

# Central Nervous System Tuberculosis in Children: A Review of 214 Cases

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**ABSTRACT.** *Objective.* To study the clinical, laboratory, and treatment features observed in pediatric patients with tuberculous meningitis in Turkey.

*Study Design.* Retrospective case review study.

*Methods.* Review of medical records for demographic data, medical history, clinical manifestations, auxiliary test results, complications, and treatment of 214 children with central nervous system tuberculosis (TB) admitted to Dicle University's hospital between August 1988 and February 1996.

*Results.* Of the 214 patients with tuberculous meningitis, 112 (52%) were male. The mean age at presentation was 4.1 years, with 165 patients (77%) younger than 5 years. Twenty-two patients (10%) were in the first stage of the disease, 120 (56%) in the second, and 72 (34%) in the third. Our epidemiologic data showed that 141 (66%) of the patients had a family history of TB, and 64 (30%) had a Mantoux skin test result of >10 mm of induration. Radiographic studies demonstrated abnormal chest findings in 187 patients (87%) (hilar adenopathy, 33%; infiltrates, 33%; miliary pattern, 20%; and pleural effusions, 1%, and 172 (80%) cases with hydrocephalus, 26% with parenchymal disease, 15% with basilar meningitis, and 2% with tuberculomas. Only 22 (13%) of 164 children had a positive acid-fast bacilli smear in cerebrospinal fluid, and *Mycobacterium tuberculosis* was isolated in 49 patients (30%). All the patients were treated with Isoniazid, rifampin, and streptomycin or pyrazinamide for 2 months, followed by 10 months of Isoniazid and rifampin alone. Also, all the patients received adjuvant treatment with steroids early in the course of treatment, and 140 of 172 cases with hydrocephalus had surgical intervention. The overall mortality rate was 23%.

*Conclusion.* One or more of these findings: a family history of TB, positive tuberculin skin test results, abnormal cranial computed tomography, and/or cerebrospinal fluid analysis compatible with TBM were found in all but 3 children in our study. *Pediatrics* 1998;102(5). URL: <http://www.pediatrics.org/cgi/content/full/102/5/e49>; *central nervous system, tuberculous meningitis, diagnosis, hydrocephalus, children.*

**ABBREVIATIONS.** TBM, tuberculous meningitis; CNS, central nervous system; BCG, bacilli Calmette-Guérin; CT, computed tomography; VSI, ventricular size index; CSF, cerebrospinal fluid; AFB, acid-fast bacilli; Mtb, *Mycobacterium tuberculosis*; HIV, human

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immunodeficiency virus.

The prevalence of tuberculous meningitis (TBM) in developing countries, including Turkey, remains high, and the disease also continues to have a high mortality rate among infants and children. In Turkey, the national TB prevalence is 0.4%. Neurologic complications are common, and early diagnosis and specific treatment against TB are essential for prevention of sequelae or fatal outcome.<sup>1</sup> Despite effective chemotherapeutic agents, the mortality rate is still high, estimated to vary from 15% to 32%.<sup>2,3</sup> We have reviewed our experience with pediatric central nervous system (CNS) TB during the past 8 years and have assessed the epidemiologic, clinical, and laboratory findings, and the response to therapy in this disease.

## METHODS

Medical records of 214 children diagnosed with CNS TB, from a total of 931 pediatric patients with TB at Dicle University in Diyarbakir, Turkey, were reviewed retrospectively from August 1988 to February 1996. The information obtained includes demographic data, epidemiologic characteristics, clinical manifestations, treatment, and outcome for these patients. Case criteria used for diagnosis are presented in Table 1.<sup>4</sup>

The severity of the disease was classified as follows: stage I involves patients with nonspecific symptoms such as fever, anorexia, intermittent headache, or vomiting, and with no definite neurologic manifestations. Stage II includes patients with drowsiness and disorientation and with signs of meningeal irritation and/or evidence of increased intracranial pressure. In stage III, patients were usually unconscious with paralysis and signs indicating severe intracranial hypertension.<sup>5</sup>

At our institution, the Mantoux skin test was performed with 5 TU PPD solution, and induration was measured after 48 to 72 hours in all patients. A test response of >10 mm was considered positive for children without bacilli Calmette-Guérin (BCG) immunization. If the patients had received BCG immunization, the Mantoux skin test result was considered positive only if it was >15 mm.

All of the patients had radiologic examinations that included chest roentgenography (posteroanterior and lateral views) and cranial computed tomography (CT). Ventricular enlargement, as an indirect predictor of increased intracranial pressure, was calculated on CT scans by ventricular size index (VSI is the relation between bifrontal diameter over the frontal horn diameter).<sup>6</sup>

Cerebrospinal fluid (CSF) as well as gastric aspirate and sputum specimens were obtained for acid-fast bacilli (AFB) stain and culture, following standard methods for collection and processing of the samples. Cultures were performed using Lowenstein-Jensen medium.<sup>7</sup>

Initial treatment regimens for all patients included daily doses of Isoniazid (10 to 15 mg/kg), rifampin (15 to 20 mg/kg), and streptomycin (20 to 25 mg/kg) or pyrazinamide (25 to 35 mg/kg). Patients received Isoniazid and rifampin for a total of 12 months, 1 to 2 hours before breakfast, either orally or by nasogastric tube.

**TABLE 1.** Case Definition of CNS TB by Either Microbiologic or Clinical Criteria

|   |
|---|
| Microbiologic case definition; one of the following:<br>Isolation of <i>M tuberculosis</i> from CSF<br>Abnormal neurologic signs and symptoms, CSF, or cranial CT consistent with CNS TB, and isolation of Mtb from any site.   |
| Clinical case definition; abnormal neurologic signs and/or symptoms and more than two of the following:<br>Discovery of adult source case with contagious TB who had significant contact with child<br>Presence of Mantoux (5 TU) skin test reaction >10 mm of induration, or >5 mm of induration if child had close contact with infected adult*<br>CSF abnormalities without evidence of other infectious cause<br>Abnormalities on cranial CT consistent with CNS TB |

\* >15 mm of induration was considered positive for children with BCG (BCG is in the routine immunization program of Turkey).

Pyrazinamide or streptomycin also was used during the first 2 months for all patients. A glucocorticoid (dexamethasone at 0.3 to 0.5 mg/kg per day) was given to every patient in the first month of treatment, and the dose was tapered over 7 to 10 days.

## RESULTS

### Demographic and Clinical Characteristics

Of the patients, 112 (52%) were boys, and the male-to-female ratio was 1.1:1.0. Age ranged from 3 months to 15 years, with a mean age of 4.1 years (Fig 1). Seventy-seven percent of the children were younger than 5 years, and ~44% of the patients were between 12 and 24 months of age. More than half (52%) of the patients came to our hospital from rural areas (villages), 73 (34%) from townships, and the remainder (14%) from cities (urban areas).

Our data showed that 63 patients (29%) had malnutrition and 28 (13%) had a recent history of measles (considered predisposing diseases for TB). To date, no cases of children with human immunodeficiency virus (HIV) have been reported in our hospi-

tal. A family history of TB was encountered in 141 patients (66%), and a delay (average,  $8.2 \pm 4.8$  months) in the time from identification of a known adult contact to the diagnosis of TBM in the child also was found in our study.

Only 25 patients (12%) had a history of single BCG vaccination, and in 18 of these patients the vaccination time was >5 years before the admission time. The other children did not receive BCG vaccination.

A small percentage of patients were admitted in the first stage of disease (10%). The other 90% had a neurologic manifestation (120 in the second stage and 72 in the third stage), with a longer duration of preadmission symptoms (Table 2). Table 3 illustrates the most common preadmission clinical manifestations. Fever was reported in 91%, vomiting in 87%, personality change in 63%, seizures in 62%, nuchal rigidity in 59%, and headaches in 58%.

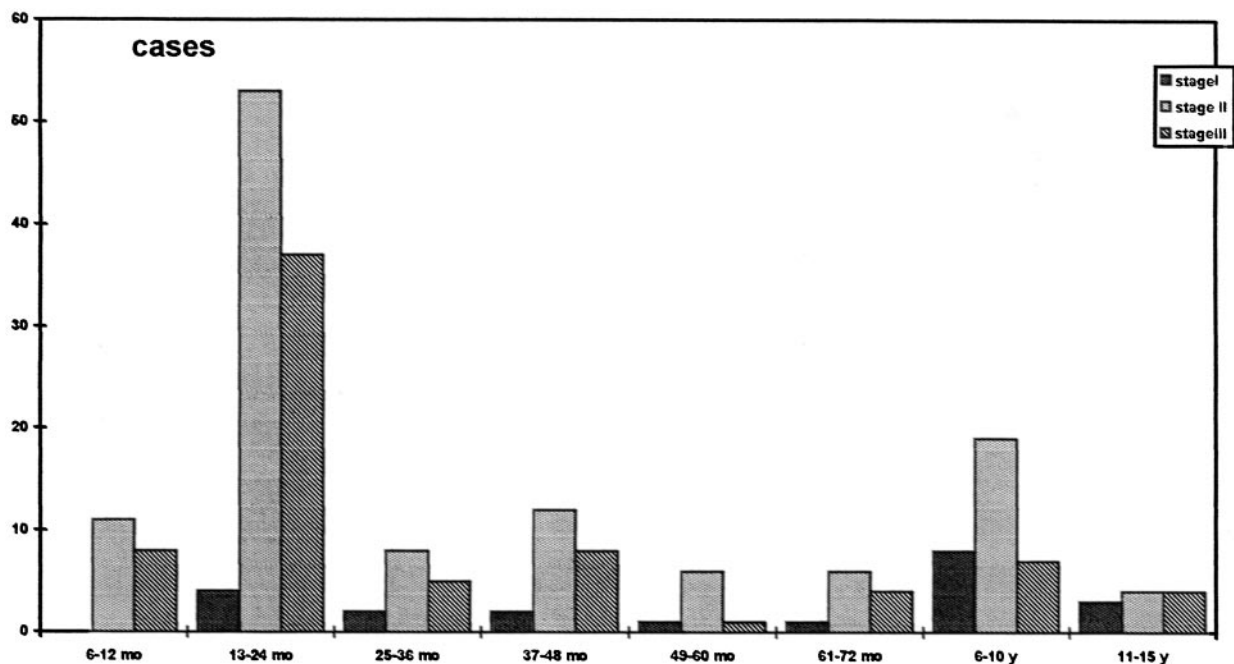
### Initial Radiography Findings

Cranial CT was performed for all patients and showed 172 patients (80%) with hydrocephalus, 26% with parenchymal disease, 15% with basilar meningitis, and only 2% with tuberculomas of the brain.

Abnormal chest radiography was noted in 187 patients (87%), with a variety of abnormalities including hilar adenopathy (34%), miliary pattern (20%), pneumonic infiltrate (18%), bronchopneumonic infiltrate (15%), and pleural effusion (1%).

### Skin Testing

All patients were checked for Mantoux tuberculin (5 TU) skin test reaction, and only 64 patients (30%) had a positive result (>10 mm of induration). Thirteen patients (6%) had a reaction of between 5 and 9 mm, and the other patients were anergic on presen-



**Fig 1.** Age distribution of 214 cases of central nervous system tuberculosis and stage at presentation. Stage I is defined as isolated meningeal disease without focal neurologic abnormalities; stage II, isolated parenchymal disease and neurologic abnormalities without altered consciousness; and stage III, parenchymal and meningeal disease with stupor or obtundation.

**TABLE 2.** Duration of Symptoms Before Admission

| Duration (wk) | Total |     | Stage I |    | Stage II |    | Stage III |    |
|---------------|-------|-----|---------|----|----------|----|-----------|----|
|               | No.   | %   | No.     | %  | No.      | %  | No.       | %  |
| 0-1           | 31    | 14  | 14      | 45 | 16       | 52 | 1         | 3  |
| 1-3           | 150   | 70  | 8       | 5  | 89       | 60 | 53        | 35 |
| >3            | 33    | 16  | 0       | 0  | 15       | 45 | 18        | 55 |
| Total         | 214   | 100 | 22      | 10 | 120      | 56 | 72        | 34 |

tation. Of the 25 patients who received BCG immunization, 18 received it >5 years before the diagnosis of TBM and had an induration of only 10 to 15 mm, whereas the remaining 7 showed a positive reaction (>15 mm).

### Microbiology

Only 49 of the 164 CSF samples that were cultured grew *Mycobacterium tuberculosis* (Mtb), and only 22 of the 214 patients (10%) had a positive AFB smear in the CSF. Cultures of sputum and gastric aspirate tested positive in only 2 (1%) of 164 patients and 19(9%) of 164 patients, respectively (Table 4).

Because of our lack of laboratory facilities, all of our Mtb strains were not tested for sensitivity to antituberculous agents. The only information available from strains isolated in the southeast of Turkey are 451 culture-positive isolates tested for in vitro susceptibility at the Tuberculosis Reference and Research Laboratory of Refik Saydam Hifzisiha Institute in Ankara between 1988 and 1993. Resistance to rifampin, streptomycin, and Isoniazid was similar with 4.9%, 4.7%, and 4.4% of resistant strains, respectively. Simultaneous resistance to Isoniazid and rifampin was found in 35 (7.8%) strains, whereas resistance to both Isoniazid and streptomycin was 3.1% and to both streptomycin and rifampin was 1.8%.<sup>8</sup>

### Laboratory Data

Lumbar puncture was performed on all patients, and the CSF was analyzed for protein and glucose concentrations and for cell count and differential. Approximately 80% of our CSF results were compatible with TBM (ie, predominance of lymphocytes with elevated protein and reduced glucose concentrations) (Table 5).

Complete blood cell count and serum alanine, aspartate transaminase, serum uric acid, creatinine, blood urea nitrogen, and bilirubin levels were determined at the time of diagnosis for all patients. These

**TABLE 3.** Symptoms and Signs at Presentation

|                        | N = 214 | % |
|------------------------|---------|---|
| Fever                  | 91      |   |
| Vomiting               | 87      |   |
| Changes in personality | 63      |   |
| Seizures               | 62      |   |
| Nuchal rigidity        | 59      |   |
| Headaches              | 58      |   |
| Loss of appetite       | 45      |   |
| Weight loss            | 38      |   |
| Irritability           | 30      |   |
| Cough                  | 29      |   |
| Cranial nerve paresis  | 26      |   |
| Diarrhea/constipation  | 10      |   |

**TABLE 4.** Number of Cases With Positive Culture Results According to Stages\*

| Specimen             | Stage |    |     | Total |
|----------------------|-------|----|-----|-------|
|                      | I     | II | III |       |
| CSF                  | 9     | 19 | 21  | 49    |
| Sputum               | 0     | 1  | 1   | 2     |
| Gastric aspirate     | 1     | 7  | 11  | 19    |
| CSF smear positivity | 3     | 9  | 10  | 22    |

\* Nine case had at least one positive test result.

levels were monitored in only 10 patients who developed symptoms and signs of drug toxicity (jaundice, widespread skin rash, etc). The dose of rifampin was reduced to 10 mg/kg per day in those patients for whom serum transaminase concentrations were elevated to three times the normal values. Medication was not discontinued in any patient.

### Clinical Course

All the patients were hospitalized for diagnosis and initial treatment, and the median hospital stay was 38 days (range, 11-95 days).

Our patients were treated with a 12-month regimen, initially with Isoniazid, rifampin, and pyrazinamide or streptomycin, and changed to only two drugs (Isoniazid and rifampin) after 2 months of therapy. No patient was treated with only one anti-tuberculous drug or acute short-course intermittent chemotherapy. All patients with tuberculoma responded to anti-TB medications, but the duration of treatment was extended to 2 years in 2 patients before complete regression of the lesion could be assumed.

Steroids were used as adjunctive therapy in all patients for 3 to 4 weeks and then gradually tapered as tolerated over a period of 7 to 10 days. Of 172 cases with hydrocephalus, 140 (81%) underwent surgical management.

Forty-nine patients (23%) died (Table 6); 32 (65%) of these deaths occurred during the first 3 days after admission to hospital. Sixty-three percent of deaths were of children age 5 years or younger, 31% were of children 6 to 10 years of age, and only 6% (3) were of children older than age 10 years.

### DISCUSSION

The total number of pediatric cases with TB admitted to our hospital between 1988 and 1996 was 931.

**TABLE 5.** CSF Findings at Time of Presentation

| CSF Findings                           | No. of Cases | %  |
|--|--------------|----|
| Cell count (WBC) (mm <sup>3</sup> )    |              |    |
| <500                                   | 183          | 85 |
| >500                                   | 31           | 15 |
| Predominance cells                     |              |    |
| Lymphocytes                            | 178          | 83 |
| Polymorphonuclear leukocytes           | 36           | 17 |
| Protein (mg/dL) (mean ± SD = 142 ± 29) |              |    |
| <100                                   | 49           | 23 |
| 100-200                                | 132          | 62 |
| >200                                   | 33           | 15 |
| Glucose (mg/dL) (mean ± SD = 27 ± 10)  |              |    |
| <10                                    | 26           | 12 |
| 10-40                                  | 152          | 71 |
| 40-80                                  | 36           | 17 |

**TABLE 6.** Outcome of Treatment

| Stage                 | I   |    | II  |    | III |    | Total |    |
|-----------------------|-----|----|-----|----|-----|----|-------|----|
|                       | No. | %  | No. | %  | No. | %  | No.   | %  |
| Complete recovery     | 13  | 59 | 67  | 56 | 6   | 8  | 86    | 40 |
| Seizures              | 1   | 5  | 8   | 7  | 6   | 8  | 15    | 7  |
| Developmental sequela | 8   | 36 | 31  | 26 | 27  | 38 | 66    | 31 |
| Deaths                | 0   | 0  | 14  | 12 | 35  | 49 | 49    | 23 |

According to data from the Turkish Ministry of Health, the number of admissions to hospitals dropped from 108 per 100 000 in 1971 to 51 per 100 000 in 1988.<sup>9-11</sup> Despite the availability of effective chemotherapeutic agents, the morbidity and mortality rates of CNS TB remain high, and in developing countries such as Turkey, TBM remains a significant public health problem.<sup>12</sup>

The disease can occur at any age but is uncommon in children younger than 6 months and rare in those younger than 3 months of age.<sup>13</sup> In our study, 77% of patients were younger than 5 years of age, whereas 94 of our patients (44%) were between 13 and 24 months of age. The mean age of our patients was 4.1 years, higher than the mean age of 3 years found in the clinical series of 282 children with CNS TB in South Africa.<sup>14</sup>

It is known that there are certain predisposing factors for TB such as malnutrition; infections (measles, varicella, pertussis, HIV, and other viral illnesses); corticosteroid and other immunosuppressive therapies; stress; and hormonal changes. In this study, we found 63 patients (29%) with malnutrition and 28 (13%) with a recent history of measles.

Waecker and Connor<sup>1</sup> reported that an adult source of contact was identified in 70% of cases of children with CNS TB. In another study in Turkey, an adult source was found in 42%,<sup>15</sup> whereas our data showed a family history of TB in 66%. Thus, it is important that the patients be questioned persistently about contact with a person with TB and that family members be examined for TB, especially because of the delay from development of symptoms to diagnosis of TBM. In this study, 86% of children had symptoms for >1 week and 16% for >3 weeks before admission (Table 3). The presence of undiagnosed TBM is considered an important factor in the spread of the disease.

An incidental finding was that all of our cases vaccinated with BCG received only one dose, although in the routine immunization program of the Turkish Ministry of Health, BCG immunization is suggested at ages 0 to 2 months, 6 years, and 11 years of age. Factors in our region that affect vaccination opportunities are the low rate of hospital births and the large number of children who do not attend schools; most vaccines are given to children at hospitals or schools.

An early diagnosis of TBM is highly relevant to its treatment and prognosis. Approximately 90% of the patients were diagnosed at stage II or III of TBM. The severity of this presentation was probably attributable to the low socioeconomic and educational levels of most of our patients' families, who did not seek medical assistance until the terminal stages of the

disease. TBM occurs with a variety of nonspecific clinical manifestations. In children, apathy, lack of interest in play, irritability, restlessness at night, minor headaches, loss of appetite, nausea, vomiting, and abdominal pain are the usual presenting symptoms.<sup>13</sup> Fever, vomiting, changes in personality, seizures, and headache were present in ~60% to 75% of our cases, whereas cough, weight loss, and night sweats, which are commonly associated with pulmonary TB, were present in ~25% of our patients. Cranial nerve palsies were found in 26% in our study (within the range of 20%-30% reported in the literature).<sup>16,17</sup> The most common cranial nerves affected were the seventh (10%) and sixth (9%), followed by the third. In this study, cranial nerve paralysis was seen primarily in children younger than 2 years and usually was associated with other neurologic findings.

Hydrocephalus was seen on cranial CT in 80%, parenchymal disease in 26%, and basilar meningitis in 15%. Bhargava and associates<sup>18</sup> described 60 adults and children with CNS TB in whom 83% had hydrocephalus at presentation. Waecker and Connor<sup>1</sup> described 30 children with CNS TB in stage I, II, and III disease, all <6 years of age, in whom 100% had hydrocephalus at presentation. Bullock and Welchman<sup>19</sup> reported 34 patients with stages II and III disease. In another study in Turkey, hydrocephalus was present in 98% of 52 patients with TBM.<sup>20</sup> Finally, in a Chinese study of children with CNS TB diagnosed between 1961 and 1984, the clinical stage at presentation and age were the primary predictive variables of prognosis.<sup>21</sup>

Communicating hydrocephalus in CNS TB usually is caused by blockage of the basilar cistern with thick tuberculous exudates in the acute stage and adhesive leptomeningitis in the chronic stage of disease.<sup>18</sup> In some cases, blockage and dilatation of the fourth ventricle can produce structural hydrocephalus. It is important to remember that communicating hydrocephalus is not specific for CNS TB and can follow fungal meningitis, bacterial meningitis, cytomegalovirus infection, toxoplasmosis, and subarachnoid hemorrhage.

The outcome of treatment of patients with TBM is influenced by many factors, such as severity of the disease, effectiveness of antituberculous drugs, management of neurologic complications (particularly hydrocephalus), and appropriate use of general supportive measures.<sup>13,22</sup> Enhanced resolution of the basal exudate and improved survival rate were shown to be associated with the use of corticosteroids in TBM.<sup>23</sup>

Early ventriculoperitoneal shunting in children with significant hydrocephalus has been shown to reduce morbidity and mortality, and is a potentially favorable predictor of good outcome. Of the patients, 140 received surgical intervention. CT has proved to be a reliable method for the diagnosis of hydrocephalus.<sup>6</sup> The degree and significance of hydrocephalus were calculated by VSI to determine which children might benefit from early ventriculoperitoneal shunting. The accepted parameters for shunting were moderate enlargement of the ventricles (VSI >39%)

or mild enlargement of the ventricles (VSI >30%) with parenchymal signs. The Ayala index (quantity of fluid removed  $\times$  final pressure/initial pressure) also is helpful in the diagnosis of hydrocephalus,<sup>24</sup> and an index >7.0 is interpreted to indicate a large reservoir (as in hydrocephalus).

Positive results were detected in only 30% of the total CSF samples cultured, below the reported range of 42% to 74% in other series.<sup>1,25</sup> Serial lumbar punctures to obtain large CSF volumes have been used to increase the likelihood of recovering Mtb in the CSF, and one study has shown that AFB smear positivity increased from 39% to 87% and culture positivity from 52% to 83%.<sup>25</sup>

The Mantoux test result was positive in 30% of the cases. However, an additional 6% of patients had reactions of 5- to 10-mm induration. These results are similar to those reported previously in the literature: PPD was found positive only at a rate of 16% in TBM.<sup>26</sup> Approximately 12% of our patients were vaccinated with BCG, and in 72% of these patients, the vaccination time was years before the onset of CNS TB. The protective efficacy of BCG vaccination is not known and ranges from 0% to 80%;<sup>27</sup> however, it has been stressed that in childhood, the vaccination protects against serious complications such as TBM.<sup>9,27,28</sup>

All but 3 children in our series had one or more of the positive findings of family history, tuberculin skin test, cranial CT, or compatible CSF analysis.

The initial choice of therapy should include Isoniazid, rifampin, streptomycin, and pyrazinamide. The Committee on Infectious Diseases of the American Academy of Pediatrics currently recommends antituberculous therapy for 12 months.<sup>29</sup> All of our patients underwent a 12-month regimen but beginning only with three drugs (Isoniazid, rifampin, and streptomycin or pyrazinamide) and then proceeding to a combination of Isoniazid and rifampin after streptomycin or pyrazinamide was discontinued. Many experts believe that in non-HIV-infected children, therapy <12 months for drug-susceptible TBM may be appropriate.<sup>30</sup> In patients with tuberculomas, a paradoxical increase in lesion size at the initiation of antituberculous therapy was not noted, in contrast to previous reports.<sup>31</sup>

Therapy for CNS TB should be initiated early (within 48 hours of presentation) whenever an increased index of suspicion is present, even if the patient has both a negative PPD reaction and a normal chest radiography finding. In addition, early therapy can minimize the incidence of neurologic sequelae and death.

Absence of adverse drug reactions in our series of patients may suggest that routine liver function tests and laboratory monitoring are not required and perhaps should be reserved for children who develop clinical manifestations of toxicity.

In summary, TBM is a significant public health problem in children in Turkey, with an overall mortality rate of 23%. Important indicators that help establish the diagnosis of this disease are not only positive AFB smears and CSF cultures, but also a family history of TB, a positive Mantoux skin test result, and cranial CT findings and CSF chemical and morphologic findings compatible with TBM.

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