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CNS Tuberculosis

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In contrast to less developed nations where it remains a major problem, central nervous system (CNS) tuberculosis is a relatively rare clinical problem in the industrialized West, accounting for somewhat less than 0.5 per cent of cases of tuberculosis in the United States. This relative rarity often leads to delay in recognition in the few cases that are seen each year on most medical, pediatric, and neurologic services, with the notably unfortunate result of delay in therapy, as the promptness with which treatment is initiated is the most important physician-controlled factor influencing prospects for recovery and avoidance of serious neurologic sequelae.[30] Reviews of the subject, therefore, seem justified out of proportion to the size of the problem from a purely numerical point of view.

PATHOGENESIS

Meningitis

The most important point to be emphasized is that tuberculous meningitis can occur without any evidence of associated extracranial tuberculosis.

It is generally believed that the critical event in the development of meningitis is rupture of a suitably located juxtaependymal tubercle (the so-called Rich focus after Arnold Rich) resulting in delivery of antigenic and infectious material into the subarachnoid space, in which location there are, at least initially, virtually no host-defense mechanisms to impede the proliferation of the organisms.[1, 43] This indirect pathway of CNS contamination accounts for the fact that when meningitis supervenes in established miliary tuberculosis, as it does with such frequency as to be the rule in the absence of treatment, it usually does so after a period of several weeks of

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clinical illness. The association of meningitis with miliary disease is so frequent that the presence of a miliary infiltrate on chest radiographs in a patient with meningitis suffices for diagnosis of tuberculosis with a high degree of certainty.[38] Some other form of extracranial tuberculosis in the lung or elsewhere in the body will be clinically detectable in the majority of cases of meningitis.[1] In children with meningitis, extracranial tuberculosis will frequently be a manifestation of a primary infection or early post-primary event such as pleural effusion or, most importantly, miliary dissemination.[24, 48] In adults, there is also an important association with clinically apparent progressive miliary disease, but meningitis may develop from other less apparent or entirely hidden foci of chronic organ tuberculosis as well. Therefore, as mentioned, a significant proportion of cases of CNS tuberculosis will occur in the absence of demonstrable extracranial tuberculosis, and, accordingly, the absence of such does not argue against a tuberculous etiology in a given case of meningitis.

The widespread and dense distribution of infectious foci in progressive miliary tuberculosis greatly increases the chance that a juxtaependymal tubercle will be established and from this critical location breakdown to contaminate the subarachnoid space. However, lymphohematogenous dissemination with the potential to establish such a juxtaependymal focus occurs in settings other than progressive or clinically apparent active disease. In the few weeks between infection and the development of specific tissue hypersensitivity (tuberculin positivity) *all* infected persons undergo a period of asymptomatic lymphohematogenous dissemination. This *preallergic bacillemic phase* can establish metastatic foci of infection, which can then either arrest or become active after variable periods of clinical latency. It is probable that foci of chronic organ tuberculosis established in this way themselves are often the source of episodes of *secondary hematogenous dissemination,* usually per se abortive but capable of establishing other metastatic foci, including some adjacent to the subarachnoid space, with the potential for subsequent breakdown. The frequently noted association between head trauma and the development of meningitis suggests that juxtapial foci can be destabilized by physical factors. Whether the critical subependymal tubercle can evolve from foci seeded in an otherwise nonprogressive preallergic lymphohematogenous phase or is always due to secondary hematogenous spread from an area of extrameningeal chronic organ tuberculosis is a matter of disagreement but one of really little clinical importance.[1, 43] Finally, when age or intercurrent conditions such as drugs, malignancy, viral infections, or alcoholic excess significantly compromise the immune response of persons with smoldering chronic organ tuberculosis, such intermittent and previously abortive episodes of lymphohematogenous spread may slowly become progressive, leading to the clinical syndrome of *chronic hematogenous tuberculosis* or, as it has been called in a recent and excellent summary, *late generalized tuberculosis.*[47] It is of note that meningeal involvement was found in 54 per cent of the cases in that study in which sufficient postmortem anatomic examination of the brain had been carried out. Reports of CNS tuberculosis occurring in patients with the acquired immunodeficiency syndrome (AIDS) will undoubtedly increase.[13] Moreover, it is important to note the occur-

rence of tuberculous infection in the elderly nursing home population.[51] Tuberculous meningitis can also result from spread from an adjacent focus in the vertebral bodies or cranium.[43]

Tuberculomas

Tuberculomas defined clinically as space-occupying lesions producing neurologic symptoms are quite rare in the West although they are common in children in India. However, if they are to be defined roentgenographically as lesions apparent on computerized tomographic (CT) scanning, they may be seen in a large minority of cases of tuberculous meningitis, suggesting that tuberculomas may serve as the source of contamination of the subarachnoid space.[2, 35] Information deriving largely from CT scanning and clinical correlations therewith indicate that foci in the brain parenchyma may cause poorly localized areas of cerebritis with or without meningitis, may go on to abscess formation with surrounding encapsulation, may become the more classical solid encapsulated tuberculomas, or may reach the surface of the brain and cause meningitis.[2, 35, 36]

PATHOLOGY

Three features dominate the pathology and explain the clinical manifestations of tuberculous meningitis: (1) proliferative inflammatory, meningeal exudate, (2) vasculitis of the arteries traversing this exudate, and (3) disturbance of cerebrospinal fluid circulation or resorption.[1]

Proliferative arachnoiditis is most marked at the base of the brain, and in cases of more than a few days in duration may become quite thick, gelatinous, and mass-like, extending from the pons to the optic nerves but most prominent in the area of the optic chiasm.[8] As the process of optochiasmatic arachnoiditis becomes more chronic, it may come to resemble a fibrous mass, involving and compromising the function of cranial nerves one through eight in some combination. Uncommonly, a similar gelatinous or fibrous process can surround the spinal cord, producing various symptoms by encroaching on exiting spinal nerves.

Vasculitis with inflammation, spasm, constriction, and eventual thrombosis resulting in cerebral infarction develops in vessels that traverse this basilar (or spinal) exudate. The middle cerebral arteries or branches thereof are most frequently and seriously involved, the anterior cerebral circulation less so, and the posterior least. Much importance is also attached to spasm or thrombosis of perforating branches of the middle cerebral arteries that supply the basal ganglia, compromise of which may result in disturbances of motion, and to thrombosis of the anterior spinal artery, which may result in infarction of the spinal cord.

Hydrocephalus develops in the majority of cases of tuberculous meningitis that have been symptomatic for more than 2 or 3 weeks.[2] This is most often communicating in nature, due to inflammatory obstruction of the basilar cisterns. Less frequently, there will be obstruction of the aqueduct by contraction of exudate surrounding the brain stem, by inflammation of the ependymal lining of the ventricles, or by a strategically placed

brain-stem tuberculoma.[34] Swelling of the brain due to accumulation of cerebrospinal fluid (CSF) and increased intracranial pressure can cause brain-stem compression with tentorial herniation.

CLINICAL FINDINGS

Symptoms and Signs

Classically, tuberculous meningitis has been divided into prodromal, meningitic, and paralytic stages. The usual history describes a subacute prodrome of insidious onset with fever, malaise, and intermittent headache in some combination, followed by more prominent neurologic findings including meningismus, severe headache, altered consciousness, cranial nerve palsies, and long tract signs.[23] Without treatment, death usually occurs in 5 to 8 weeks.[37] As mentioned earlier, evidence of tuberculosis elsewhere in the body will be found in 20 to 70 per cent of cases, more often in children than adults. The symptoms and signs compiled in a recent well-studied series are presented in Table 1.

For purposes of prognosis, it is helpful to categorize patients into clinical stages according to the degree of illness. Stage 1 comprises patients who are conscious and rational, with or without meningismus but with no focal neurologic signs or signs of hydrocephalus. In stage 2, patients are confused or have focal neurologic signs such as cranial nerve palsies or hemiparesis, and in stage 3, patients are deeply comatose or delirious and some have dense hemiplegia or paraplegia.[30] The stage of the illness on presentation is significantly related to its duration, although some patients may progress to advanced illness within a few days.[56] Importantly, prognosis is very much determined by the clinical stage at the time therapy is initiated. The data in Table 2 are also from the series of Kennedy and Fallon. In essence, all patients in clinical stage 1 at time of diagnosis recovered, and only one had minor neurologic sequelae; in contrast, almost one quarter of those with clinical stage 2 and 3 at time of diagnosis died, and several survivors had major neurologic sequelae.

Laboratory

A positive *tuberculin test* may be of some diagnostic importance, especially in very young children. However, a negative test even in the very young is of no help at all, as it can be falsely negative in a significant minority or even a majority of various series.[24, 37, 48] A mild anemia may be present, but often the CBC and even the sedimentation rate are entirely normal. Blood chemistries are usually normal except as altered by a chronic febrile state. The only exception to this with some degree of diagnostic importance is hyponatremia and the clinical and biochemical features of inappropriate secretion of antidiuretic hormone, which have been observed in a substantial minority of cases of miliary tuberculosis complicated by meningitis.[28, 38, 50, 54]

Table 1. *Preadmission Symptoms and Admission Clinical Signs*

SYMPTOM	NO. OF CASES
General	
Respiratory	16 (31)
Pains	16 (31)
Fever	10 (19)
Weight loss	10 (19)
Fatigue	9 (17)
Irritability	9 (17)
Gastrointestinal	
Vomiting	37 (70)
Anorexia	26 (50)
Constipation	19 (37)
Neurologic	
Headache	38 (73)
Drowsiness	14 (27)
Confusion	9 (17)
Diplopia	6 (12)
Convulsions	5 (10)
SIGN	
General	
Pharyngitis	11 (21)
Lung adventitial sounds	9 (17)
Lymphadenopathy	8 (15)
Neurologic	
Meningeal irritation	47 (90)
Drowsiness	23 (44)
Confusion	15 (29)
Stupor	6 (12)
Coma	2 (4)
Papilledema	16 (31)
Extensor plantar	13 (25)
Cranial nerve palsies	10 (19)
Hemiparesis	2 (4)
Choroidal tubercle	1 (2)

(*From* Kennedy, D. F., and Fallon, R. J.: Tuberculous meningitis. J.A.M.A., *241*:264, 1979; with permission.)

Table 2. *Clinical Stage on Admission and at Start of Treatment*

			CATEGORY OF OUTCOME			
STAGE	ADMISSION	TREATMENT	1	2	3	4
1	16*	10	9	1	0	0
2	28	30	21	5	1	3
3	8	11	5	0	1	5
Total	52	51	35	6	2	8

*One patient was not treated (patient recovered)

Outcomes: 1—Normal; 2—Minor neurologic sequelae; 3—Major neurologic sequelae; 4—Death.

(*From* Kennedy, D. H., and Fallon, R. J.: Tuberculous meningitis. J.A.M.A., *241*:264, 1979; with permission.)

Cerebrospinal Fluid

The key to diagnosis is most often *examination of the CSF.* The classic CSF findings are an elevated protein, decreased glucose, and lymphocytosis. Again, using the data in Kennedy and Fallon's series, 65 per cent of patients had between 100 and 500 cells per mm^3. Fourteen per cent contained 99 or less, and 21 per cent were between 500 and 1500.[36] Lymphocytes were the preponderant cells in 73 per cent of this series, but the remainder demonstrated a majority of polymorphonuclear (PMN) leukocytes, usually early on in the course. The CSF protein was between 100 and 500 mg per 100 ml in 65 per cent of cases but under 100 in 25 per cent and greater than 500 in 10 per cent. Cases with subarachnoid block, particularly those with spinal meningitis, may develop extremely high protein contents associated with xanthochromia, a sign of poor prognostic import. CSF sugar content, said to be characteristically low, was less than 45 mg per 100 ml in only 17 per cent of the cases in this series. *The importance of repeated, careful examination of spinal fluid specimens cannot be overemphasized.* AFB were visible on the stained CSF sediment in 37 per cent of Kennedy and Fallon's patients on initial examination, but the *percentage diagnosable by smear rose to 87 per cent when fluid from four serial spinal taps was examined.* Although this percentage is much larger than in most experiences, other series using multiple samples have reported equally good results.[25, 53] It is advisable to use the centrifuged sediment of 10 or more ml of CSF for acid fast staining and to spend at least 30 minutes examining each specimen. Fluorescent staining is advantageous in terms of ease of diagnosis, but simultaneous staining with the Kenyoun stain or its equivalent is also advisable in view of the great importance of diagnostic accuracy. With regard to cell content, it is always observed that fluids that are atypical at the onset, such as containing no cells at all or an unusually large number of cells with PMN predominance, will evolve in the direction of more typical findings with repeated taps.[26] The initial PMN response has been conceptualized as essentially allergic, analogous to a tuberculin reaction, and quite transient, being replaced by cells reflecting the character of the mononuclear cellular response to tuberculosis as time passes. Misinterpretation of this sequence as improvement or as response to antibacterial therapy when an erroneous diagnosis of pyogenic meningitis is being entertained can have very severe consequences.[31, 37] An initial mononuclear pleocytosis may briefly change in the direction of PMN preponderance when therapy is initiated, and this may be associated with clinical deterioration.[57, 60] Smith has stated that such a "therapeutic paradox" is almost pathognomonic of tuberculous meningitis.[49] A lowered CSF chloride, presumably due to the presence of anionic protein, is characteristic of tuberculous meningitis but of no real diagnostic or prognostic importance.[37] Attempts have been made to develop sensitive assays for tuberculous antigen or antibody in the CSF.[21, 27, 44] Although these assays promise a rapid means of diagnosis, the tests are not widely available nor has their sensitivity and specificity been confirmed. Cultures of CSF will be positive in as many as 80 per cent of cases, but if the patient is to survive, therapeutic decisions have to be joined long before the results

of culture are available. Routine cultures of CSF when normal chemistries and cell count are present are not warranted.[17]

Atypical Cases

The typical case of tuberculous meningitis should be easily diagnosed by a thoughtful and thorough clinical analysis. It is more useful in a review such as this to emphasize the atypical case. Cranial nerve symptoms in tuberculous meningitis are usually due to pressure on the nerves as they traverse the basilar optochiasmatic arachnoiditis. However, instances of internuclear ophthalmoplegia have been observed in tuberculous meningitis.[45] This condition, usually due to multiple sclerosis in younger individuals and to atherosclerotic or hypertensive cerebrovascular disease in older persons, is a result of disease involving the medial longitudinal fasciculus. It is characterized by adduction paresis of one or both eyes on lateral gaze, often with nystagmus of the abducting eye and failure of convergence. Cases of tuberculous meningitis with both the clinical and CSF picture of acute bacterial meningitis have been described; and on the other end of the spectrum are cases in which low grade symptoms of headache and intermittent fever have been present for months before diagnosis. The designation of serous tuberculous meningitis has been applied to cases with low-grade meningeal symptoms and a low-grade pleocytosis but no culturable or stainable organisms, often recurring over a prolonged period.[59, 60] A patient reported by Taylor and associates had miliary tubercles throughout the brain and an encephalitic course but negative spinal fluid examinations at weekly intervals on eight occasions until death.[56] The rapidity with which a case can progress emphasizes the need for immediate therapeutic decision. Case 2 reported by Gerstenbrand and associates had a normal CSF and normal neurologic examination on the day of admission, on day 12 developed oculomotor nerve palsies and bilateral pyramidal signs, at which time the CSF contained 112 cells and increased protein. On day 20, a full "midbrain syndrome" had developed, antituberculous therapy was initiated, and the condition further deteriorated. On day 35, the patient died with deep coma and extensor rigidity. A partial list of differential diagnostic considerations (Table 3) is really only useful if it serves to bring up the possibility of tuberculosis when these other conditions are entertained.

CT Scans

Various neurodiagnostic procedures such as radionuclide brain scanning, air contrast ventriculography, and contrast cerebral angiography that previously had some place in CNS tuberculosis have now been virtually entirely replaced by the *head CT scan*. This has considerably enlarged concepts of pathogenesis, particularly with respect to the unsuspected frequency of *tuberculomas* (as defined by the CT scan) in cases clinically classified as meningitis; the demonstration of *basilar optochiasmatic arachnoiditis* with its implications for the development of vasculitis and infarction; and particularly in detecting with precision the development, course, and response to therapy of *hydrocephalus*. Enhanced CT scans in cases of miliary disease with no clinical meningitis have demonstrated multiple small cerebral lesions compatible with tuberculomas.[52, 63]

Table 3. *Differential Diagnostic Considerations*

Partially treated bacterial meningitis
Focal parameningeal infection
Fungal meningitis (cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis)
Subdural empyema
Dural sinus thrombophlebitis
Viral meningitis
Viral encephalitis
Amoebic (Naeglaria) meningoencephalitis
Pyogenic brain abscess
Toxic encephalitis
Metabolic encephalitis
Alcohol withdrawal syndromes
Acute dementia
Cerebrovascular accident
Listerial meningitis
Neoplastic meningitis, lymphomatous or epithelial
CNS sarcoidosis

In a study from India, CT scans of 60 patients with tuberculous meningitis revealed hydrocephalus in 83 per cent.[2] The incidence of hydrocephalus correlated with duration of illness and was present in all patients who survived 4 to 6 weeks without therapy. It was more frequent in children than adults and was thought to be most frequently communicating in nature, although in a large minority aqueduct compression or obstruction had resulted in obstructive hydrocephalus. The CT scan was thought to be important prognostically. *Those with entirely normal scans all recovered completely without residua.* Those with moderate basilar exudate and hydrocephalus responded well to early ventriculoatrial shunting. Those with severe basilar exudate did not improve even with shunt surgery, and exudate enhancement after contrast injection was said to have negative prognostic import. Cerebral infarcts were seen in 28 per cent of cases, involving not only the distribution of the main middle cerebral artery, but also its thalamoparietal and lenticulostriate branches, leading to basal ganglia infarcts. Tuberculomas were discovered in 10 per cent. Another series of 37 patients emphasized the poor prognostic import of "basilar edema" on CT scan, which was believed to be due to infarction in the region of the basal ganglia.[5]

The term *tuberculoma* as defined by CT scan clearly connotes a broader range of pathologic changes than when it is applied to clinical cases with syndromes of intracerebral space-occupancy or pathologic material with clearly defined cerebral granulomas. Tuberculomas as defined by CT scanning are often multiple, early on have a hypodense center that with aging proceeds to isodensity and then hyperdensity, it may or may not have a surrounding capsule of granulomatous inflammatory tissue with contrast enhancement, and in some cases may demonstrate another yet more peripheral concentric ring of low density due to cerebral edema without inflammation.[22, 35] Although disappearance with therapy is the rule, cases have been described in which symptomatic tuberculomas have developed some years after successful therapy of tuberculous meningitis with an initially negative CT scan.[57]

Tuberculous brain abscess, by which is meant a lesion containing frank pus and not associated with clinical meningitis, cannot be differentiated from more solid tuberculomas on the basis of CT scanning. Reichenthal and colleagues described one patient with weakness in the left arm for 5 years and severe headaches for 4, who was finally operated on when left leg weakness supervened and was found to have an appropriately located abscess containing 15 ml of pus.[42] In commenting on the differences and similarities of pyogenic brain abscesses and tuberculous brain abscesses on CT scanning, the authors stated that although there were many similarities, tuberculous abscesses demonstrated thicker and more regular enhancing capsules and generally had a longer symptomatic period. Another variation on the theme of parenchymal CNS tuberculous lesions has been designated as "focal tuberculous meningoencephalitis" by Trautmann and associates.[58] A variety of clinical presentations were described including hemiplegia, paraplegia, sudden onset of confusion with lack of meningismus, and focal (Jacksonian) epilepsy. Examination of the CSF demonstrated either nearly normal or predominantly PMN pleocytosis. The CT scan in these cases showed ill-defined areas of increased density that were enhanced with contrast injection but no encapsulation. The clinical and pathologic descriptions suggest that "focal tuberculous cerebritis" would be just as descriptive a name. Tuberculoma, tuberculous brain abscess, and focal tuberculous meningoencephalitis seem to be very closely related processes, or different stages of the same process in some cases. Further, although expertise will surely develop, review of the literature at present warrants little confidence that these various tuberculous pathologic entities can really be distinguished with accuracy; or more importantly, that tuberculomas and related conditions can really be differentiated from brain abscesses and tumors with certainty sufficient for therapeutic decisions.

Prognostic Factors. As mentioned, prognosis in an individual case is influenced by duration of illness, the clinical stage at the time treatment is instituted, and the presence and course of the CT scan features enumerated, particularly the presence, extent, and character of optochiasmatic arachnoiditis, whether or not infarctions are present, and the presence and course of hydrocephalus.[2, 30] Mortality is greatest under age 5 and over age 50: 20 per cent and 50 per cent, respectively, in the recent series of Kennedy and Fallon quoted here.[30]

Tuberculous Spinal Meningitis. Discussion of Pott's paraplegia and related neurologic syndromes caused by tuberculous spondylitis is beyond the scope of this review. However, rarely, tuberculosis can cause spinal-cord disease without spondylitis and in the absence of clinical meningeal or intracerebral involvement. Several different pathologic mechanisms may be operative. Meningitis may be confined to the cord and result in its partial or complete encasement in a gelatinous or fibrous exudate, with impingement on nerves producing some combination of nerve root and cord signs, or with thrombosis of the anterior spinal artery producing cord infarction.[31] Tuberculoma is an uncommon spinal-cord tumor. In one recent series of 145 intradural and intramedullary spinal-cord tumors, tuberculomas were found in two cases.[8] A collected series of 104 such cases has been reported by Lin.[33] An epidural granulomatous mass or abscess may also

cause symptoms of a cord mass-lesion with no evidence of meningeal involvement.[29, 41] A wide variety of clinical symptoms can result including pain, hypesthesia, paresthesia, or anesthesia in the distribution of a nerve root; a lower motor neuron type of paralysis; upper motor neuron paralysis; and bladder or rectal sphincter incompetence. All of these spinal lesions, epidural, meningeal, and intramedullary, can cause spinal subarachnoid block, with extremely high concentrations of protein in the CSF, with or without a cellular response.[31, 62]

Complications. Residual neurologic defects after recovery from tuberculous meningitis are observed in about one fourth of patients and include chronic brain syndrome, hemparesis, paraplegia, optic atrophy with blindness, oculomotor palsy, deafness, convulsive disorders, and various symptoms of hypothalamic or pituitary dysfunction, including Cushing's syndrome, sexual precocity in children, obesity, diabetes insipidus, and somnolence.[12, 30, 60]

Tuberculomas. The appearance of tuberculomas on CT scanning and the fact that they are much more frequent defined roentgenographically than clinically, has been discussed. In areas of the world in which these are frequent intracerebral tumors or in circumstances in which the diagnosis seems probable, the effects of antimicrobial therapy should be assessed before resorting to surgery, as good resolution is often observed and residual neurologic defects are often less with medical therapy than with surgical excision.[20, 36] When diagnosis has been made at craniotomy, chemotherapy will prevent spread of infection. In areas of the world such as India, in which tuberculomas are frequent, biopsy at craniotomy and assessment of the results of chemotherapy without further excision are being advised.[20] Intramedullary tuberculomas of the cord can probably be approached in the same way, although experience with a conservative medical approach based on chemotherapy in cord lesions is much less extensive, and excision will often be carried out before the nature of the process is known.

THERAPY

The most important principle of therapy is that it should be initiated when the disease is suspected, not delayed until proof has been obtained. Much more harm results from delay, even of only a few days, than from inappropriate therapy as long as one persists in continuing to try to confirm the diagnosis.

CHEMOTHERAPY

It should be emphasized at the outset that there are really no clinical trials that can be relied upon concerning the chemotherapy of tuberculous meningitis other than the early demonstration that the prognosis was radically altered by the advent of isoniazid.[12] Furthermore, it is unlikely, given the incidence of the disease, that reliable, large, controlled trials of the sort that are available with respect to pulmonary tuberculosis will ever

be forthcoming. Recommendations are generally made on the basis of reasoning by analogy to pulmonary tuberculosis, the appropriateness of which is by no means certain. In pulmonary tuberculosis, the severest test of chemotherapy, other than drug resistance, is the huge number of organisms often present in cavitary lesions. In meningeal tuberculosis, the number of organisms is really quite small, the challenge to chemotherapy is delivery of drugs to the point of infection and, perhaps more importantly, promptness of onset of action so as to forestall the damage that can result from the host response to infection.

Isoniazid

In any event, it is clear that the advent of isoniazid (INH) radically changed the prognosis of tuberculous meningitis, and it remains the cornerstone of treatment.[12] Its CSF-serum concentration ratio, even in the presence of normal meninges, is approximately 0.4, and with meningeal inflammation, the concentration equals that in serum.[9] Dosages of 10 mg per kg in adults and slightly higher in children are advisable until a favorable course has been established. Administration of pyridoxine at a dosage of 50 to 100 mg a day is necessary when using these doses of INH, especially as some of the neurologic features of INH-induced pyridoxine deficiency may be confused with the complications of meningitis. An injectable form of INH can be obtained when the drug cannot be administered by mouth or by nasogastric tube. The dosage is the same as by mouth.

Rifampin

It is customary to advise the use of the other major antituberculous agent, rifampin (RMP) as well, although, as mentioned, suitably large controlled series supporting that recommendation are really not available. One retrospective analysis reported that a combination of INH and RMP was significantly better than regimens not containing RMP, although this difference was not apparent in patients treated with INH at a dosage of 15 mg per kg, and the series suffered from the faults intrinsic in retrospective analysis.[32] One small prospective series comparing INH, RMP, and streptomycin (STM) with INH, para-aminosalicylic acid (PAS), and STM in Indian children recorded slightly more rapid recovery and slightly less neurologic residua in those treated with the RMP-containing regimen; neither of these differences was statistically significant or impressive.[40] However, these gains appeared to have been more than offset by a major incidence of early onset (within 33 days) hepatotoxicity in six cases (27 per cent), one of which was fatal. A similarly large incidence (eight of 27 or 30 per cent with one fatality) of early onset hepatotoxicity in patients receiving both INH and RMP was noted by Traub and coworkers.[57] RMP penetrates poorly into the CSF in the absence of inflammation of the meninges, but in the presence of meningeal tuberculosis reaches levels about 20 per cent of those in serum that are maintained for a long period.[10, 46] These RMP concentrations are well above the minimal inhibitory concentration for sensitive tubercle bacilli.

Ethambutol

Ethambutol (EMB) also does not appear in the CSF after oral administration in the absence of meningeal inflammation, but in clinical tuberculous meningitis reaches levels (0.5 to 5 μg per ml) that are roughly equivalent to the minimal inhibitory concentration of EMB which sensitive *M. tuberculosis*.[3] A recommendation of a dosage of 35 mg per kg has been made by one authority, at which dosage the incidence of optic neuritis is probably as high as 5 per cent, at least with prolonged use.[6, 57] Most authorities recommend using 25 mg per kg (at which dosage the incidence of optic atrophy is approximately 2 per cent with prolonged administration) and decreasing the dose to the much safer 15 mg per kg within 2 months or so, a period too short for most cases of optic neuritis to develop.

Pyrazinamide

Pyrazinamide (PZA) has much to recommend it in the treatment of CNS tuberculosis, although there are no clinical trials to support its use. Nevertheless, it is biochemically very similar to INH and penetrates both inflamed and noninflamed meninges to about the same extent as INH.[14, 16] It has substantial bactericidal activity at an acid pH. Although there was initially a good deal of concern about the use of three hepatotoxic drugs (INH, PZA, and RMP) in so-called ultrashort course chemotherapy of pulmonary tuberculosis, in fact, in the dosages used (30 to 35 mg per kg) and for the length of time employed (usually 2 months or less), PZA has been strikingly free of hepatotoxicity.[4] It is our recommendation that PZA be used with INH and RMP, especially if corticosteroids are to be employed, as the anti-inflammatory effect of steroid therapy in all probability impairs the delivery of both RMP and EMB to the subarachnoid space.

Streptomycin

Streptomycin (STM) and other aminoglycosides penetrate the blood-brain barrier (BBB) poorly even in the presence of inflamed meninges and not at all in the absence of inflammation. Nevertheless, it is worth recalling that STM, sometimes administered intrathecally with enormous eighth nerve toxicity, was life saving in many cases of tuberculous meningitis before the availability of INH. With situations in which drug resources are limited, it is certainly appropriate to use an aminoglycoside, probably STM, in the conventional dosage of 1 gm daily in adults by intramuscular injection. There is probably no place now for intrathecal STM.

Recommended Regimen

Although the choice is somewhat arbitrary, we are at present recommending treatment with INH, RMP, EMB, and PZA given together, in view of the striking success of these drugs in ultrashort course chemotherapy of pulmonary tuberculosis. This seems to be particularly advisable in patients from areas of the world (Asia, Latin America, and probably Africa) in which the incidence of primary drug resistance is quite high. It has been the almost invariable experience in treatment of pulmonary tuberculosis

that the presence of initial drug resistance does not influence the outcome when maximal chemotherapy is used in this fashion.[15] We would stop EMB and PZA after 2 months in the presence of a good response, decrease the dosage of INH, and continue INH and RMP for a total of 1 year. Biochemical monitoring for hepatitis should be done to detect drug-induced liver disease at an early stage. It is to be emphasized that this is a personal and arbitrary recommendation and that in fact, the most important aspect of chemotherapy of tuberculous meningitis is that it be initiated early and that it contain INH as a component.

ADJUNCTIVE THERAPY

Although, again, controlled data supporting the practice are lacking, most authorities advise the use of *corticosteroids* (in dosage equivalent to 60 mg of prednisone in adults and 1 to 3 mg per kg in children) in most cases of tuberculous meningitis.[11, 39] One recent review has listed as indications any of the following: altered consciousness, focal neurologic abnormalities, spinal fluid pressure in excess of 300 mm of water, and spinal block.[37] To this list is seems reasonable to add evidence of either hydrocephalus or basilar optochiasmic pachymeningitis on CT scanning. Patients without neurologic compromise and a normal CT scan have an excellent prognosis, and it is probable that the risk of steroid-related complications are not warranted in this small subset of patients. It is to be recalled that it is likely that steroids will decrease the CSF penetration of both RMP and EMB. Use of steroids presupposes a positive or highly probable diagnosis.

Surgical Decompression of the Ventricles

This is conventionally carried out when hydrocephalus is present and fails to resolve on therapy, especially when there is substantial neurologic compromise. Although results have been by and large good enough that the procedure continues to be recommended, some authorities with broad experience indicate that there is a substantial incidence of complications, largely infections, and satisfactory results are not always forthcoming.[55, 61]

Hyaluronidase

Although the procedure remains experimental and cannot be recommended here for routine use, a very impressive study by Gourie-Devi and Satish recommends the use of hyaluronidase administered intrathecally in the cases of intrathecal arachnoiditis complicating tuberculous meningitis.[19] The results were said to be superior to those obtained by ventricular decompressing operations.

SUMMARY

Tuberculous meningitis is a rare, treatable neurologic disorder, in which early recognition is paramount because outcome depends greatly on

the speed with which therapy is initiated. Patients with meningitis and CSF findings of low glucose, elevated protein and pleocytosis with evidence of tuberculosis elsewhere in the body (chest radiographs, positive tuberculin skin test), or a history of exposure to tuberculosis should be treated immediately with antituberculous medication. When the diagnosis remains uncertain, serial examination of the CSF for tuberculous organisms will often yield positive results. The CT scan may show hydrocephalus, a basilar arachnoiditis, or intraparenchymal lesions: tuberculomas. Hydrocephalus may respond to early shunting. Tuberculomas are best treated medically. Therapy should include INH and rifampin; ethambutol and pyrazinamide are suggested for the first 2 months of therapy. Steroids may be useful in diminishing the inflammatory response when altered consciousness or focal neurologic signs are present.

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