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section 24 Neurological disorders 6100 Lorber B (1997). Listeriosis. Clin Infect Dis, 24, 1–9. Mathisen GE, Johnson JP (1997). Brain abscess. Clin Infect Dis, 25, 763–79. Matthijs BC, et al. (2014). Brain abscess. N Engl J Med, 371, 447–56. Ratnaike TE, et al. (2011). A review of brain abscess surgical treatment— 78 years: aspiration versus excision. World Neurosurgery, 76, 431–6. Report of the Quality Standards Subcommittee of the American Academy of Neurology (1998). Evaluation and management of intracranial mass lesions in AIDS. Neurology, 50, 21–6. Sharma R, Mohandas K, Cooke RPD (2009). Intracranial ab- scesses: changes in epidemiology and management over five decades in Merseyside. Infection, 37, 39–43. 24.11.4 Neurosyphilis and neuro-AIDS Hadi Manji ESSENTIALS Neurosyphilis Invasion of the central nervous system occurs early in the course of syphilis infection. Neurosyphilis causes a meningitis, a myeloradiculopathy due to pachymeningitis, gummatous (granu- lomatous) cord and brain lesions; endarteritis may cause infarction and a low-grade meningoencephalitis affecting the brain results in dementia (general paralysis of the insane) and in the spinal cord, a sensory ataxic syndrome (tabes dorsalis). Clinical features—these are protean: neurosyphilis should always be considered in the diagnosis of neurological disorders without a convincing explanation, including (1) stroke—especially in young patients; (2) ocular abnormalities (e.g. optic neuritis/neuropathy, choroidoretinitis, pupillary abnormalities); (3) unexplained cranial nerve disease, especially sensorineural deafness and vertigo; (4) de- mentia (5) a sensory ataxia caused by pathology within the dorsal roots and ganglia and the posterior columns (tabes dorsalis). Diagnosis, treatment, and prognosis—diagnosis requires specific serological tests and examination of the cerebrospinal fluid (see Chapter 8.6.37). Treatment with antimicrobials is often curative in patients with meningitic or meningovascular disease, but is only partially effective in those with late forms of dementia or tabes. Follow-up after treatment should include repeat examinations of the cerebrospinal fluid until the cell count is restored to normal limits. Neurological complications of HIV infection The neurological consequences of HIV infection include (1) op- portunistic infections—toxoplasma encephalitis, cryptococcal meningitis, tuberculous meningitis, cytomegalovirus retinitis and encephalitis and John Cunningham virus infection causing pro- gressive multifocal leucoencephalopathy; (2) neoplasms—primary central nervous system lymphoma; (3) HIV itself can also affect the central

and peripheral nervous systems causing HIV-associated neurocognitive disorders which, in its most severe form, manifests as a subcortical dementia, a vacuolar myelopathy, and a peripheral neuropathy. The introduction of highly active antiretroviral therapies has greatly reduced the frequency of these complications in patients with access to these treatments. However, newer complications are now increasingly recognized such as a neurological immune reconstitution inflammatory syndrome, a compartmentalization syndrome (cerebrospinal fluid escape). There is a suggestion that some patients may continue to decline cognitively despite having an undetectable plasma viral load. the aetiology of which may be multifactorial including drug toxicity, poor cerebrospinal fluid penetration of some antiretroviral drugs, a low-grade HIV-related immune reconstitution inflammatory syndrome, cerebrovascular disease, and an accelerated ageing processes. Neurosyphilis The incidence of primary and secondary syphilis in the United Kingdom (excluding Scotland) increased from 2500 cases in 2008 to 6000 in 2016. In 2012 there were 5.6 million new cases world- wide. Syphilis, similar to other ulcerating genital infections such as herpes and chancroid, increases by a factor of three the risk for the acquisition and transmission of infection with the HIV, so disease has once again come under scrutiny. T. pallidum has been isolated from the cerebrospinal fluid of up to 40% of neurologic- ally asymptomatic patients with untreated primary and secondary syphilis. Despite this, cohort studies of untreated patients with late syphilis documented an incidence of clinical neurosyphilis of 9.4%. Thus, it would seem as if, at least in the immunocompetent patient, T. pallidum has a low virulence for the central nervous system (CNS). Clinical features (See Table 24.11.4.1.) Acquired syphilis is divided into: (a) an early, infectious stage (this includes primary, secondary, and early latent syphilis in asymptomatic patients where less than 2 years have elapsed since infection (World Health Organization definition)) and (b) the late, noninfectious stage includes late, latent syphilis where in asymp- tomatic patients more than 2 years have elapsed; gummatous (granulomatous) disease which can affect the skin, viscera, men- inges and also the brain parenchma, cardiovascular syphilis, and GPI/tabes). Although there is a rough time course to the develop- ment of the various neurological syndromes, there is considerable overlap; these syndromes are, in reality, part of the spectrum of disease. The broad term ‘neurosyphilis’ includes meningitis (acute and chronic), a myeloradiculopathy due to a pachymeningitis, and granulomatous lesions (gummas) that present as space-occupying lesions within the brain, spinal cord, or epidural space, causing com- pression; meningovascular syphilis, which can occur in both early and late phases of the infection, involves the small- and medium- sized arteries, typically causing an endarteritis (Heubner’s endarter- itis obliterans), results in infarction. The so-called late manifestations

24.11.4 Neurosyphilis and neuro-AIDS 6101 of neurosyphilis result from a low-grade meningoencephalitis. In patients with general paralysis (also called general paralysis of the insane or dementia paralytica), the focus is on the frontotemporal cortex. Therefore, during the early stages, vague symptoms may include personality and mood changes, with impaired faculties of concentration and attention being the presenting features; memory difficulties develop later. In tabes dorsalis (taboparesis), which may coexist with general paralysis, the clinical presentation results from involvement of the dorsal roots and ganglia as well as the posterior columns within the spinal cord, with the clinical presentation of mainly a sensory ataxia. Diabetes can produce a similar clinical pic- ture with a sensory neuropathy and pupillary abnormalities (dia- betic pseudotabes). The optic nerve can be involved with or without other evidence of neurosyphilis, but must always be treated as if it were part of a systemic infection. Uveitis, chorioretinitis, optic neuritis, papillitis, and optic atrophy have all been reported at different stages of the disease.

Extraocular presentations include nerve palsies involving the eye muscles and a superior orbital fissure syndrome. Although the Argyll Robertson pupil may occur in any form of the disease, it is generally encountered in tabes dorsalis. The pupils are small and irregular, being unreactive to light, but constrict normally to ac- commodation and convergence. Unilateral involvement is rare. The light/near dissociation is the result of gliosis in the periaqueductal grey midbrain tegmentum, which may also account for the bilateral ptosis seen in some individuals. Diagnosis Neurosyphilis has a myriad of neurological manifestations and, therefore, the diagnosis enters the differential of most neurological conditions (see Table 24.11.4.1). Treatment in the early stages of the disease (i.e. of the meningitic and meningovascular syndromes) may well result in recovery, whereas the late forms—with general paralysis and tabes dorsalis—may cease to progress with only par- tial recovery. These neurological presentations include stroke, and should enter the differential diagnosis especially in younger patients, chorioretinitis, optic neuropathy of unknown cause, and single or multiple cranial neuropathies, particularly those involving cranial nerve VIII with vertigo and sensorineural deafness. Syphilis ser- ology should be performed routinely in patients with dementia and psychiatric illnesses. The nontreponemal serum reaginic tests, Venereal Diseases Research Laboratory (VDRL) test and rapid plasma reagin test (RPR), are almost always positive in secondary syphilis when the first neurological complications may be encountered. However, a false-negative result may occur due to the prozone phenomenon if undiluted serum is used. This occurs in 1 to 2% of cases of secondary syphilis and is due to blockage of agglutination caused by the satur- ation of antigenic sites by excess antibody. The specific serological tests—T. pallidum haemagglutination test (TPHA), T. pallidum par- ticle agglutination test (TPPA), fluorescent treponemal antibody ab- sorption test (FTA-abs), and the treponemal enzyme immunoassay (EIA)—are invariably positive. In late syphilis (meningovascular syphilis, gummatous, general paralysis, and tabes dorsalis), the serum VDRL/RPR tests are nega- tive in 30% of untreated cases. All the specific tests have a sensitivity approaching 100%, so that a negative treponemal antigen test has an extremely high predictive value for excluding neurosyphilis. It is recommended that all patients with positive syphilis ser- ology who have ocular and/or neurological symptoms and signs should undergo cerebrospinal fluid examination, as should pa- tients with latent infection of unknown duration. In order for these tests to be correctly interpreted, it is important that the cerebro- spinal fluid is not significantly (macroscopically) contaminated with blood. In patients with neurosyphilis there is usually a lymphocytic pleocytosis (>5 cells/μl), with an elevated protein (>0.4 g/l). In the late stages, particularly in tabes, the cerebrospinal fluid may be qui- escent.
A reactive cerebrospinal fluid (CSF) VDRL establishes the diagnosis of active neurosyphilis, but a nonreactive test does not ex- clude it. The sensitivity of the CSF VDRL is 50%, with a specificity of 100%. A nonreactive CSF FTA-abs or TPHA excludes the diagnosis. However, a reactive CSF FTA-abs or TPHA does not establish the diagnosis because the presence of treponemal antibodies in the cere- brospinal fluid could result from passive transfer from the blood, or from a previous episode of treated syphilis. The sensitivity for the CSF FTA-abs is 100%, with a specificity of 30%. The role of the polymerase chain reaction (PCR) in the diagnosis of neurosyphilis is unclear at present, because the technique cannot discriminate between viable and nonviable organisms. T. pallidum DNA has been detected in cerebrospinal fluid up to 3 years after intravenous treatment with penicillin. Table 24.11.4.1 Clinical features of neurosyphilis Syphilitic meningitis Meningovascular General paralysis Tabes dorsalis Time course Acute Within first year during secondary syphilis syndrome (rash, fever, lymphadenopathy, hepatitis, arthritis, glomerulonephritis) Months to years after infection, average 7 years 15–20 years 20–25 years Clinical features Cranial nerve palsies (III, VI,

VII, VIII), hydrocephalus Stroke (hemiparesis, dysphasia), seizures, cranial nerve palsies, encephalitic syndrome, anterior spinal artery syndrome, myelitis Frontal–temporal dementia, psychiatric symptoms (delusions, apathy), personality change, seizures, dysarthria, tremor (tongue, face, hands), optic atrophy Lightning pains (limbs, viscera); loss of pain and temperature (Charcot's joints), joint position (sensory ataxia, positive Romberg's sign), areflexia, Argyll Robertson pupils autonomic and sphincter dysfunction Chronic Myeloradiculopathy due to pachymeningitis

section 24 Neurological disorders 6102 Treatment In patients with symptomatic neurosyphilis or ocular disease, the World Health Organization/United Nations Programme on HIV/ AIDS (WHO/UNAIDS) and the European guideline on the man- agement of syphilis recommend treatment with benzylpenicillin (3–4 million units intravenously every 4 h for 14 days). An alternative is procaine penicillin (1.2–2.4 million IU intramuscularly once daily, plus probenecid 500 mg by mouth four times daily, for 17–21 days). In patients with a history of penicillin allergy, one option is to per- form skin testing to confirm the allergy and to then consider desen- sitization. The other is to treat with doxycycline 200 mg by mouth twice daily for 28 days. After treatment of neurosyphilis, a repeat lumbar puncture should be performed at 6-monthly intervals until the cell count is normal. The cell count should have decreased by 6 months and be entirely normal by 2 years. Syphilis in the era of HIV Since the onset of the AIDS epidemic there have been anecdotal re- ports of an accelerated course of syphilis and of treatment failures in patients who are dually infected. As cell-mediated immunity, which is necessary to eradicate T. pallidum, may be impaired in HIV in- fection, this seems plausible. As a result of altered B-cell function there has also been concern about the validity of the serological tests; however, the current consensus is that there is no difference between HIV-infected and noninfected individuals clinically or serologically. A CSF examination is only recommended in early syphilis if pa- tients have neurological, ocular, or audiological symptoms, as in the non-HIV group. In late syphilis some specialists recommend a CSF examination to exclude asymptomatic neurosyphilis, especially if the CD4 count is less than 350 cells/mm3 and /or the VDRL/RPR titre is more than 1:32, however, there are no data to support this recommendation. Neuro-AIDS (the neurological complications of HIV infection) Soon after the onset of the AIDS epidemic, it became clear that the nervous system was frequently involved. However, opportunistic in- fections, such as toxoplasmosis and cryptococcal meningitis, as well as neoplasms (such as primary central nervous system lymphoma, PCNSL) accounted for only 30% of the neurological problems en- countered. It also became evident that, in the later stages of the AIDS illness, patients developed neurological complications due to the HIV itself (Box 24.1.4.1). This included a progressive decline in cognitive function in association with motor abnormalities—the AIDS—Dementia Complex (ADC) or, as it is now known, HIV- associated neurocognitive disorder (HAND), a vacuolar myelop- athy, and a painful distal sensory peripheral neuropathy. With the introduction of highly active antiretroviral therapy (HAART) in 1996, there has been a dramatic decline in the incidence of neurological opportunistic infections, as well as HIV-related dis- orders such as HIV–dementia. The downside has been an increase in the peripheral nerve complications of some of the antiretroviral drugs, but also newer increasingly recognized syndromes such as neurological immune reconstitution inflammatory syndrome (IRIS) and HIV compartmentalization (or CSF escape). There is also concern regarding the continued high prevalence of milder forms of cognitive dysfunction in cohorts (20%) as well as a suggestion that some patients may continue to decline cognitively despite having an undetectable plasma viral load. The aetiology maybe multifactorial including drug toxicity, poor CNS penetration of antiretroviral drugs, a low-grade HIV-

related IRIS, cerebrovascular disease, and an accelerated ageing processes. Clinical approach All areas of the neuraxis are vulnerable in individuals infected with HIV. Differing pathological processes occur simultaneously in various parts of the nervous system. Thus, Occam's razor—the principle of diagnostic parsimony, often used in medicine—does not always apply. Another aspect to be considered is the possibility of simultaneous infection with more than one organism (e.g. men- ingitis due to Mycobacterium tuberculosis and Cryptococcus neo- formans). Mass lesions in the brain, with some not responding to antitoxoplasma therapy, could be due to lymphoma or another in- fective cause, such as a tuberculoma. The nervous system is involved early in the course of primary HIV infection, as evidenced by neurological seroconversion illnesses (Box 24.11.4.2). Furthermore, during the asymptomatic phase of the illness (i.e. when patients are well), the cerebrospinal fluid shows abnormalities in up to 60% of cases. This may be a lymphocytic pleo- cytosis of up to 50 cells/mm3, an elevated protein, or the presence of oligoclonal bands. The cerebrospinal fluid glucose level is usually Box 24.11.4.1 Neurological complications in HIV infection Opportunistic infections • Toxoplasma gondii—abscesses and encephalitis • Cryptococcus neoformans—meningitis • JC virus (John Cunningham) progressive multifocal leucoencephalopathy (PML) • Cytomegalovirus—retinitis, encephalitis, cauda equina syndrome, vasculitic neuropathy • Mycobacteriun tuberculosis—meningitis, abscesses Tumours • Primary CNS lymphoma (PCNSL) • Metastatic systemic lymphoma HIV-related disorders • HIV-associated neurocognitive disorder (HAND) • Vacuolar myelopathy • Distal sensory peripheral neuropathy • Polymyositis Drug-induced complications • Neuropathy (didanosine, stavudine, isoniazid) • Myalgia, mitochondrial myopathy (NRTIs) • Cognitive dysfunction (efavirenz) Immune reconstitution syndrome • Cryptococcus neorformans • PML • M. Tuberculosis • HIV (brain and peripheral nerves) CSF compartmentalization syndrome (CSF escape)

 normal. Therefore, these cytobiochemical markers are unhelpful in making a diagnosis of a meningitic or encephalitic illness. Reliance is, therefore, placed on specific markers such as the cryptococcal antigen or antibody tests such as the CSF VDRL or TPHA tests. As a result of the impaired immune response, a rise in anti- body titres to specific infections may not occur, especially during the later stages of HIV infection. Furthermore, the typical clinical picture—the presentation of which, at least in some infections, such as meningitis, is the result of a brisk inflammatory response such as fever—may not occur. In cryptococcal meningitis, only a third of patients exhibit the classic signs of meningism (i.e. neck stiffness, photophobia, and positive Kernig's sign). The specific type of opportunistic complications encountered depends on several factors, including the degree of immunosup- pression. During the early stages when individuals are relatively im- munocompetent, with CD4 counts above 500/mm3, autoimmune disorders such as demyelinating neuropathies may occur. With CD4 counts of between 200 and 500/mm3, multidermatomal herpes zoster infections and tuberculosis (TB) may present. Once the level declines below 200/mm3, patients are vulnerable to all the major opportunistic infections and the complications due to HIV itself. Symptomatic infection with cytomegalovirus (CMV) tends to occur at very low levels below 50/mm3. With the introduction of antiretro- viral therapy (ART), these guidelines are less robust because, despite immunoreconstitution, pathogen-specific memory T-cell clones may not have been fully restored. Opportunistic infections Toxoplasmosis Toxoplasma gondii, whose definitive host includes members of the cat family with humans as the intermediate hosts, is an obligate intracellular protozoan. Human infection occurs through the inges- tion of tissue cysts in undercooked meat. Variations in dietary habits therefore explain the differing seroprevalence rates worldwide— 90% in

French adults compared with 50% of residents in the United Kingdom. Symptomatic toxoplasmosis is usually due to a reacti- vation of latent infection in individuals with HIV. The risk of an HIV-infected patient who is seropositive for IgG T. gondii antibody developing toxoplasmosis is around 25%. Toxoplasmosis is the most common cause of mass lesions in the brains of patients with HIV infection, including those in areas where TB is endemic. The clinical presentation is variable, but headache, confusion, seizures, and focal neurological deficits such as hemi- plegia, dysphasia, and visual field defects are the most common. Other presentations described include: a variety of movement disorders (choreoathetosis, dystonia, and hemiparkinsonism); psychiatric illness such as depression; brainstem syndromes; and a rapidly progressive diffuse encephalitis. Rarely, the spinal cord may be involved with myelitis or cauda equina syndrome. A definitive diagnosis of toxoplasma encephalitis can be made only by brain biopsy. With increasing experience and pragmatism, it is now standard practice to treat any HIV-infected individual who has a low CD4 count and multiple lesions on imaging with antitoxoplasma therapy (Fig. 24.11.4.1). A response, clinically and radiologically, con- firms the diagnosis. Although a negative blood toxoplasma serology result makes the diagnosis less likely, this may occur in up to 17% of cases. This loss of seropositivity may be the result of impaired anti- body synthesis with increasing immunosuppression. It is, therefore, useful to document an individual's toxoplasma serostatus when HIV is diagnosed. For similar reasons, the expected rise in IgM and IgG levels does not occur. A single lesion on MRI is most likely to be due to lymphoma. A single lesion on CT should, if possible, be followed by MRI, which is a more sensitive method of detecting other lesions, particularly in the posterior fossa (Fig. 24.11.4.2). Box 24.11.4.2 Neurological HIV syndromes in Primary Infection Aseptic meningitis Meningoencephalitis Acute disseminated encephalopmyelitis Transverse myelitis Cauda Equina syndrome Acute demyelinating polyradiculopathy (Guillain–Barré syndrome) Brachial neuritis (Parsonage–Turner syndrome) Mononeuritis multiplex (vasculitis) Acute polymyositis CT/MRI Single lesion Multiple lesions Treatment for toxoplasmosis Positive Improvement (clinical and radiological) Negative Yes BIOPSY Continue for 4–6 weeks followed by prophylaxis Notes: (i) MRI may detect lesions not apparent on CT; (ii) In patients with significant mass effect and danger of herniation additional treatment with a reducing course of dexamathsone is necessary. Any deterioration subsequently on reduction of the steroids requires consideration of a biopsy. Blood toxoplasma serology No Fig. 24.11.4.1 Management of mass lesions in AIDS. Fig. 24.11.4.2 Cranial CT: multiple lesions with mass effect and cerebral oedema due to toxoplasmosis.

 The main differential diagnosis is that of primary CNS lymphoma, which presents at similar CD4 counts and has a similar presentation both clinically and on imaging studies (Box 24.11.4.3). A clinical response is seen in 90% of patients by the second week of treatment (Table 24.11.4.2). It is necessary to reimage 2 weeks after treatment even if there is clinical evidence of improvement, because occasionally some lesions improve but others due to, for example, Mycobacterium tuberculosis, continue to enlarge, which then makes it necessary to consider a biopsy. The radiological improvement gen- erally lags behind the clinical improvement. Corticosteroids are only indicated in patients with significant mass effect and should be used for short periods only, as it makes it difficult to interpret the trial of anti—toxoplasma treatment. Secondary prophylaxis is required after resolution of the acute episode. Patients infected with HIV who are seropositive for IgG against T. gondii should be offered primary prophylaxis with 980 mg co-trimoxazole (trimethoprim and sulfamethoxazole) if their CD4 count is below 200/mm3. This also provides prophylaxis against Pneumocystis jirovecii pneumonia. After

the initiation of HAART, primary prophylaxis maybe discontinued after successful suppres- sion of HIV viral replication and the CD4 counts exceed 200 cells/ mm3 for 3 months. Secondary prophylaxis after an episode of toxo- plasmosis can be discontinued after 6 months of successful suppres- sion of HIV viral replication and a CD4 more than 200 cells/mm3. Cryptococcus neoformans This encapsulated yeast is a ubiquitous organism in the environ- ment acquired by humans through inhalation. Although dissemin- ated infection can involve the skin, bones, lungs, eyes, and prostate, Box 24.11.4.3 Focal neurological syndromes Infections • Toxoplasma gondii (abscesses, encephalitis)* • JC virus (PML)* • Mycobacterium tuberculosis (tuberculoma)* • Fungal microabscesses (Cryptococcus neoformans, • Cytomegalovirus (brain stem syndrome) Neoplasms • Primary CNS lymphoma* • Metastatic tumours (non-Hodgkin's lymphoma, Kaposi's sarcoma) Cerebrovascular • Ischaemic stroke (coagulopathies) • Embolic stroke (bacterial and nonbacterial endocarditis) • Vasculitis (meningovascular syphilis, herpes zoster)

- Most common. Table 24.11.4.2 Treatment of neurological opportunistic infections Infection Drug Dose Duration Side effects Notes Toxoplasmosis Acute Pyrimethamine + Loading dose of 200 mg, then 75 mg orally 4–6 weeks Myelosuppression Sulfadiazine + 6–8 g/day orally or intravenously 4–6 weeks Nephrotoxicity, renal calculi, crystalluria Clindamycin 2.4 g/day oral or intravenously is an alternative to sulfadiazine. Side effect pseudomembranous colitis Folinic acid 15 mg/day orally 4–6 weeks To counteract the myelosuppressive effects of pyrimethamine Maintenance Pyrimethamine + 25–50 mg/day orally Until CD4 count >200 cells/mm3 + undectable viral load for >6 months Sulfadiazine + 2 g/day orally Clindamycin 1.2 g/day Folinic acid 15 mg/day orally Primary prophylaxis Co-trimoxazole 480 mg/day orally Nausea, Stevens– Johnson syndrome, thrombocytopenia CD4 count <200/µl and toxoplasma serology positive Cryptococcal meningitis Acute (induction) Amphotericin B + 1.0 mg/kg per day intravenously Combination of amphotericin + flucytosine for one week. Followed by one week of fluconazole 1200mg/day for adults, 12 mg/kg/day for children and adolescents up to maximum oif 800mg daily Hypokalaemia, renal failure, anaemia Via central line because of thrombophlebitis. Pre- emptive hydration, electrolyte replacement and toxicity monitoring necessary with amphotericin and flucytosine regimens. Alternative regimens: two weeks of fluconazole 1200mg for adults, 12 mg/kg/day for children

- flucytosine 100mg/kg/day, divided into four doses per day. Consolidation phase: fluconazole 800mg daily for adults, 6 - 12 mg/kg/day for children upto maximum of 800mg daily) for eight weeks following induction phase of two weeks 5-Flucytosine 100 mg/kg per day in four divided doses Myelosuppression Maintenance Fluconazole 200 mg daily for adults, 6 mg/kg/ day for children Until CD4 count

> 100 cells/mm3 and undetectable viral load for >3 months Nausea, vomiting, abnormal liver function tests Amphotericin 1 mg/kg per week if intolerant or relapse on fluconazole

24.11.4 Neurosyphilis and neuro-AIDS 6105 symptomatic infection with C. neoformans most often presents as meningitis. Cryptococcal infection is the most common infectious cause of meningitis

in patients with AIDS (Box 24.11.4.4). Although the presentation may be acute, it is usually subacute with symp- toms of malaise, headache, fever, and vomiting. The classic signs of meningism—neck stiffness, photophobia, and Kernig's sign—are present in only one-third of patients. Other, less common symptoms include altered mental status, seizures, and focal neurological signs. The last are the result of parenchymal cryptococcal abscesses. Brain imaging is usually normal, although the basal meningitis may result in hydrocephalus or sometimes, particularly on MRI, small abscesses—cryptococcomas—may be evident. Cerebrospinal fluid examination is essential for the diagnosis, with culture of the fungus being the 'gold standard'. The cytochemical markers in the cerebrospinal fluid may be normal. India ink staining of the cerebrospinal fluid will reveal the fungal hyphae in 70 to 80% of cases. Immunoassays (latex agglutination or ELISA) measuring cryptococcal antigen (CRAG) in CSF are rapid and have a sensitivity and specificity of more than 95%. Serum antigen measurements should also be measured, since in early disease (cryptococcaemia) these may be positive and CSF negative. Treatment with amphotericin B plus 5-flucytosine is the com- bination of choice for the treatment during the induction phase of cryptococcal meningitis for a minimum of two weeks with evidence of clinical improvement and sterile CSF. Liposomal amphotericin is less toxic but more expensive. The consolidation phase for 8 weeks is with fluconazole 400 mg/day and then maintenance fluconazole 200 mg for 12 months. The mortality rate still remains around 10%. Features that have been identified with a poor outcome include a relapsed infection, abnormal mental status, cerebrospinal fluid cryptoccal antigen titre greater than 1:1024, cerebrospinal fluid white cell count less than 20 cells/mm3, positive India ink staining, hyponatraemia, and positive culture from an extrameningeal site. A cerebrospinal fluid opening pressure of more than 250 mm H_2O is also a marker of poor prognosis. In milder cases, where none of these features is present, oral fluconazole may be used. A specific complication that requires close monitoring is the development of raised intracranial pressure due to obstruction of the arachnoid villi and cerebral oedema. This should be managed with repeated lumbar puncture or, if necessary, by the insertion of a lumbar or ventricular drain. Maintenance therapy is essential, with relapse rates approaching 100% if secondary prophylaxis with oral fluconazole is not adhered to. The serum cryptococcal antigen titre is not useful in predicting relapse. The timing for the initiation of ART after an episode of men- ingitis is controversial due to the risk of precipitation of the immune reconstitution syndrome (IRIS). Current opinion suggests starting between two and ten weeks after starting antifungal treatment with evidence of a sterile CSF. The patients at greatest risk of IRIS are those patients who are retroviral drug naïve with a high HIV RNA load and those with a poor CSF inflammatory response. Once the viral load has been fully suppressed and the CD4 count has risen above 200 cells/mm3 for 3 months, secondary prophylaxis can be discontinued. JC virus (John Cunningham) Progressive multifocal leucoencephalopathy (PML) is caused by the reactivation of latent John Cunningham virus. This polyomavirus in- fection is acquired by most of the population during childhood as a banal upper respiratory infection. The virus is frequently found in the urine of healthy individuals. Before the AIDS epidemic, progressive multifocal leucoencephalopathy was a rare condition encountered in patients immunosuppressed as a result of haematological malig- nancies, drugs used in the treatment of post-transplant recipients, autoimmune disorders such as systemic lupus erythematosus, and granulomatous disorders such as sarcoidosis. Nowadays, underlying HIV infection accounts for 85% cases, but the infection has also been highlighted following cases developing after immunomodulatory treatment in multiple sclerosis with drugs such as natalizumab. Before the introduction of HAART, the incidence of progressive multifocal leucoencephalopathy was 4%. The clinical presentation is subacute, with progressive focal

neurological deficits such as a hemi- paresis, visual field defects, and a cerebellar syndrome. The disorder is not restricted to the white matter because patients may also de- velop dysphasia and seizures. Occasional patients may present with a progressive dementia with focal neurological signs. MRI characteristically shows multiple areas of high signal on T1-weighted images and a low signal on T2-weighted ones (Fig. 24.11.4.3). There is little or no enhancement, with no mass effect or oedema around the lesions. Serological testing is un- helpful because 80% of the general population is seropositive. It is possible to confirm the diagnosis of progressive multifocal leucoencephalopathy by detecting JC viral DNA in cerebrospinal fluid by PCR techniques. This has a sensitivity of 75% with a spe- cificity of 95%. In PCR-negative cases it may be necessary either to repeat the cerebrospinal fluid examination or to perform a brain bi- opsy. The typical histological features show areas of focal demyelin- ation, bizarre enlarged astrocytes, and abnormal oligodendrocytes with inclusion bodies that stain for J viral antigens. Box 24.11.4.4 Meningitis in HIV infection Infections • Cryptococcus neoformans • Mycobacterium tuberculosis • Listeria monocytogenes • Treponema pallidum Neoplasms • Non-Hodgkin’s lymphoma
Fig. 24.11.4.3 T2-weighted MRI in a patient with progressive multifocal leucoencephalopathy.

 There is, to date, no specific treatment for progressive multifocal leucoencephalopathy. However, improving immune function with ART improves survival. Recently, there have been anecdotal data sug- gesting that the antidepressant mirtazipine may have some benefi- cial effects. Adequate trial results are awaited. Progressive multifocal leucoencephalopathy IRIS is not an infrequent complication—this is treated with corticosteroids and continuation of ART. Cytomegalovirus The neurological complications from this herpesvirus result from reactivation in severely immunocompromised patients. Almost all patients infected with HIV are seropositive for CMV. Postmortem studies of the brains of patients who died from AIDS show evidence of CMV in 25% of cases. However, clinical CMV disease, apart from CMV retinitis, is rare. CMV retinitis is the most common manifestation of CMV dis- ease and can affect up to 20% of patients with AIDS. The slowly pro- gressive necrotizing retinitis results in characteristic white irregular lesions with central necrosis and haemorrhages—the ‘cheese and tomato ketchup’ appearance. Retinal detachment may occur in pa- tients with extensive retinal involvement. The retinitis presents with symptoms of reduced visual acuity, floaters, and loss of peripheral vision. As the condition may be asymptomatic in the early stages, regular ophthalmological screening is recommended for high-risk patients with CD4 counts below 50 cells/mm3. A necrotizing ventriculoencephalitis has been described, usually in patients with evidence of CMV disease elsewhere (Box 24.11.4.5). The onset is subacute over a period of days or weeks with confusion, seizures, and brainstem signs such as internuclear ophthalmoplegia, ataxia, and cranial nerve palsies. Imaging studies typically show periventricular enhancement. CMV polyradiculopathy presents over a period of days with back pain, leg weakness, sensory impairment, and sphincter disturbance. The differential diagnosis includes syphilitic polyradiculopathy and infiltration with lymphoma. The cerebrospinal fluid reveals a poly- morphonuclear leucocytosis which is unusual for a viral infection. Early recognition and treatment are necessary to stabilize and, in some cases, improve the neurological impairment. Drugs licensed for the treatment of CMV disease include ganciclovir, cidofovir, and foscarnet. Oral ganciclovir is prescribed for secondary prophylaxis. Opportunistic tumours Primary CNS lymphoma (PCNSL) is the second most common cause of mass lesions after toxoplasmosis in adults, and the most common in children with AIDS. Histologically, this is a high-grade, non-Hodgkin’s, B-cell lymphoma. The Epstein–Barr virus is causally linked to PCNSL, with the identification of the viral DNA incorpor- ated into that of the neoplastic cells. The

common presenting symptoms are those of headache with focal neurological deficits, altered level of consciousness, and seizures. Brain imaging reveals enhancing mass lesions with surrounding oedema and mass effect. These are similar to those found in toxo- plasmosis. PCNSL is more likely to present as a single mass lesion than toxoplasmosis and is also more likely to invade the ventricular walls. Recent studies using thallium-201 single photon emission computed tomography (SPECT) suggest that it may be possible to differentiate between an abscess and a tumour, with the former having little uptake compared with the high uptake of the mitotically active lymphoma. There is no effective treatment for PCNSL. Whole-brain radio- therapy provides, at best, only a modest benefit, with most patients succumbing within 2 months. Current evidence suggests that ART may improve survival in this group of patients. HIV-associated neurological disorder (HAND) (Previously known as AIDS–dementia complex) Before the introduction of ART (and in areas of the world where these drugs are still unavailable) approximately 15 to 20% of indi- viduals infected with HIV developed a variably progressive de- mentia with associated motor deficits. HAND is now classified to three degrees—asymptomatic neurocognitive disorder (ANI), mild neurocognitive impairment (MND) with only mild functional ef- fects and HIV dementia (HAD) where there is marked functional impairment. In children, a similar HIV-1-associated progressive encephalopathy occurs more frequently than with opportunistic in- fections. This usually occurs within the context of severe immuno- suppression in those with a CD4 count of less than 200/mm3. In around 3% of cases, HIV–dementia is the AIDS-defining illness. Large cohort studies, using clinical, MRI, and neuropsychological methods, have largely discounted the early reports of evidence of cognitive changes in asymptomatic HIV-positive patients. The risk factors for the development of HAND are shown in Box 24.11.4.6. The clinical presentation in the early stages is with vague symp- toms of apathy, mood changes, and difficulty with memory and concentration. These are features of a subcortical dementia with no features of cortical involvement such as language, visuospatial, or calculation difficulties. This picture may be mimicked by de- pression, metabolic encephalopathy, and drugs, both therapeutic and recreational. At this stage, there may be few physical signs apart from brisk reflexes, impaired fine finger movements, and unsteady gait. Box 24.11.4.5 Encephalitis in HIV Virus • Cytomegalovirus • Herpes simplex • Herpes zoster • Human herpesvirus 6? Protozoa • Toxoplasmosis Box 24.11.4.6 Risk factors for HIV-associated dementia • Nadir CD4 count (so-called HAND legacy) • Increasing age • Systemic features—anaemia, low body weight, systemic symptoms • substance abuse • Host genetic factors—E4 isoform of apolipoprotein E; polymorphisms in TNF-α promoter and CCR2 • Coinfection with other viruses (e.g. hepatitis C) • Viral clade subtypes

 Later, the memory impairments are obvious, as is the psycho- motor retardation—which may progress to frank mutism and a global dementia. Some patients develop seizures. The motor signs, due to the associated vacuolar myelopathy with a spastic paraparesis and sphincter disturbances are also present in a significant number of patients (Box 24.11.4.7). In addition, some patients will have HIV-related distal sensory peripheral neuropathy. Thus, this group will have absent ankle jerks and extensor plantar responses. The diagnosis of the HIV–dementia is made by clinical assessment—there are usually no focal signs and the tempo of the disorder is an insidious one (Table 24.11.4.3). Investigations are performed to exclude other infective or neoplastic pathologies and, therefore, necessitate imaging, preferably with MRI, and a cere- brospinal fluid examination. MRI may show evidence of cerebral atrophy with compensatory ventricular dilatation, a diffuse white- matter high signal on T2-weighted images with no enhancement. A cerebrospinal fluid examination may be nonspecifically abnormal with a

pleocytosis, elevated protein level, and oligoclonal bands. It important to exclude cryptococcal and tuberculous meningitis, pro- gressive multifocal leucoencephalopathy, and neurosyphilis. The HIV RNA viral load in cerebrospinal fluid correlates with the se- verity of clinical dementia, but there is too much overlap between nondemented and demented patients for the measurement to be of use as a diagnostic aid. There is no correlation between the plasma HIV RNA viral load and dementia. The pathological hallmark of HIV encephalitis is the pres- ence of multinucleated giant cells. These conglomerates of in- fected and uninfected microglia/macrophages are indicative of productive HIV infection. Other pathological findings include a leucoencephalopathy and atrophy as a result of dendritic, synaptic, and axonal loss. There is no clear correlation between the clinical and pathological findings. One hypothesis for the entry of the virus into the CNS is the 'Trojan horse' theory, with invasion occurring by infected peripheral blood macrophages penetrating the blood–brain barrier that has been disrupted by damage to the capillary endo- thelial cells. Although neuronal cells are rarely invaded by HIV, neuropathogenesis is driven by productive infection of endogenous microglial cells and astrocytes. Neuronal injury, which may be par- tially reversible, occurs as a consequence of the release of txic viral gene products such as Tat and gp41 as well as proinflamatory cyto- kines including tumour necrosis factor (TNF), quinolinic acid, and platelet-activating factor. After the introduction of the first antiretroviral agent, zidovu- dine, and especially after HAART, the incidence of HAD has de- clined dramatically. Neurocognitive profiles of individual patients also improved while on ART. However, more recent studies have revealed a high prevalence of neurocognitive impairment, albeit mild, in 20%. There are concerns that as a result of poor CNS drug penetration, there may be continuing low-grade viral persistence in the brain parenchyma. As a result, the CNS penetration effect- iveness score has been proposed. This is an arbitrary score based on pharmacokinetic data and drug properties. Some, but not all, studies have suggested beneficial effects on neurocognitive func- tioning when ART regimens with higher scores are used. Other possible causes of the high level of neurocognitive impairment in- clude drug toxicity and a persistent low-grade chronic inflamma- tion and immune activation. Between 3% and 10% may develop a CSF viral escape or com- partmentalization syndrome. This is the discordance in viral load between plasma and CSF. Usually the plasma viral load is undetect- able or may show a blip in titres, with CSF loads being significantly higher. The clinical presentation includes an acute or subacute en- cephalitis, myelitis, and/or a meningitis. Modification of ART leads to improvement. All patients with good virological control who present with neurological symptoms should have the CSF viral load measured. HIV-associated neuropathy The most common neurological complication encountered in pa- tients infected with HIV is a distal sensory polyneuropathy, which may occur in 30% of those with AIDS (Box 24.11.4.8). It is a signifi- cant cause of morbidity. Typically, patients complain of numb, burning feet, with shooting stabbing pains and hyperaesthesia developing over a period of months. There is little or no weakness. The hands are infrequently involved. Since this is mainly a small fibre neuropathy the ankle jerks may be retained, Sensory testing reveals impaired pain and Box 24.11.4.7 Myelopathy in HIV Infections • HIV-associated vacuolar myelopathy* • Herpes zoster* • Cytomegalovirus • HTLV-1 (coinfection) • Treponema pallidum • Toxoplasmosis • Epidural abscess Neoplasm • Metastatic non-Hodgkin's lymphoma Other causes • Vitamin B12 HTLV-1, human T-cell leukaemia/lymphoma virus-1.

- Most common. Table 24.11.4.3 Clinical neurological features of HIV-associated dementia Early symptoms Apathy, depression Poor concentration Poor short-term memory Agitation, mania Early signs Tremor Hyperreflexia Impaired fine finger movements Late features Global dementia Frontal release signs Cerebellar signs Myelopathy Neuropathy

section 24 Neurological disorders 6108 temperature perception, with joint position and vibration sensation affected later. Further investigations are usually unnecessary in a patient with a CD4 count below 200 cells/mm3 and showing the typical clin- ical picture, but it is always worth checking a fasting blood sugar, vitamin B12 level, and syphilis serology. It is important to enquire about alcohol intake and nutrition. Neurophysiological studies may reveal abnormal thermal thresholds initially with axonal involve- ment of large fibres on standard nerve conduction tests later in the course of the disease. If there is significant weakness, such as a foot drop, other diagnostic possibilities including vasculitis, malignant infiltration, and diffuse inflammatory lymphocytic syndrome need to be considered. As antiretroviral therapy has no therapeutic benefit, treatment is symptomatic with drugs used for the management of diabetic neuropathy, which it resembles. Drugs used include the tricyclic antidepressants and anticonvulsant drugs such as gabapentin, pregabalin, and also duloxetine. The nucleoside analogues didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) cause a dose-dependent sensory neuropathy that may be indistinguishable from distal sensory peripheral neur- opathy. Clues to this drug-induced neuropathy include the shorter history of weeks rather than months, it is more painful than distal sensory peripheral neuropathy and improves on stopping the offending drug. However, there may be a continued worsening of symptoms for a period of 4 to 8 weeks after stopping—the phenom- enon of ‘coasting’. The underlying mechanism appears to be the im- pairment of mitochondrial protein synthesis. A significant number of patients will improve on stopping the drug, but others are left with neuropathic symptoms due to the unmasking of an underlying distal sensory peripheral neuropathy. Fortunately, these older drugs are rarely, if ever, used these days. Neurological immune reconstitution inflammatory syndrome (IRIS) The introduction of ART results in the recovery of CD4 T lympho- cytes, including memory T-cells. This may result in the ‘paradoxical deterioration’ of clinical or laboratory markers, including imaging studies, despite a favourable response in the viral load and CD4 count. This may be due to treatment of an overzealous CD8+ lymphocyte cytotoxic inflammatory response against antigens of the infective agent. Sometimes the IRIS occurs because unrecognized pathogens are ‘unmasked’ and the immune reaction leads to symptomatic dis- ease. The onset ranges from a few days to a few months but usually within the first 8 weeks. Risk factors for IRIS include a low baseline CD4 count, a greater than 2 log drop in viral load, a greater than 50 cell increase in CD4 count and antiretroviral drug naivety (Box 24.11.4.9). Neurological immune reconstitution inflammatory syndrome has now been described with Mycobacterium tuberculosis causing men- ingitis and brain abscesses, cryptococcal meningitis, CMV with the development of vitritis, uveitis, and cystoid macular oedema, and progressive multifocal leucoencephalopathy with MRI showing en- hancement and oedema which is usual in progressive multifocal leucoencephalopathy. An aggressive form of IRIS with a high mor- tality rate directed against HIV itself has been described. Brain biop- sies reveal extensive infiltrates of CD8 + cytotoxic lymphocytes The management in such cases is difficult, and although cor- ticosteroids are often used, there are no controlled trials. In life- threatening situations stopping the ART may be necessary. FURTHER READING Bruce JB (ed) (2018). Handbook of Clinical Neurology 3rd Series 152. The Neurology of HIV Infection. Elsevier. Centner CM, et al. (2013). Manifestations of HIV infection in the per- ipheral nervous system. Lancet Neurol, 12, 295–309. Clifford D (2015). Neurological immune reconstitution inflammatory syndrome: riding the tide of immune recovery. Current Opin Neurol, 28, 295–301. Janier M, et al. (2014). 2014 European guideline on the management of syphilis. J Euro Acad of Dermatol Venereol,

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- Most common. Box 24.11.4.9 Neurological IRIS syndromes Opportunist Infection associated • PML • M. tuberculosis (meningitis, tuberculoma) • C. neoformans (meningitis, intracranial cryptococcomas) • Herpes viruses (VZV, CMV, HSV)—(encephalitis, cerebral vasculitis, retinitis) • T. gondii (encephalitis) HIV associated • Subacute generalized encephalopathy (altered mental status, seizures, coma). MRI: Multifocal diffuse high signal on T2 weighted images. Histopathology—massive CD8 infiltration on brain biopsy. • Acute inflammatory demyelinating encephalitis (ADEM) • CNS vasculitis • Chronic low-grade HIV IRIS causing HAND

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