RAPIDLY PROGRESSIVE DEMENTIA INFECTIONS

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CHRONIC MENINGITIS

Chronic meningitis is defined as meningitis progressing or persistent without signs of improvement for at least six weeks. The full syndrome is headache, cognitive symptoms and pleocytosis. Symptoms of meningeal irritation (stiff neck), cranial neuropathies and fever are not required, but can be part of the clinical syndrome. There are both infectious and non-infectious (meningeal cancer, sarcoidosis) causes. Infectious causes can present as a rapidly progressive dementia without headache or other signs.

Fungal Infections

Fungal infections of the central nervous system most commonly present as chronic meningitis. When they occur as intraparenchymal abscesses, the pathogenesis is either infection from a leptomeningeal source along the Virchow-Robin spaces into the brain, or dissemination to the nervous system via a blood-borne fungal infection. Because of their indolent growth pattern, fungal disease in the nervous system typically produces subacute to chronic neurocognitive syndrome, with or without headache or fever. The patient does not have to be immunosuppressed, but it is a clue. Proof of diagnosis rests on culture of the organism from the CSF which may take extended periods, up to two weeks for results, or serologic tests in the CSF which are incompletely sensitive.

In considering the differential diagnosis of chronic fungal meningitis, geographic risk or risk behaviors need to be considered. Endemic associations are common in fungal infections, so patients from the southwest United States should be considered strongly for coccidioidomycosis. Patients from upper Midwest states (Wisconsin, Minnesota, etc.) should be considered for blastomycosis. Physical examination of organ systems outside of the nervous system, especially focusing on the chest, is important, since this is the most common site for primary fungal infection. Histoplasmosis is endemic in patients from the Mississippi and Ohio River valleys with asymptomatic infection of the lungs being common, so serum serology often does not help. CSF antibody is helpful, but is only about 50% sensitive. Often active pulmonary disease is coincidentally present when meningitis is present.

Nothing is specific in the spinal fluid formula for fungal infections of the nervous system. Typically, fungal infections are associated with high spinal fluid protein, an elevated white blood cell count (typically predominantly lymphocytes, usually less than 500 per mm^3), and low spinal fluid glucose, but hypoglycorrachia is not universally present. The spinal fluid should be cultured repeatedly because of the insensitivity of isolating fungal organisms if fungal meningitis is suspected.

Cryptococcal meningitis may be the most common fungal infection causing a subacute encephalopathy or dementia. It is regarded to be the most common cause for subacute meningitis in the United States (Pyrgos et al. 2013). CSF examination for cryptococcal antigen is appropriate in a dementia of six months or less duration. This agent is also the most common cause of meningitis in AIDS.

For the diagnosis of cryptococcal meningitis, testing for cryptococcal antigen in spinal fluid is best (Perfect 1997; Roberts 1979). This test can be performed on serum as well. Serum cryptococcal antigenemia, if present, is pathologically significant. Any titer may be considered significant. Spinal fluid antigen testing is estimated to be 90% sensitive in patients with cryptococcal meningitis. There are occasional false positives, but repeated testing can usually segregate them. By contrast, the India ink stain test is less sensitive, estimated to be only 25% sensitive in spinal fluid samples of patients with cryptococcal meningitis.

Fungal serology from CSF is helpful in limited ways for other fungal meningitis. At the Mayo Clinic Fungal Serology laboratory, the complement fixation testing is regarded to be only approximately 40% sensitive and immunodiffusion techniques, depending on the organism, are estimated to be between 50 and 80% sensitive (Roberts 1985). Therefore, negative results do not exclude the diagnosis of fungal infection in the nervous system. Some serologies cross-react, leading to confusion about diagnosis. More specifically, antibodies against Histoplasma antigens can cross-react with Blastomyces, and vice-versa making segregation of these infections difficult on serological basis. PCR results can be used to segregate these if needed. Sensitivities are defined by individual laboratories.

Serological tests for coccidioidomycosis are both reliable and specific. Antibodies are found in approximately 90% of patients with active, invasive infection. The complement fixation test gives a reliable correlation between titer and severity of disease. Even low titers found in the spinal fluid are suggestive of active infection.

Finally, rarely*Sporothrix* can cause central nervous system chronic meningitis. Diagnosis is established by detection of spinal fluid antibodies against the organism. The sensitivity and specificity data about this test are not available. A positive spinal fluid serology, however, should be considered pathologic (Nan Scott 1987).

Other fungal organisms not mentioned here do not have reliable serologic or other non-invasive means of detection beyond culture from the spinal fluid or biopsy of brain or leptomeninges. Though PCR analyses have been reported for Candida and Aspergillus, too little data exist to comment on clinical utility when applied to nervous system infections.

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Evaluation of Chronic Meningitis
1. In virtually every patient with chronic meningitis syndrome: - Spinal tap (up to 3 times for cytology, and fungal and mycobacterial cultures with large collection volumes) - Cryptococcal antigen on CSF - Bacterial culture of CSF - CSF protein, glucose, cell count - CSF serology for VDRL, fungal serologies (Histoplasmosis, Blastomycosis, Coccidiomycosis) - MRI head imaging with gadolinium - Serum serology for syphilis, HIV, Lyme disease - Chest x-ray and/or chest CT scan (for lymphadenopathy, granuloma, or neoplasm) - PPD skin test with anergy panel
2. Additional helpful tests to consider: - Serum serologies for Toxoplasmosis, Brucella, Leptospirosis, Sporothrix - ANA, ENA, ANCA antibodies - PCR in CSF for TB, Lyme disease (see limitations above) - Ophthalmologic exam for uveitis (sarcoid, lymphoma) - Serum ACE level (for sarcoidosis)

Tuberculous Meningitis

The diagnosis of tuberculous meningitis (TBM) remains enigmatic because of the difficulty in culturing the organism from spinal fluid and the idiosyncrasies of PCR testing for it. Yet identification of *Mycobacterium tuberculosis* in the spinal fluid is the only way to specifically confirm the diagnosis and render the proper treatment.

There is some variability to the temporal profile of the illness, i.e. acute, subacute and at other times more chronic; and the CSF pattern of reaction cannot be relied upon to specifically identify TBM. Clinical series of CSF abnormalities published from both non-HIV and HIV-related TBM patients have not suggested differences in the findings of the CSF formula. Mean protein elevations range from 65-504 mg percent with most in the 100-200 mg percent range. In 10-38 percent of patients the protein content can be normal. With extreme exudation reaction and block of CSF pathways, especially at spinal levels, CSF protein concentration can be very high exceeding 1 gram/dL, and produce a clot or pellicle in a standing CSF tube (Froin's syndrome) because of the presence of serum clotting factors, normally not present in the spinal fluid.

CSF glucose is usually low in TBM. Cellular reaction in the CSF is usually lymphocytic. However, polymorphonuclear cells can predominate in up to 32 percent of patients (Stocksill 1983). The presence of polymorphonuclear cells does not necessarily correlate with the acuteness of the clinical evolution of symptoms but does correlate with severe clinical signs (Davis 1993). Mean cell counts are in the range of 110-270 cells per mm^3, but total cell count in individual cases can be as high as 4000 cells per mm^3. Seven to nine percent will have normal CSF cell counts (Berenguer 1992).

Smears performed on CSF for acid-fast bacilli (AFB) have been reported in older publications to have a sensitivity of up to 87 percent. However, the more routine use of AFB stains in clinical laboratories has an estimated sensitivity of 4-24 percent. The sensitivity of the staining technique is enhanced by centrifugation of large volumes of CSF onto a single slide for staining and intensive examination of the stained pellet for organisms.

CSF culture for *Mycobacterium tuberculosis* remains the gold standard to which other methods of identification of the organism must be compared. From a practical clinical standpoint, however, the culture is insensitive based on clinical criteria (i.e., systemic signs of tuberculosis and response of CSF parameters to anti-tuberculous therapy). Also, isolation of *M. tuberculosis* from TBM patients requires long incubation times, often two to six weeks after the CSF has been collected, for growth. This latency before specific identification of the organism makes clinical treatment decisions difficult when faced with a sick patient and deteriorating neurological status.

The polymerase chain reaction (PCR) detection of *M. tuberculosis* DNA in the CSF holds the greatest promise, and yet has not fully realized its potential, as a rapid and sensitive diagnostic tool in tuberculous meningitis. Because of PCR sensitivity and the low abundance of the tubercle bacillus in the CSF, the test and tuberculous meningitis seem ideally matched. Likewise, the rapidity with which PCR can be performed and the amplified products identified as specific for TB would be a great improvement over culture techniques and insensitive acid fast stains. However, practical application of this technique to the diagnosis of TBM has proved difficult. Enthusiasm for PCR confirmation of TBM has been attenuated because of difficulty of variability between laboratories (Macher 1995; Noordloek 1993) and inconsistent standards. These studies had examined the unreliability of PCR to accurately determine the presence of tuberculosis, and have lead the Food and Drug Administration to still not recommend this test for routine clinical use for spinal fluid. An analysis estimates a 55% sensitivity across multiple laboratories (*Health Technology Assessment* UK 2007; Vol. 11: No. 3; www.hta.ac.uk). Currently, PCR for TB in the CSF from suspected TBM patients can be used but routinely sensitivity and specificity needs to be defined by individual labs (CDC 2009). A recent iteration of PCR for TB, Gene Xpert, estimates in CSF sensitivity of 59.3% (108/182 [95% confidence interval {CI}, 51.8 to 66.5%]), There was one false-positive (99.5% specificity) (Nhu et al. 2014).

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VIRAL INFECTION

HIV-1-associated dementia and mild neurocognitive disorder

This is a severe subacute to chronic dementia characterized as a "subcortical" type with prominent attentional difficulty and personality changes early. This may be the presenting manifestation of AIDS. It is the most common neurologic complication of AIDS. It is rarely present to a severe degree without systemic symptoms of AIDS. CT head scan shows generalized atrophy, and MRI shows diffuse periventricular ill-defined white matter changes, bilaterally involving the cerebral hemispheres.

HIV direct infection of the brain is the cause, but the pathogenesis remains unclear. Pathologically, gliosis, multinucleate giant cells, microglial nodules, and myelin pallor correlate with the clinical syndrome. Principally multinucleate giant cells, macrophages/microglia, and mononuclear cells have been conclusively shown to contain HIV virus. Antiretroviral therapy (ART) has been suggested to have a positive influence on this disease.

Subacute Sclerosing Panencephalitis (SSPE)

This neurologic syndrome caused by measles infection usually occurs in late childhood or early adolescence, but has been reported as late as the third decade in life. Cognitive changes, myoclonic jerks (with EEG periodic complexes), seizures, and chorioretinitis are usual clinical features. This usually occurs in patients with primary measles infection occurring in infancy.

This is a true "slow virus" infection in that primary infection of the CNS occurs early in life and "persists". Measles virus is the etiologic agent, so cases are rare in the post-vaccination era (since about 1965). It is still present in the developing world where vaccination practices are incomplete. Recent vaccine failures or reluctance to vaccinate for fear of complications may be associated with a re-emergence of this disease. Recent clinical measles cases should heighten vigilance for this disorder. Diagnosis can be made based on presence of CSF antibodies to measles virus.

PML (progressive multifocal leukoencephalopathy)

PML can present as a subacute encephalopathic or dementing illness when the frontal lobes are selectively affected early. Clues are focal imaging abnormalities and an accompanying immune deficiency (AIDS, sarcoid, lupus, CLL, lymphoma, transplantation, etc.). The disease commonly presents as a subacute neurologic deficit with the dementia.

On imaging there is a unifocal or multifocal demyelinating process typically at the cerebral cortical gray-white junction without mass effect or contrast enhancement on the MRI scan. MRI is very sensitive. The cause is a DNA papovavirus designated JC virus (no relation to Creutzfeldt-Jakob disease). JC virus selectively infects and kills oligodendrocytes, and leads to demyelination. Prognosis is grim, though a limited number of AIDS cases have responded to ART-induced improved immune status or non-AIDS patients have responded to cytosine arabinoside treatment. A few cases of "spontaneous" remission have been reported including in AIDS. Patients on immunosuppressants like natalizumab have a better prognosis with early recognition.

BACTERIAL

Lyme Disease (*Borrelia burgdorferi*)

Clinical diagnosis of lyme disease is suspected after a tick bite and/or the classical skin lesion of erythema chronicum migrans (ECM). ECM and inflammatory CNS syndrome, particularly facial nerve palsy, is enough for clinical diagnosis of lyme nervous system disease. Another neurologic syndrome initially described as "Bannwarth's syndrome", is meningoradiculitis and cranial nerve palsies. More diverse neurologic syndromes including a subacute dementia have been described, which pathologically is a chronic meningoencephalitis.

This spirochete (*Borrelia burgdorferi*) is readily treatable with penicillin, but neurologic syndromes are sometimes resistant. Ceftriaxone penetrates the CSF well and is the drug of choice. Other chronic systemic involvement includes arthritis and carditis.

Diagnosis is dependent on serum serology which has problems with false positives and false negatives. Serology performed on CSF is probably the most sensitive and specific test, but is still not 100% reliable. PCR detection in CSF is available, but sensitivity is low (probably less than 25%), though specificity is high.

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Syphilis

Though a rare syndrome in the last 50 years, it continues to remain in the differential diagnosis of "reversible dementia" (general paresis). The major forms presenting as subacute or chronic dementia are meningovascular syphilis and general paresis. Peripheral serology for nonspecific antigen (i.e. VDRL, RPR) may be negative even with active CNS disease.

CSF protein and cell count are the most sensitive though nonspecific indicators of active disease. Modern serum serology is more specific for serologic reaction to the organism. CSF VDRL or RPR is required for diagnosis, and CSF should be examined in any patient with a positive serum serology.

Whipple's Disease

The source of *T. whipplei* and its means of transmission to people are, as yet, unknown. The organism is presumed to be environmental, with ingestion and infection of the gastrointestinal tract as the primary site for disease. One proposed concept is that although many people are exposed to *T. whipplei*, immune factors are required to predispose to invasive infection; however, no specific immune compromised state has been associated with disease (Marth et al., 2003; Fenollar et al., 2007). *T. whipplei* replicates in macrophages and other monocytic cells. Humoral responses do not appear to play a role in this disease

Central nervous system (CNS) involvement in Whipple's disease is thought to occur in three circumstances: neurologic involvement with systemic disease, neurologic relapse in patients treated for systemic disease, and neurologic disease without systemic disease. The frequency of neurologic involvement is controversial, with estimates ranging from 6 to 63%. One review estimated an incidence of 4% (Fleming et al., 1988) when ophthalmoplegia was included as evidence for neurologic involvement. Based on a review of 99 patients from seven case series, one-third had neurological signs (Fenollar et al., 2007). Neurologic involvement without gastrointestinal symptoms has been known for more than fifty years (Lampert 1962)

The most characteristic primary presentation associated with CNS Whipple's disease is the triad of cognitive changes, ophthalmoplegia, and myoclonus. The complete triad, however, may only be present in 15% of cases (Louis 1996). The myoclonus type that is most specific for Whipple's disease is oculomasticatory myorhythmia. Other characteristic manifestations include psychiatric, vegetative, cranial nerve, epileptic or ataxic symptoms.

The dementia of Whipple's disease usually occurs subacutely to chronically. It may or may not be associated with systemic symptoms of weight loss, diarrhea, arthralgias, and other overt manifestations of systemic disease. Dementia is often associated with prominent behavioral changes (Halperin et al., 1982). Difficulty with working memory may be a prominent feature, correlating with frontal and temporal lobe involvement. Dementia, with prominent vegetative symptoms such as hypersomnolence, autonomic symptoms or hyperphagia, suggests hypothalamic involvement. Psychiatric signs, typically occurring as part of the cognitive disorder, have been estimated to occur in 44% of patients (Louis 1996).

Myoclonus may be generalized, but the most pathognomonic feature of Whipple's disease is oculomasticatory myorhythmia. Oculomasticatory myorhythmia (OMM) is so rare a disorder that it is felt to be diagnostic of CNS involvement by Whipple's disease (Louis 1996). A related movement disorder, oculo-facial-skeletal myorhythmia (OFSM) is defined as convergence of oscillations of the eyes associated with rhythmic movements of the face and proximal extremities that persist into sleep (Adler and Galetta 1990, Louis 1996).

OFSM can be a manifestation of isolated CNS involvement, along with OMM, is felt to be a brainstem generated form of segmental myoclonus.

Hypothalamic involvement can manifest as hypersomnia, hyperphagia, or personality change (Lampert et al., 1962). Hyponatremia, polydipsia, or impotence may also be seen (Halperin et al., 1982). More rare manifestations of CNS involvement include headache, optic neuropathy, trigeminal neuropathy, or meningitis.

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PARASITES

Neurocysticercosis (*Tania solium*)

This illness usually presents as a focal parenchymal cyst(s) (cellulose) usually rather than cysts in the meninges (racemose). Cysts are often multiple. Symptoms develop as the larval cyst dies because of host inflammatory reaction. Imaging and CSF serology can be diagnostic. Dementia occurs because of multiple cerebral cysts or because of hydrocephalus as a consequence of CSF obstruction by the racemose form.

CNS cysts of larval forms occur by ingesting food contaminated with *Tania* eggs from human feces, not by eating pork (which causes intestinal infection by ingesting larvae). Because of the life cycle of this worm, stool cultures for parasites are usually unremarkable in the neurologic patient.

Not all patients need treatment. Inactive, calcified cysts are unaltered by therapy. Albendazole therapy is recommended for multiple lesions, if organisms are still viable. It induces fever and meningismus from inflammation against dying organisms. Steroids are used in conjunction to prevent reactive edema. CSF eosinophilia is present in 14-40%. Surgery is indicated only when mass effect cannot be treated or with CSF obstructive problems particularly with racemose disease.

Toxoplasmosis

Toxoplasmosis is the most common cause for focal mass lesion in the brain of patients with HIV complications (Quality Standards Subcommittee of the American Academy of Neurology, 1998). Radiographic imaging clinically helps the diagnosis with MRI studies, and SPECT scanning (Quality Standards Subcommittee of the American Academy of Neurology, 1998). Multiple cerebral lesions can produce a rapidly progressive dementia. It has been the recommended that patients with multiple lesions who have suspected CNS toxoplasmosis be treated empirically with anti-toxoplasmosis therapy and followed.

Since toxoplasmosis is essentially a reactivation infection in the brain of immunosuppressed patients with AIDS or transplantation, positive serology is helpful in knowing about the patient's past exposure. Differentiation of toxoplasmosis from CNS lymphoma is aided therefore by examining patients for the presence of Toxoplasma antibodies in the serum. Seronegativity however for toxoplasmosis does not exclude the diagnosis of central nervous system toxoplasmosis (Porter 1997; Quality Standards Subcommittee of the American Academy of Neurology, 1998). Therefore, additional studies on spinal fluid may be indicated to try to confirm diagnosis in uncertain circumstances.

The dementia of toxoplasmosis is usually associated with multifocal cerebritis or brain abscesses easily detectable by CT or MRI brain imaging. MRI is more sensitive. However, if in the individual case, spinal fluid can be obtained safely, PCR analysis of spinal fluid can help to demonstrate whether there is active infectious *Toxoplasma* present in the brain. It is in this stage of infection that PCR is able to detect Toxoplasma DNA in the

spinal fluid. A realistic sensitivity for PCR analysis of patients with suspected toxoplasmosis in the nervous system is probably reflected in an estimated sensitivity of 60 to 80 percent range, respectively, in prophylactically treated and untreated patients. Because of incomplete sensitivity, a negative Toxoplasma PCR does not exclude the diagnosis of toxoplasmosis (Antinori 1997).

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