Extrapulmonary tuberculosis, part 2: CNS involvement

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Abstract: Tuberculous meningitis has several different clinical presentations, including an acute meningeal syndrome simulating pyogenic meningitis, status epilepticus, stroke syndrome, and movement disorders. Cranial nerve palsies and seizures occur in about one third of patients, and vision loss is reported by almost 50%. The cerebrospinal fluid (CSF) typically shows moderately elevated levels of lymphocytes and protein and low levels of glucose. The demonstration of acid-fast bacilli in the CSF smear or Mycobacterium tuberculosis in culture confirms the diagnosis. CNS tuberculosis may also manifest as intracranial tuberculomas. The characteristic CT and MRI finding is a nodular enhancing lesion with a central hypointensity. Antituberculosis treatment should be initiated promptly when either tuberculous meningitis or tuberculoma is suspected. (J Respir Dis. 2005;26(9):392-400)

Tuberculosis can have a variety of extrapulmonary manifestations in addition to the classic pulmonary disease. In the August 2005 issue of The Journal of Respiratory Diseases, we reviewed the most common extrapulmonary manifestations of tuberculosis—pleural and lymph node involvement. In this article, we will focus on the presentation of neurologic tuberculosis.

OVERVIEW

Neurologic tuberculosis occurs in 10% to 15% of patients who have extrapulmonary involvement. It occurs more frequently in children than in adults and is most common in children aged 3 years or younger. The prognosis is generally poor in young children, children of any age who have not received BCG vaccination, and adults who are older than 50 years.

Neurologic involvement is 5 times more frequent in HIV-positive patients than in HIV-negative patients. HIV infection does not generally alter the clinical presentation or response to antituberculosis therapy, although a poorer prognosis can be expected in patients with CD4+ T-lymphocyte counts below 200/µL.1,2 Poor outcomes have also been associated with infection with drug-resistant mycobacterial strains.1

The 3 clinicopathologic categories of neurologic tuberculosis are meningitis, tuberculoma (intracranial and spinal), and arachnoiditis (basal, opticochiasmatic, and spinal).3

MENINGITIS

Almost 80% of patients with neurologic tuberculosis have meningitis. Tuberculous meningitis continues to be a significant public health concern in developing countries. Pathogenesis CNS tuberculosis is invariably secondary to tuberculosis elsewhere in the body. Meningitis is the result of the rupture of a subependymally located tubercle (Rich focus) that developed during primary hematogenous dissemination into the subarachnoid space.

The pathology includes inflammatory meningeal exudates, ependymitis, vasculitis, and encephalitis. The blockage of the basal cisterns by the exudate in the acute stage and adhesive leptomeningitis in the chronic stage results in the development of communicating hydrocephalus in most patients who have been symptomatic for more than 2 to 3 weeks.

The hydrocephalus is more severe in children than in adults. Infrequently, the hydrocephalus is of the obstructive type.3,4 Clinical presentation

The clinical presentation of tuberculous meningitis has evolved in the past decade and includes an acute meningeal syndrome simulating pyogenic meningitis, progressive dementia, status epilepticus, psychosis, stroke syndrome, and movement disorders. The factors responsible for this changing pattern include delay in the age at onset of primary infection, BCG immunization, and HIV infection.3,4 The prodromal phase of constitutional features (low-grade fever, anorexia, and lethargy) lasts about 3 weeks. Subsequently, headache and vomiting occur, and the patient has a more toxic appearance. Cranial nerve palsies (especially sixth nerve involvement) and seizures occur in approximately one third of cases.

The loss of vision (clinical and/or impaired visual evoked response) is a major complication of optic pathway involvement and is reported in almost 50% of patients. There is progressive deterioration in sensorium as a result of increasing hydrocephalus and tentorial herniation. The disease is usually...
fatal within 2 months, if it is untreated. Encephalopathy is the result of a hypersensitivity reaction to tuberculoproteins. It typically occurs in children and is characterized by diffuse brain edema and white matter disease with minimal evidence of meningitis.

**Diagnosis**

The diagnosis of tuberculous meningitis is based on clinical signs, symptoms, and cerebrospinal fluid (CSF) findings. Clear CSF with moderately elevated levels of cells (predominantly lymphocytes) and protein and low glucose levels constitutes the typical CSF picture. The leukocyte count is usually 100 to 500/µL. In addition to increased levels of lymphocytes in the CSF, a polymorphonuclear (PMN) response is not unusual in the acute stage.

The only CSF parameter that correlates with a poor outcome in this setting is a high protein level (greater than 2 g/L). This finding is associated with a more advanced disease at presentation. However, CSF protein levels may be normal in patients with AIDS.

A negative Gram stain, a negative India ink capsule stain, and a sterile culture for bacteria and fungi are prerequisites for the diagnosis of tuberculous meningitis. The demonstration of acid-fast bacilli in the CSF smear or *Mycobacterium tuberculosis* in culture confirms the diagnosis. The yield of CSF smear by Ziehl-Neelsen stain and auramine O fluorescent stain is low, ranging from 4% to 40%.

Supporting features include CT or MRI findings, such as basal exudates, gyral enhancement, infarcts, tuberculosis, and hydrocephalus. The common sites of exudate are the basal cisterna ambiens, suprasellar cistern, and Sylvian fissures. The evidence of tuberculosis elsewhere in the body is supportive. The Mantoux tuberculin test is positive in 40% to 65% of adults and 85% to 90% of children with tuberculous meningitis. However, it lacks specificity in developing countries because of previous sensitization to mycobacteria and BCG vaccination.

Immunodiagnostic test results can be supportive but are not diagnostic. The specificity of these tests depends on the antigen or antibody used. Antibodies against glycolipids and proteins isolated from *M tuberculosis*, bacille Calmette Guérin, purified protein derivative, antigen 5, and lipoarabinomannan (mycobacterial cell wall component) have been tested using techniques of enzyme-linked immunosorbent assay, radioimmunoassay, and immunoblot methods. Various authors have reported sensitivity ranging from 60% to 90% and specificity ranging from 58% to 100%.

These tests should be considered research tools at present.

The adenosine deaminase level is elevated in the CSF of 60% to 100% of patients with tuberculous meningitis. However, false-positive results have been reported as a result of other causes of meningitis.

Amplification of *M tuberculosis*-specific DNA sequence by polymerase chain reaction (PCR) has been evaluated as a means of rapid diagnosis of neurologic tuberculosis. The sensitivity of PCR in CSF for the diagnosis of tuberculous meningitis varies from 48% to 90%. However, the specificity is 100%.

**Complications**

The complications of tuberculous meningitis include raised intracranial pressure, hydrocephalus, cerebral edema, basal meningitis with cranial nerve palsies, focal neurologic deficits, tuberculosis, abscess, opticochiasmatic pachymeningitis resulting in visual loss, arteritis manifesting as stroke, and endocrine disturbances (namely, diabetes insipidus and syndrome of inappropriate secretion of antidiuretic hormone [SIADH]).

Patients with dense exudates in the basal cisterns and visual loss resulting from organized exudates over the opticochiasmatic region respond poorly to treatment. The diencephalic infarcts result in SIADH, which also indicates a poor prognosis.

**Treatment**

The most important principle of therapy is that antituberculosis treatment should be initiated when tuberculous meningitis is suspected. Treatment should not be delayed until the diagnosis has been proved.

Primary therapy is with first-line antituberculosis agents (Table). A 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol is recommended in the initial phase, followed by isoniazid and rifampin in the continuation phase. There is substantial evidence suggesting that treatment for 6 to 12 months may be adequate. Ethambutol is preferred over streptomycin because of its better CSF penetration. Isoniazid is non-protein-bound and rapidly penetrates into the CSF, whether or not the meninges are inflamed, yielding concentrations more than 30 times the minimal inhibitory concentration for *M tuberculosis*. Pyrazinamide also has excellent penetration into CSF irrespective of meningeal inflammation.

The role of corticosteroids in the treatment of tuberculous meningitis has been relatively controversial. Corticosteroids are most beneficial in patients with severe disease and complications.
The recommended daily dose of prednisolone is 60 mg in adults and 1 to 2.5 mg/kg in children. The duration of therapy depends on the clinical response, and therapy should be titrated on an individual basis. \(^{13}\) Management of complications

Hydrocephalus, tuberculoma, and rarely, tuberculous abscess are the most important complications requiring surgery. Both hydrocephalus and tuberculoma can develop after initial improvement with antituberculosis therapy and can result in clinical deterioration. Ventriculomegaly is not always caused by hydrocephalus; it may also be caused by cerebral atrophy. Moderate to severe hydrocephalus is often associated with features of increased intracranial pressure. The degree of hydrocephalus correlates with the duration of disease. Early drainage of hydrocephalus by ventriculoperitoneal or ventriculoatrial shunt has been recommended. The high protein content or raised PMN cell count in CSF often increases the probability of shunt complication. In these situations, external ventricular drainage may have to precede shunt surgery. Mortality appears to be related to the severity of hydrocephalus. \(^{14}\)

**INTRACRANIAL TUBERCULOMA**

Tuberculoma is a mass of granulation tissue made up of a conglomeration of microscopic tubercles. The center of the tuberculoma becomes necrotic, forming caseous material, while the periphery tends to be encapsulated with fibrous tissue. There may be liquefaction of the caseous material, resulting in the formation of an abscess.

Solitary tuberculomas are more frequent than multiple lesions. The size of a cerebral tuberculoma is highly variable—the diameter ranges from a few millimeters to 3 to 4 cm. Intracranial tuberculomas in patients younger than 20 years are usually infratentorial; supratentorial lesions predominate in adults. Tuberculomas constitute about 5% to 10% of intracranial space-occupying lesions in patients in the developing world and occur in 10% of patients with tuberculous meningitis. \(^{3,4,15}\)

Most patients who have tuberculoma present with a history of fever, seizures, and focal neurologic signs, depending on the location of the tuberculoma in the brain. **Diagnosis**

CT and MRI have facilitated the assessment of intracranial tuberculomas (Figures 1, 2, and 3). The characteristic finding is a nodular enhancing lesion with a central hypointensity. The pattern of enhancement can be quite variable; homogeneous, patchy, serpentine, and ring enhancement have all been observed. Edema is nearly always present and can be quite marked. These findings are nonspecific and may simulate the appearance of glioma, metastasis, abscess, cysticercosis, and fungal granuloma. \(^{15}\)

**Management**

A therapeutic trial with antituberculosis drugs in patients with a solitary lesion suspected of being a tuberculoma is a widely accepted strategy. The efficacy of short-course chemotherapy for intracranial tuberculomas is not yet established. Corticosteroids are helpful in select symptomatic patients who have cerebral edema.

Tuberculomas begin to decrease in size within the first 2 months of antituberculosis treatment. However, paradoxical expansion of tuberculomas during treatment has also been observed. \(^{16}\) Surgery is indicated for large lesions that produce midline shift and severe intracranial hypertension and for lesions that expand during antituberculosis treatment. Surgery may also be indicated in patients who do not have improvement with therapy and who have clinical and neuroimaging findings that are consistent with a diagnosis such as glioma or metastasis.

The role of CT-guided excision biopsy for lesions larger than 20 mm is also an option, since these lesions can have a varied etiology. \(^{17}\)

**References:** REFERENCES

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