Intracranial Tuberculoma in Children: A New Look at an Old Problem

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ABSTRACT: Intracranial tuberculoma has become a rare cause of space-occupying intracranial lesions in childhood, but it must still be considered in the differential diagnosis. Tuberculosis remains a significant disease in developing countries and in the United States, and tuberculoma is a well known presentation of childhood tuberculosis. This diagnosis must be considered especially in persons traveling or living in developing countries and in immigrants from third-world areas. We report three cases of tuberculoma in children seen during one year at our institutions to illustrate the need for continued suspicion. We summarize the clinical presentation and current treatment recommendations and review the available literature.

INTRACRANIAL TUBERCULOMA is a well known complication of *Mycobacterium tuberculosis* infection in childhood. Despite the rapid decline in the incidence of tuberculosis in industrialized countries since the advent of effective antituberculous therapy, the disease continues to be a significant problem in third-world countries. In India, about 20% of intracranial mass lesions are tuberculomas,[1] with corresponding figures of 16% in South America[2] and 10% to 20% in Africa.[3] For comparison, tuberculomas accounted for only 0.18% of all brain tumors examined by biopsy in a New York study between 1955 and 1981.[4]

Because tuberculosis is an important treatable cause of intracranial mass lesions in childhood, a history of any exposure to tuberculosis must be actively sought in all such cases. Suspicion must be higher in persons living in third-world countries or immigrants coming to the United States from such areas. We describe two such patients seen during one month at The University of Texas M. D. Anderson Cancer Center, and one patient during the same year at Texas Children's Hospital.

CASE REPORTS

Case 1. A 15-year-old Cambodian girl had a five-month history of left parietal headaches. She had had one seizure characterized initially by aphasia and progressing to generalized clonic activity. An EEG showed a nonspecific irritative discharge emanating from the left temporal region. A CT scan (Fig 1) showed a hyperdense mass in the left temporal lobe with some mass effect and edema; there was diffuse contrast enhancement of the mass around a pinpoint area of central lucency. She had a five-year history of left-sided suppurative otitis media. The patient had been born in Cambodia and had immigrated to the United States four years previously, at which time she had a mildly positive PPD test result with normal chest x-ray findings, as did two of her siblings and her parents. One brother had a positive PPD result with hilar adenopathy, and was treated with isoniazid and rifampin for eight months; our patient had been treated with isoniazid for five months. Physical examination was unremarkable except for bilaterally retracted and scarred tympanic membranes with a 2 mm perforation in the posterior quadrant on the left. Results of neurologic examination were normal except for a mild palsy of the right seventh cranial nerve and right palmar graphesthesia. Chest x-ray findings were normal, and a PPD test was nonreactive.

At craniotomy, a 1.0 x 1.0 x 1.0 cm firm, gray, well circumscribed mass was resected from the anterior portion of the left temporal lobe. Postoperatively, she was treated with broad spectrum antibiotics and also with isoniazid, rifampin, ethambutol, and pyridoxine. Histopathologic study of the lesion showed a necrotizing granuloma with surrounding gliosis and chronic inflammatory cells, especially in perivascular areas. All stains and cultures were negative, and broad spectrum antibiotic coverage was discontinued.

Eighteen months after diagnosis, the patient is doing well and has had no seizures since operation. Antituberculous therapy is being discontinued and CT scan of the brain (Fig 1) remains stable.

Case 2. A previously healthy, 4-year-old girl had been sent home from her nursery school in the Philippines with a note stating she had suddenly become cross-eyed. The right eye deviated medially, and the patient was unable to maintain it in the midline position. Though no other abnormalities were initially noted, right facial weakness developed one week later. A CT scan of the brain was interpreted as normal, although later review suggested slight enlargement of the medulla and lower pons with mild compression of the fourth ventricle; no

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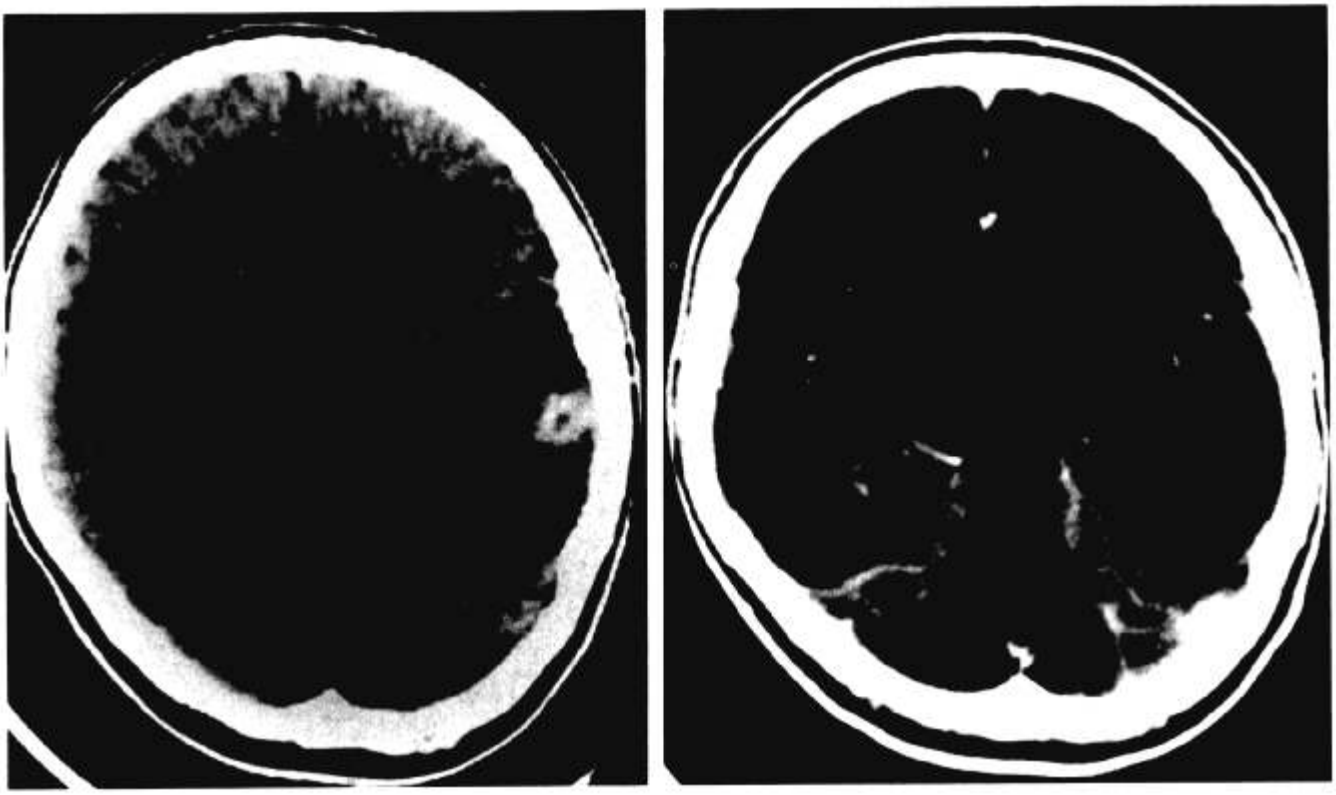

FIGURE 1. (Case 1) *(Left)* Preoperative CT scan with contrast enhancement shows left temporal mass with surrounding edema. *(Right)* One year after resection, CT scan shows only a small area of lucency.

discrete mass was seen, however, with or without contrast. Magnetic resonance imaging (MRI) showed a very discrete area of increased signal in the brain stem in the area of the lower pons and upper medulla and impinging upon the right posterior quadrigeminal plate (Fig 2). Because these findings were believed to be consistent with a glioma, the patient was given dexamethasone, and radiation therapy was proposed. The child was referred to us for a second opinion.

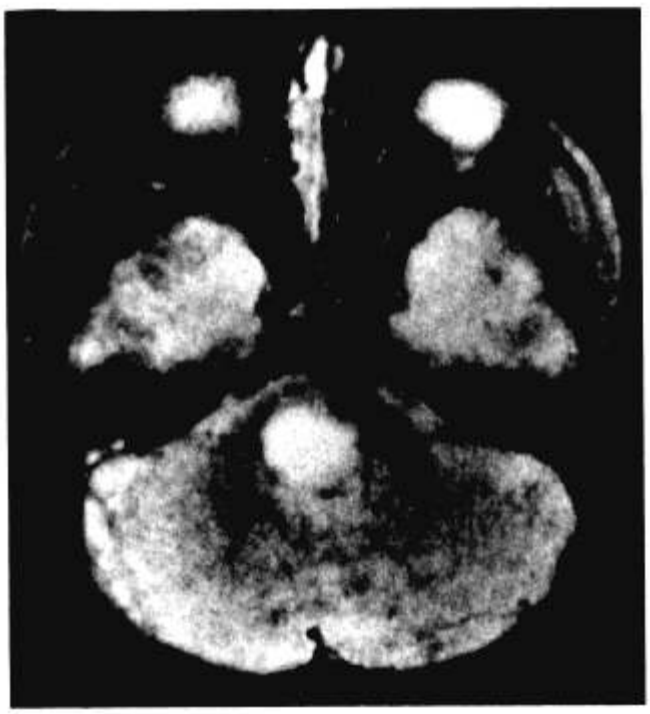

FIGURE 2. (Case 2) MRI appearance of brain stem lesion.

The patient had been hospitalized at 13 months of age with bilateral pneumonia and atelectasis that had responded to intravenous antibiotics. Eighteen months before her current illness, she had had a positive tuberculin skin test and had been treated with isoniazid for one year. Her father, a United States Army officer stationed in the Philippines, had no history of tuberculosis, but her mother, who was of Filipino/Caucasian descent, had a history of a positive skin test and antituberculous therapy. The family lived off base in the Philippines, and their other child, a boy, had no history of tuberculosis. They had traveled only in the United States and the Philippines.

The only positive findings on physical examination were palsies of the right sixth and seventh cranial nerves. Because of her history of exposure to tuberculosis, a diagnosis of tuberculoma was suspected, and the patient was given triple-drug therapy with isoniazid, pyrazinamide, and rifampin. Dexamethasone therapy was continued for two weeks. Both cranial nerve palsies resolved gradually; at 15-month follow-up, the child remained symptom free.

Case 3. A 10-month-old Hispanic-American girl had right head tilt, medial deviation of the right eye, and increasing weakness. One week before admission she had begun falling to one side when sitting. Her grandfather had weight loss, cough, and hemoptysis; he also had a positive PPD test result, but only an old fibrotic lesion showed on chest x-ray examination. Several of the patient's aunts and cousins also had positive results of PPD testing.

Physical examination showed no abnormalities except for palsy of the right sixth cranial nerve and intermittent right

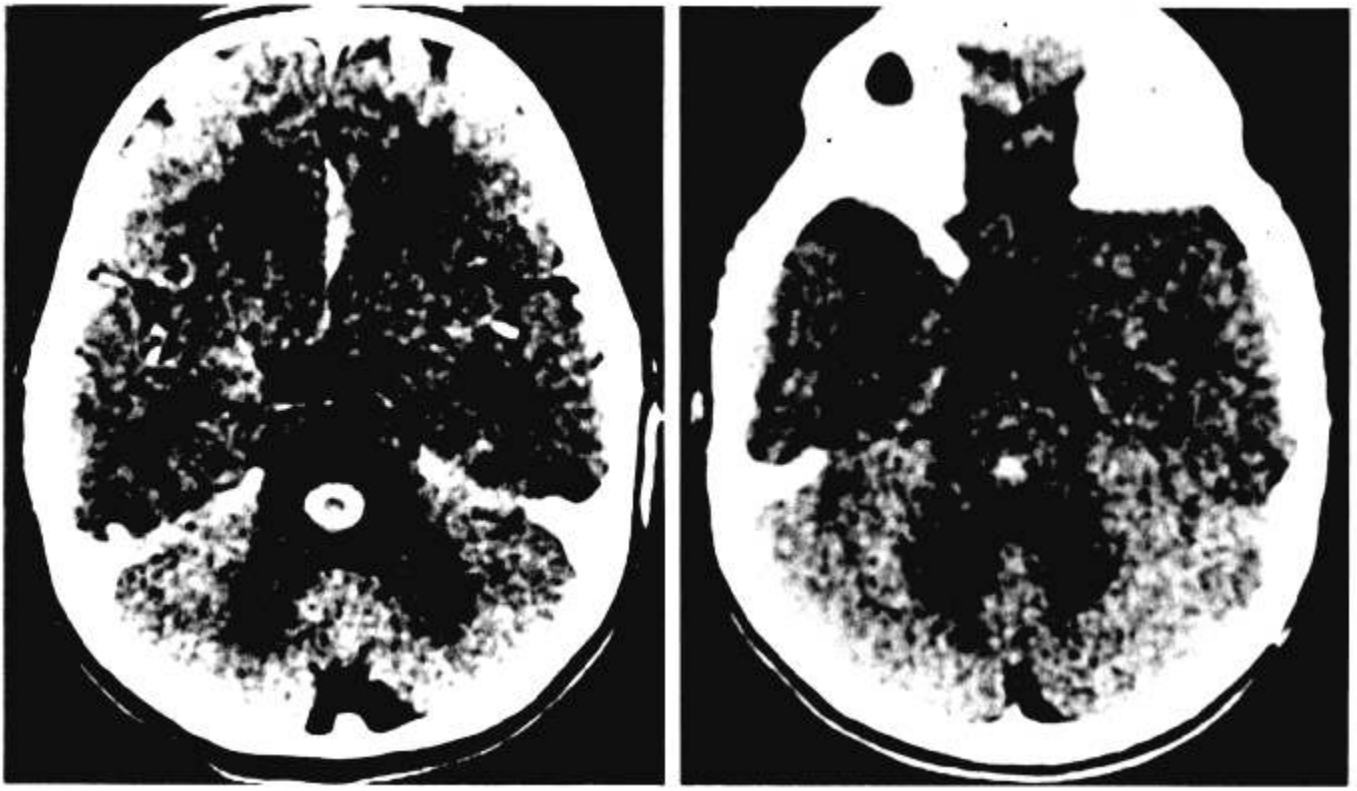

FIGURE 3. (Case 3) *(Left)* CT scan shows pontine lesion with contrast enhancement. *(Right)* After seven months of antituberculous therapy, CT scan shows only punctate calcifications remaining.

ptosis. A CT scan showed a small ring-enhancing lesion in the mid pons with surrounding edema extending through the pons and medulla; there was marked enhancement with contrast (Fig 3). A lumbar puncture showed a normal opening pressure with 15 white blood cells (94% monocytes and 6% eosinophils), one red blood cell, a protein level of 13 mg/dl, and a glucose level of 86 mg/dl. Results of all special studies, stains, serologic tests, and cultures were negative.

Five days after initiation of a course of dexamethasone, PPD and tetanus skin tests were negative, but because of the suggestive history and appearance of the lesion, isoniazid, rifampin, and pyrazinamide were administered. The patient's symptoms and the CT appearance of the lesion improved dramatically during the next two weeks. She was weaned from steroids after six months of treatment, completed one year of antituberculous therapy, and has done well. Follow-up CT scan (Fig 3) showed resolution of the lesion with punctate calcifications visible at the site. Her mother recently became PPD-positive.

DISCUSSION

In the minds of most pediatricians and pediatric oncologists trained in the United States over the last few decades, tuberculosis is not high on the list of differential diagnoses of brain lesions in children. The current unprecedented population migrations force us to consider tuberculosis in the differential diagnosis, as the first two cases illustrate. Tuberculosis continues to be quite common in many parts of the world, especially in Central and South America, Southeast Asia, India, parts of Africa, and many island nations. Clinicians must have a high level of suspicion, and should always question patients from such areas specifically about tuberculosis.

Despite the rapid decline of tuberculosis in the United States, it continues to be an endemic disease here, with almost 22,000 cases reported to the Centers for Disease Control in 1985.[5] Consequently, as our third case illustrates, tuberculomas may occur even in patients who have never traveled outside of the United States. Many clinicians underestimate the prevalence of tuberculosis in the United States.

Generally, tuberculomas are solitary, although they are multiple in 15% to 34% of cases.[4] Children are slightly more likely to have infratentorial lesions,[6] whereas supratentorial lesions are usually reported to be more common in adults.[4] Grossly, the lesions are well circumscribed, grayish white masses; central areas of necrosis may be found, as in our first patient. The lesion is often surrounded by cerebral edema. At craniotomy, the gross appearance of tuberculoma is similar to that of other intracranial lesions, and the diagnosis of tuberculoma often is not made until specimens are viewed microscopically.

Histology shows a central necrotic core surrounded by chronic inflammatory cells and Langhans' giant cells,[4] often with vascular changes

and perivascular inflammation.

Pathophysiologically, tuberculoma usually results from granuloma formation when the meninges are seeded during mycobacteremia, which may be primary or secondary to another primary site of infection. Meningeal infection may also result from contiguous infections, such as the chronic suppurative otitis in our first patient; although it was never documented in that case, a history of a unilateral, chronically draining, painless ear infection with a perforated tympanic membrane is typical of tuberculous otitis media.[7]

Contiguous infection may also result in bacterial superinfection of a tuberculoma,[8] and all brain abscesses should be thoroughly cultured for *M tuberculosis* if biopsy specimens are obtained. Likewise, care must be taken to assure that tuberculomas are not superinfected with other bacteria.

Tuberculomas, by definition, exhibit characteristic granuloma formation that distinguishes them from tuberculous abscesses.[9] The condition must also be distinguished from tuberculous meningitis, which has a far more dismal prognosis. Tuberculomas may be seen in patients with tuberculous meningitis, but such patients are generally more seriously ill.

The signs and symptoms of intracranial tuberculoma are nonspecific, and they are identical to those of any space-occupying intracranial lesion. Signs of increased intracranial pressure, such as headaches, vomiting, and visual disturbances, are common, but they may be minimal in younger children in whom suture separation occurs. Seizures are common and are often focal.[10] Our first patient had a classic temporal lobe seizure with secondary generalization, obviously involving her dominant hemisphere and Broca's area. Focal neurologic findings are also common, one recent study reporting such abnormalities in 75% of patients.[10] Fever is relatively uncommon, the reported incidence varying from 10% to 15%.[4]

Evidence implicating *M tuberculosis* is often indirect. Historically, only 30% to 50% of patients have reported exposure to tuberculosis.[6,8] Acid-fast organisms are rarely found in smears of cerebrospinal fluid, and are found in about 70% of histologic specimens.[11] Cultures have an even lower yield, with a 50% rate of positivity.[11] Reviewing several recent case reports, we found the incidence of positive acid-fast stains to be 65%. While culture results were reported less frequently, 50% were positive, a finding consistent with the results reported earlier. Tuberculin skin test reactivity ranged from 25% to 75%,[8] and chest x-ray results were abnormal, generally showing old fibrotic healed lesions, in one third of the adults.[11]

The EEG may be normal or it may show slowing, with occasional fast spikes, in the area of the lesion.[12] Obviously, the EEG is more likely to be abnormal in patients who have cortical lesions, and most of these patients manifest seizure activity.

Plain skull roentgenograms are not generally helpful, although as many as 5% may show some calcification of the tuberculoma. Evidence of increased intracranial pressure or suture separation may also be seen.[4] Angiograms show an avascular space-occupying lesion in some cases, but they may be normal in up to 15% of patients,[8] and they are rarely indicated in view of current imaging techniques. Direct involvement by the mycobacterium produces a granulomatous vasculitis, and narrowing or actual occlusion may be seen angiographically.

The appearance of tuberculomas on CT scans is variable. On unenhanced scans, lesions appear as either isodense or minimally hyperdense rings or disks, the extent of surrounding edema depending on the stage of evolution of the lesion and the host response to the mycobacteria.[13] Tuberculomas may be virtually indistinguishable from the surrounding parenchyma, as in our second patient. In early or small lesions, contrast enhancement is homogeneous, but more advanced lesions show a more typical ring enhancement with a central punctate lucent area,[4,11] corresponding pathologically to a granuloma with central caseation.[10] Unfortunately, this ring appearance is not pathognomonic of tuberculoma; it may be seen in bacterial abscess, primary brain tumor, and metastatic tumor.

Hydrocephalus has been associated in the literature with intracranial tuberculosis,[11] but it is generally related to leptomeningeal involvement, which did not occur in our cases. Edema, believed to be due at least in part to an allergic response to the mycobacterium,[11] is variable, but it resolves quickly with treatment. Calcifications are commonly seen on follow-up scans of healing lesions.[10,11]

Although the CT appearance of tuberculoma is nonspecific, it can be highly suggestive in a high-risk patient, and often other possibilities may be excluded by a thorough history and physical examination. More importantly, CT scanning is a convenient and valuable method for following up patients treated conservatively,[13] an important point in recommending medical treatment instead of surgical intervention.

None of the previous reports included magnetic resonance imaging; thus, our Case 2 is the first such case of which we are aware. Future studies

TABLE 1. Cerebrospinal Fluid Penetration* of Antituberculous Drugs

Drug	*Crosses Normal Meninges*	*Crosses Inflamed Meninges*
Ethambutol	–	+ +
Rifampin	–	+
Pyrazinamide	?	+ + +
Isoniazid	?	+ + +
Streptomycin	Trace	+

*Relative to serum concentration.

using MRI may be helpful in the diagnosis of tuberculoma, especially those that cannot be seen well on CT scans.

Based on our experience and review of the literature, we believe that any patient in stable condition who has a suggestive intracranial lesion on CT as well as a positive PPD result and/or a history of exposure to tuberculosis merits therapeutic coverage with antituberculous drugs while a complete diagnostic evaluation is done. In certain high-risk populations, however, a positive PPD result may be relatively unremarkable. Depending on the location of the lesion, stereotactic biopsy or resection may be useful in establishing the diagnosis, although antituberculous therapy should be started preoperatively to reduce the likelihood of postoperative meningitis. In inoperable cases (as in our Cases 2 and 3 in which the lesions were in the brain stem), it may be necessary to treat the patient empirically for tuberculoma if this is the diagnosis suggested by history and CT scan. Close follow-up with CT is mandatory. If the findings worsen or fail to improve after four to six weeks, the diagnosis must be reevaluated, since most tuberculomas resolve with medical treatment.[13,14]

The treatment of tuberculoma is based on the same principles as those used in treating pulmonary tuberculosis. Because tuberculosis exists in the host in various bacterial subpopulations with differing environmental conditions and replication rates, multidrug therapy has become the standard in the treatment of tuberculosis.[15] Naturally occurring drug-resistant mutants are also suppressed by a multidrug regimen. Because a tubercle bacillus can be killed only at its time of replication, the action of a drug relative to the bacterial metabolic rate is important. Bacteria that exist in an actively dividing cavitary extracellular environment are in neutral or slightly alkaline surroundings, and they are rapidly eliminated by isoniazid, rifampin, and streptomycin. Organisms in closed caseous lesions and within macrophages metabolize much more slowly; they are killed by rifampin and pyrazinamide, and also, though more slowly, by isoniazid. Pyrazinamide has specific activity in the acidic environment in macrophages, whereas rifampin has a unique ability to kill bacteria in closed lesions, where the bacteria may be active for only short periods. Ethambutol, which is not bactericidal, is useful only in combination with at least two batericidal agents. It penetrates both extracellular and intracellular environments, however, and may help to decrease the emergence of drug-resistant mutants.[15]

Treatment of intracranial tuberculoma differs from standard antituberculous therapy in that each drug's ability to penetrate the central nervous system must be considered. Tuberculomas may be associated with both normal and inflamed meninges. Table 1 summarizes the available data on cerebrospinal fluid penetration of the various drugs in normal and meningitic patients.[16] For a patient with noninflamed meninges, isoniazid and pyrazinamide are probably useful based on their excellent (approximately 100%) penetration in meningitis, although data on their ability to cross normal meninges are lacking. Because the minimal inhibitory concentrations of isoniazid and rifampin are low, both drugs reach adequate levels in the cerebrospinal fluid even at a fraction of serum levels. Streptomycin does not cross either inflamed or normal meninges in significant amounts.

No randomized clinical trials have been done to guide antituberculous therapy, so treatment must be based on experience. We recommend triple drug therapy, consisting of isoniazid and rifampin plus a third drug, either ethambutol or pyrazinamide. Ethambutol should not be used in children less than 12 years of age because optic neuritis is a major side effect of ethambutol, and children less than 12 years old cannot cooperate with a detailed visual examination. When pyrazinamide was first studied in the 1950s as a companion drug to isoniazid, it was found to be effective but unacceptably hepatotoxic. These studies, however, involved larger doses than those presently used, and for longer treatment periods.[17] Nevertheless, hepatic function should be monitored closely. These regimens also constitute adequate treatment for pulmonary tuberculosis. Dosages and side effects of the various agents are shown in Table 2. In addition, some patients may benefit from short courses of steroids or osmotic agents to reduce intracranial pressure, and anticonvulsants are obviously useful in certain cases.

A special note of caution must be added regarding the use of anticonvulsant and antituberculous drugs, since both are hepatotoxic. More specifically, the combination of phenytoin and isoniazid must be used with caution because isoniazid in-

TABLE 2. Antituberculous Drugs

Drug	*Pediatric Dosage*	*Usual Adult Dosage*	*Route of Administration*	*Major Side Effects*
Rifampin	10-20 mg/kg/day (not to exceed 600 mg/day)	600 mg daily	Oral	Red body secretions, GI irritation, CNS disturbances (ataxia, confusion, headache), thrombocytopenia, hemolytic anemia, "flulike" syndrome
Ethambutol	15 mg/kg/day	300 mg daily	Oral	Optic neuritis, hyperuricemia, GI disturbances, transient hepatic dysfunction
Isoniazid (INH)	10-20 mg/kg/day (not to exceed 300-500 mg/day)	300 mg daily	Oral, intravenous	Hepatic dysfunction (especially hepatitis), peripheral neuropathy, GI irritation, other CNS effects, pyridoxine deficiency
Pyrazinamide	20-30 mg/kg/day or 40-50 mg/kg biweekly	1.5 gm daily	Oral	Hyperuricemia, hepatotoxicity
Streptomycin	20-50 mg/kg/day (not to exceed 2 gm/day)	1 gm daily	Intramuscular	Ototoxicity, GI irritation, vertigo, facial paresthesias, rash, urticaria, fever, angioneurotic edema, eosinophilia

creases the bioavailability of phenytoin.[18] Phenytoin levels should be monitored closely for several weeks after isoniazid therapy is begun.

Most authors recommend continuing triple drug therapy for one to two years for patients with intracranial tuberculoma, although Mayers et al[8] recommend a reduction to isoniazid and rifampin after three months of triple drug therapy. Preoperative or immediate postoperative use of these medications in patients requiring operation may prevent tuberculous meningitis. The prognosis is excellent, with most patients showing improvement in symptoms and a gradual regression of the lesion on CT scan over a period of 12 to 18 months.[15] Several authors have reported cases of paradoxical expansion of intracranial tuberculoma during healing.[19] Although rare, tuberculous abscesses are not well penetrated by drugs, and may also be a source of treatment failure.[20]

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