condition that progresses relatively rapidly over weeks to months with cognitive dysfunction, ataxia, aphasia, cranial nerve deficits, hemiparesis or quadriparesis, and eventually coma.

DIAGNOSIS

Typical CTscan findings include single or multiple hypodense, non-enhancing cerebral white matter lesions. Diagnosis is *confirmed* if histopathology or in situ hybridization from a brain biopsy or CSF PCR shows the JC virus.

Diagnosis is considered *probable* if the clinical presentation (subacute progressive focal neurological deficits including hemiparesis, field deficits, ataxia, or other abnormality referable to dysfunction of a specific brain region, and does not include cognitive impairment alone) and MRI findings are compatible with PML

Diagnosis is considered *possible* if the clinical presentation is consistent with PML, and focal lesions without mass effect or enhancement are seen on CT or MRI of brain.

TREATMENT

HAART is the only effective treatment and many studies have used even more than three drugs in HAART (mega HAART) but the current recommendation is triple-drug ART only.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) or herpes virus type 4 is a double-stranded DNA virus. Infection is common, and latency follows infection. Almost all homosexual or bisexual men and more than 75% of all HIV-infected people carry the virus. A small percentage with severely compromised immune systems actually develops CMV disease when immunosuppressant reactivates inherent CMV to cause disseminated or localized end- organ disease. Around 30% of patients with AIDS develop CMV retinitis sometime between the diagnosis of AIDS and death.

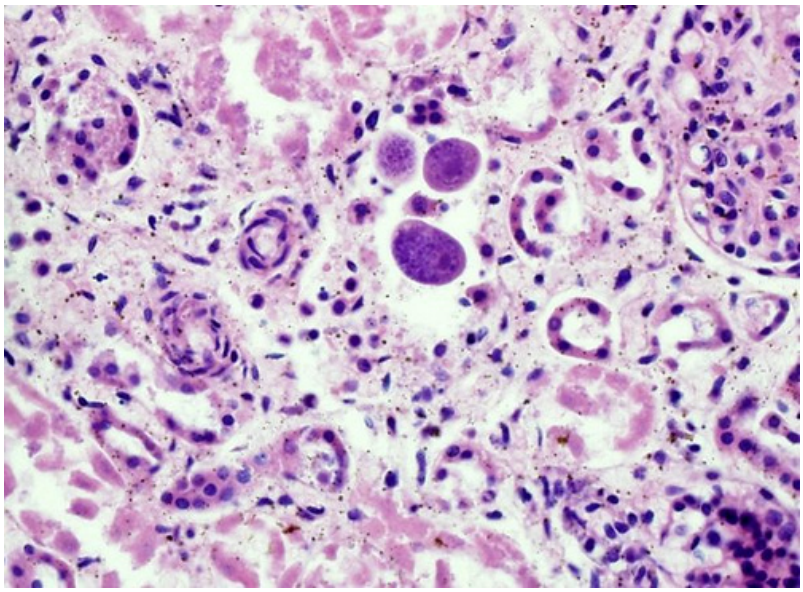


Figure 4, Cytomegalovirus Infection

CLINICAL MANIFESTATIONS

Retinitis is the most common manifestation. CMV retinitis usually occurs unilaterally, but may be bilateral. Peripheral retinitis might be asymptomatic, or may present with floaters, scotomata or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula are associated with decreased visual acuity or central field defects. The characteristic ophthalmological appearance includes perivascular fluffy yellow-white retinal infiltrates, and focal necrotizing retinitis with or without intraretinal haemorrhage. There is very little inflammation of the vitreous. Blood vessels near the lesions might be sheathed. The lesions might have a granular appearance. In the absence of HAART or specific anti-CMV therapy, retinitis progresses and causes a characteristic brushfire pattern, usually within 10-21 days after presentation. A granular, white leading edge forms, eventually resulting in an atrophic and gliotic scar leading to blindness.

CMV colitis is the second most common manifestation, and occurs in 5-10% of patients with CMV infection. The most frequent clinical manifestations are fever, weight loss, anorexia, abdominal pain, diarrhoea and malaise. Extensive mucosal haemorrhage and perforation can cause life-threatening complications.

CMV oesophagitis occurs in less than 5% and causes fever, odynophagia, nausea and mid-epigastric or retrosternal discomfort. Pneumonitis is uncommon, but can cause shortness of breath, dyspnoea on exertion, a nonproductive cough and hypoxaemia.

CMV neurological disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Patients with dementia typically have lethargy, confusion and fever.The condition might mimic HIV dementia.

DIAGNOSIS

CMV viraemia can be detected by PCR, antigen assays or blood culture. A negative IgG antibody suggests that CMV is unlikely to have caused disease. Patients with advanced immunosuppression might serorevert from being antibody-positive to -negative.

The diagnosis of CMV retinitis is based on characteristic retinal changes in the fundus. CMV colitis is recognized by mucosal ulcerations on endoscopic examination and colonoscopic or rectal biopsy. Histopathology demonstrates characteristic intranuclear and intracytoplasmic inclusions. The diagnosis of CMV oesophagitis is established by the presence of extensive large, shallow ulcers in the distal oesophagus. Biopsy shows intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer. Culturing CMV from a biopsy or cells brushed from the colon or the oesophagus is not sufficient to establish the diagnosis.

The diagnosis of CMV pneumonitis should be made with X-ray evidence of pulmonary interstitial infiltrates. CMV inclusion bodies can be identified in the lung tissue.

CMV neurological disease is diagnosed on the basis of the clinical syndrome and the presence of CMV in the CSF or brain tissue. The use of PCR enhances the detection of CMV. The CSF generally demonstrates lymphocytic pleocytosis; there may be a mixture of neutrophils and lymphocytes. The glucose levels may be low-to-normal, and protein levels normal-to-high. Periventricular enhancement on CT or MRI images helps to distinguish CMV ventriculoencephalitis from HIV-1-related neurological disease.

LABORATORY DIAGNOSIS

The diagnosis of CMV infection requires laboratory confirmation and cannot be made on clinical grounds alone. CMV antigen detection can be done using commercially available kits. Virus isolation and PCR can be done by State/National Laboratories.

The presence of CMV IgM antibody is useful but not a reliable indicator of an acute infection. IgM antibodies may not be present during an active infection (false-negative) or may persist for such a long time that the finding may not be diagnostic (false-positive).

Polymerase chain reaction (PCR): PCR using primers from a part of a genome coding for immediate early antigen has been used but this method is oversensitive. RT-PCR for CMV RNA or quantitative PCR to determine the CMV load is more useful in detecting active infection or monitoring antiviral therapy.

TREATMENT

Treatment suppresses the infection and prevents relapse. It cannot reverse damage that has already occurred. Treatment for CMV retinitis can be given intravenously, orally, or directly into the eye(s). It consists of two phases: induction therapy and maintenance therapy. Induction therapy usually takes two or three weeks.

Maintenance therapy is intended to prevent the virus from causing a relapse. This may be discontinued once the CD4 count increases to more than 200 cells/mm^3 for at least 6 months following HAART. The treatment of choice is ganciclovir 5 mg/kg twice daily IV (induction) followed by capsules (maintenance), and can treat all forms of CMV disease. IV ganciclovir is given twice daily for two to three weeks and then IV once daily 5-7 days a week. Oral treatment is given as 1000 mg capsules three times daily.

Intravenous foscarnet can be used to treat CMV retinitis and all other forms of CMV disease. It is given 2-3 times daily for two to three weeks and then once a day.

Intravenous cidofovir with probenecid (to help prevent kidney damage) is given once a week for two weeks. It has been studied only in CMV retinitis but might be effective in other forms of the disease.

Valganciclovir may be given orally as two 450 mg tablets twice a day for three weeks, followed by two 450 mg tablets once a day. It is the only treatment for CMV that can be given orally. It has been shown to be as effective as IV ganciclovir for the treatment of CMV retinitis. It has many of the side-effects of IV ganciclovir.

Ganciclovir implants have been used in the past, although they have a high incidence of recurrence and retinal detachment.

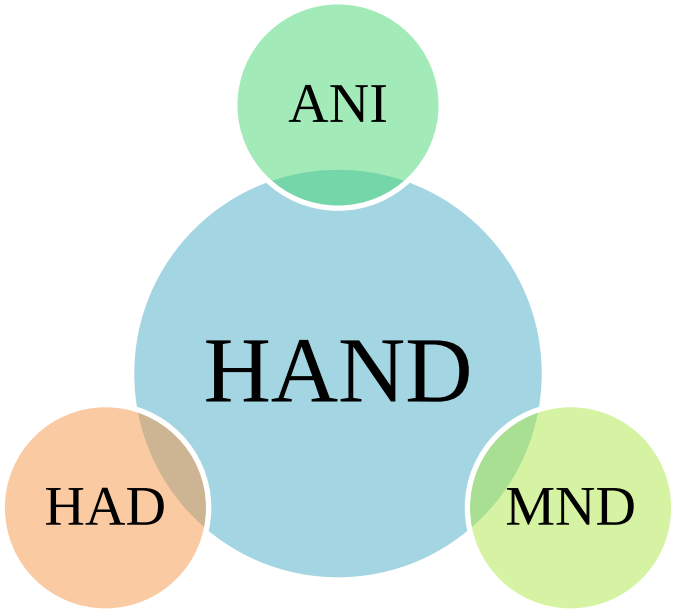
OTHER DISORDERS

HIV Associated Neurocognitive Disorders (HAND) can occur when HIV enters the nervous system and impacts the health of nerve cells. This, in turn, can impair the activity of nerves involved in:

- Attention
- Memory
- Language
- Problem solving
- Decision making
- Confusion
- Forgetfulness
- Behavioral changes
- Headaches

- Gradual weakening and loss of feeling in the arms and legs
- Problems with cognition or movement
- Pain due to nerve damage

TYPES OF HIV ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)



- **Asymptomatic Neurocognitive Impairment (ANI)** is diagnosed if testing shows HIV-associated impairment in cognitive function, but everyday functioning is not affected.
- **Mild Neurocognitive Disorder (MND)** is diagnosed if testing shows HIV-associated impairment in cognitive function, and mild interference in everyday functioning.
- **HIV-associated Dementia (HAD)** is diagnosed if testing shows marked impairment in cognitive function, especially in learning of new information, information processing, and attention or concentration. This impairment significantly limits your ability to function day-to-day at work, home, and during social activities.

DIAGNOSIS

Many factors can contribute to the same types of symptoms as HAND, making diagnosis a complex and challenging task. Depression, other psychiatric disturbances, reactions to medication, and nutritional deficiencies can all lead to similar symptoms. Infections common among people with advanced HIV can also lead to these symptoms, although typically only among those not on cART (e.g. toxoplasmosis, lymphoma, progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis).

An accurate diagnosis of HAND, therefore, requires a comprehensive examination that generally includes a mental status test, a brain scan, and sometimes lab tests on the cerebrospinal fluid (the

fluid that bathes the brain and spinal cord), which are obtained through a procedure known as a spinal tap or lumbar puncture. A mental status exam can help identify whether a person is suffering from memory loss, difficulties with concentration and other thinking processes, mood swings, and other symptoms. The best diagnosis requires a third party (e.g. friend, partner, or other family member) corroborate the behavior/memory changes.

Because no single test definitively answers the question of whether someone has HAND, the final diagnosis is made by weighing all the evidence together. Time and repeated measures are helpful in confirming a diagnosis.

TREATMENT

Although there is no cure for HAND, the single most important treatment is adherence to antiretroviral therapy to maintain a suppressed viral load in the blood. The specific medicines that make up the cART regimen appear to be less important than just being on a regimen. In rare cases, doctors may have to consider how well these medicines get into the central nervous system and there are studies underway to see if some medications may help symptoms better than others. These new findings, however, should not cloud our understanding that suppression of plasma virus to undetectable or unquantifiable levels in blood appears to be most critical.

Knowing the diagnosis is also sometimes therapeutic, as there is stigma and stress related to these symptoms and how they affect daily activities. These can be addressed with proper diagnosis. Knowing that the illness exists may also prompt compensatory approaches and, ultimately, decrease stress and anxiety.

In addition to treating HAND itself, it is important to find ways to treat the secondary symptoms when possible. Anti-depressants, anti-psychotics, and anti-anxiety drugs can help relieve some of the mental distress people with HAND may experience. However, some of these medications may cause complications when taken along with antiretroviral therapy or other drugs; caution is needed in choosing the best approach. Consultation with an HIV-knowledgeable doctor is recommended.

It is also important that patients engage in their own care to prevent factors that can contribute to cognitive symptoms. This includes aggressive treatment of depression, good health care maintenance to address common comorbidities (e.g. hypertension, lipid abnormalities, liver impairment), avoiding non-prescription drugs and excessive alcohol, working with care providers to assure that the medications taken are all required, and exercise. There is growing evidence that physical exercise is important. Optimally, this can be done while engaging in other activities, since social integration and activities may also be helpful. Keeping engaged with enjoyable activites likely translates into benefits.

HOW ARE HAND DIAGNOSED AND TREATED?

Experienced neurologists can diagnose HAND after carefully ruling out other possible causes of the symptoms. They may conduct a thorough neurological exam and history, brain MRI scan, and sometimes lumbar puncture to evaluate the cerebrospinal fluid. Neuropsychological testing can add useful information about the nature and severity of HAND. Talk to your doctor if you think you have symptoms of HAND.

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Image Credit

Figure 1; MR angiography of large vessel stenosis after cryptococcal meningitis by Arnold Kang, David Haynor

Figure 2, (Left) Axial T2-Weighted image shows a left temporal lobe mass with surrounding edema (black arrows) other small lesions are seen in right parietal lobe (white arrows) by Pinterest

Figure 3, (Right) Axial contrast T1-weighted image shows nodular and irregular ring enhancement (black arrows), small enhancing lesions are seen in bilateral cerebral hemispheres (white arrows) by Pinterest

Figure 4, Cytomegalovirus Infection by Flickr