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Since the name of the author Mehmet Fuat Gürkan, who contributed to the study, was forgotten to be added to the article by mistake, the name of the author in question was added to the article upon the corresponding author's written request.

Retrospective analysis of cases with tuberculous meningitis: single center experience

Yasemin Demir Yiğit[1], Ebral Yiğit[2], Mehmet Fuat Gürkan[3]

[1]Department of pediatrics, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey
[2]Department of General Surgery, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey
3 Department of Pediatrics, Private Genesis Hospital, Diyarbakır, Turkey

ABSTRACT

Objectives: A total of 172 patients were retrospectively investigated who were admitted to the Pediatric Department of Dicle University School of Medicine with the diagnosis of tuberculous meningitis. Demographic data, clinical, laboratory and radiological findings and responses to treatment were analyzed. Of all patients 124 (72.1%) were under 5 years of age and 109 were males. The most common symptoms on admission were fever (%71), vomiting (60%), convulsion (38%), and headache (31%). Forty-seven (23.8%) patients had positive family history of tuberculosis. Tuberculin skin test positivity was seen in 19.6% and 20.1% had positive BCG scar. Of all patients 32 (18.6%) were in stage I, 82 (47.7%) were in stage II and 58 (33.7%) were in stage III on admission. Chest X-Ray showed pathological findings in 60.9% of all patients. Hydrocephalus was detected in 149 patients on cranial tomography. Ventriculo-peritoneal shunt was performed in 79 patients with hydrocephalus. Totally, 24 deaths were detected from all patient records.

Since the diagnosis of tuberculous meningitis is difficult and the disease has a high morbidity and mortality rate, the importance of preventive measures in the control of the disease has been emphasized in this study

Keywords: children, tuberculosis, meningitis

Tuberculosis (TB), one of the oldest diseases in history, continues to be one of the most common infectious diseases in the world and constitutes an important health problem especially in developing countries, including our country. Today, more than 40% of the world's population is infected with tuberculosis bacillus, and 1-3 million new tuberculosis cases are reported each year in children younger than 15 years of age. It has been reported that the majority of these cases are located in developing countries with poor living conditions. [1] In our country, the prevalence of infection was found to be 25% (11,578,000 people), and the prevalence of the disease was 0.36% per thousand, which was last done in 1982. In addition, as seen in this study, the prevalence of tuberculosis is high in our region (0.74%), and as a result, tuberculous meningitis (TBM) is frequently encountered. [2]

Although the definitive diagnosis of tuberculous meningitis is made by direct smear from CSF(Cerebrospinal fluid) or the demonstration of Mycobacterium tuberculosis (M. Tbc) by culture, the diagnosis can still be made by clinical, demographic, radiological, and contact anamnesis since it takes time and is rarely positive.

Tuberculous meningitis occurs in 0.3% of children with untreated primary infection.[3] It is an infection with high morbidity and mortality in childhood. Tuberculous meningitis is the most common form of central nervous system tuberculosis.[4] Tuberculous

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Address for correspondence: *Ebral Yiğit MD. Gazi Yasargil Training and Research Hospital Department of General Surgery, Diyarbakır, Turkey. Email: ebralyigit@gmail.com,*

meningitis is very rare in children younger than four months because the pathological process is completed in such a short time. It is most common in children between the ages of 6 months and 4 years (first five years). At this age, it usually develops within the first 2-6 months of primary infection.[4-6]

In current study, clinical, laboratory, radiological findings and responses to treatment of 172 patients with tuberculous meningitis who were followed up in our clinic were evaluated retrospectively, and the results were evaluated in the light of today's literature.

METHODS

In this study, 172 patients were hospitalized and treated with the diagnosis of tuberculous meningitis in the Infectious Diseases Clinic of the Department of Pediatrics of the Dicle University, and then followed up in the control outpatient clinic were included.

The study was done retrospectively. General information from the follow-up cards of the patients; age, gender, residence address, application complaints, BCG (Bacillus Calmette-Guerin vaccine), PPD (Pürified Protein Derivative Test), which period they applied, family histories, PA lung grammar, cranial CT (Computed Tomography) and MRI (Manyetik rezonans) results, CSF results, blood biochemistry (ALT, AST, urea, creatinine) were recorded and the existing results were evaluated.

Diagnosis of tuberculous meningitis was based on the history, physical examination, laboratory findings, microbiological and biochemical examination findings of Cerebrospinal fluid (CSF), and radiological findings. Among these, the appearance of ARB (Acid resistant bacilli) in the "Ehrlich-ZiehlNeelsen (EZN)" staining of CSF and/or the production of Mycobacterium tuberculosis in Löwenstein-Jensen medium; Findings of more than 10 cells per mm^3 with signs of subacute meningitis (signs of meningeal irritation lasting longer than four days), biochemical features of CSF (high protein, low sugar, and chloride); M. tuberculosis growth in another anatomical region or detection of ARB in a direct stained preparation were considered as the main determinants for the diagnosis of the disease.[7]

In all patients diagnosed with TB, standard 4 antituberculous therapy (2 months INH + RIF + PZA + SM or EMB, 10 months INH + RIF) and additional methylprednisone (1-2 mg/kg/day) for the first 4-6 weeks or dexamethasone (0.5-1 mg/kg/day) and if necessary, acetazolamide (40 mg/kg/day) treatment was administered.

Descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum values, while categorical variables were expressed as numbers and percentages. Chi-square test was used to determine the relationship between groups and categorical variables, and Student-t test was used to compare group means of continuous vari-

Table 1. General information about the patients

Age(years)	n	Percent
< 5 years old	124	72.1
> 5 years old	48	27.9
Gender		
Male	109	63.4
Female	63	36.6
BCG		
Positive	30	20.1
Negative	119	79.9
PPD		
Negative	115	80.4
Positive	28	19.6
Family history		
Negative	47	23.3
Positive	125	72.7

BCG: Bacillus Calmette-Guerin vaccine, PPD: Purified Protein Derivative Test

ables. Statistical significance level was accepted as $p < 0.05$ by using the "SPSS for Windows" statistical package program in the calculations.

RESULTS

172 patients who were clinically diagnosed with tuberculous meningitis were included in the study. The mean age of the patients was 59.7 ± 45.6 months (4 months-15 years). The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the patients, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1).

Patients applied mostly in June (22.1%). (Fig. 1)

In the records of the patients, 149 patients have BCG scars. Of these, 119 (79.9%) had negative BCG and 30 had positive BCG (Table 1). One-hundred and forty-three of our patients had PPD results. PPD test results were negative in 115 (80.4%) of 143 patients, and positive in 28 (19.6%) patients. (Table 1)

While there was family history in 125 (72.7%) of our patients included in the study, there was no family history in the 47 (27.3%) patients (Table 1). BCG positivity was found to be %18.3 in those with a positive family history. When the clinical period of the patients was examined at the time of hospitalization; it was seen that 32 (18.6%) of the patients came in stage I, 82 (47.7%) in stage II, 58 (33.7%) in stage III.

Fever was among the most common symptoms in 122 (71%) of our patients at the time of admission to the clinic. (Table 2).

Pathological chest X-ray findings were found in 56 (60.9%) of 92 patients whose chest X-ray findings were recorded. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP, [3 (1.7%) unilateral, 6 (3.5%) bilateral LAP], 2 (1.2%) atelectasis, 1 (0.6%) pleural effusion, 1 (0.6%) empyema, 1 (0.6%) LAP + consolidation. 36 (39.1%) chest X-ray of the patient was normal.

Pathological cranial CT imaging results were found in 157 of 172 patients. The most common complication was hydrocephalus, and 79 (45.9%) of these patients underwent ventriculoperitoneal shunt operation (Table 3).

CSF glucose levels were below 10 mg/dL in 15 (8.7%) of the patients, between 11-40 mg/dL in 99 (57.6%), and between 41-80 in 51 (29.7%) patients. Seven (4.1%) were found to be over 80. CSF glucose was below 10 mg/dL in five patients, CSF glucose was between 11-40 mg/dL in 11 patients, and CSF glucose was between 41-80 mg/dL in 8 patients.

When the CSF protein was biochemically examined, it was found that 44 (32.9%) of the patients were between 0-50 mg/dL, 19 (14.1%) of them were between 51-100 mg/dL, 53 (39.6%) of them were between 101-200 mg/dL, 13 (9.7%) were between 201-500 mg/dL and 5 (3.7%) of them were over 500 mg/dL.

Lymphocyte dominance was observed in 143 (83.1%) of the admitted patients, while PNL was dominant in CSF in 29 (16.9%). When the number of cells in the CSF was examined, 7 (4%) of the patients were between 0-10/mm^3, 55 (32%) of them were between 11-100/mm3, and 84 (48.8%) of them were between 101-500/mm^3. and in 26 (15.2%) of them were found to be above 500/mm^3. The presence of M.Tuberculosis was demonstrated in CSF by PCR (Polymerase Chain Reaction) in 3 patients.

The white blood cell (WBC) count of the patients whose hemogram results were examined was < 4000/

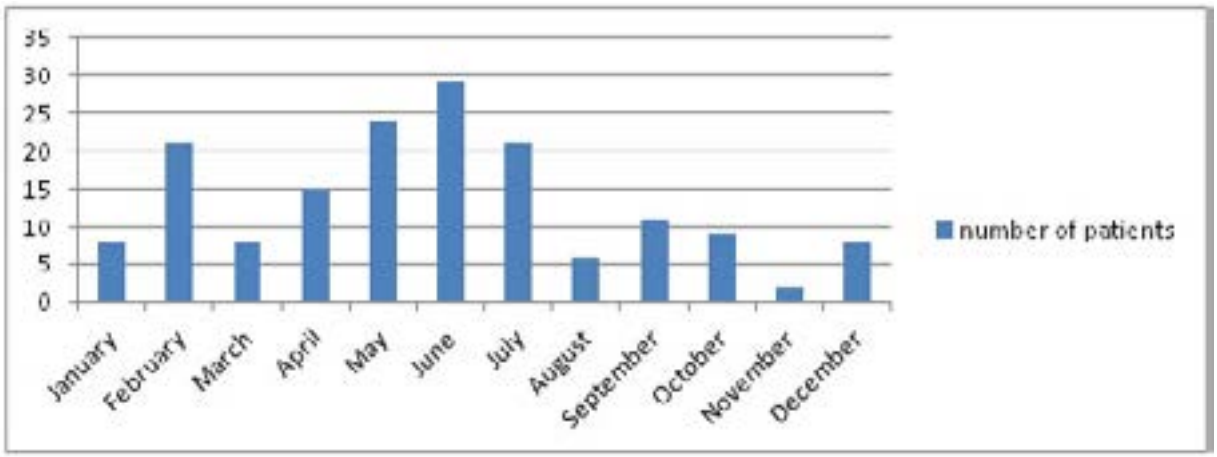

Fig. 1. Distribution of the number of patients according to the seasons

Table 2. Symptoms of the patients at the time of first admission

Symptoms	n	%
Fever	122	71
Vomiting	104	60
Epilepsy	66	38
Headache	54	31
Diarrhea	28	16
Confusion	24	14
Cough	16	9
Neurological deficit	14	8
Nausea	13	8
Abdominal pain	13	8
Dyspnea	9	6
Anorexia	5	3
Weakening	4	2
Sweating	3	2
Weakness	3	2
Not sucking	2	1
Abdominal swelling	1	1

mm3 in 3 (1.7%) and between 4000-10000/mm3 in 66 (38.4%) and > 10000/mm^3 in 103 patients. WBC mean of the patients was found as 14100/mm^3. As a result, the majority of the patients presented with leukocytosis.

When the mean AST, ALT, urea, and creatinine values of the patients whose biochemistry results were examined, it was seen that they applied with mild AST elevation. The number of patients with AST values above normal was 75. ALT, urea, and creatinine values were found to be normal.

Hydrocephalus was detected in 172 patients 149 of them who were examined retrospectively, and shunt operation was performed in 79 (45.9%) of these patients.

Toxicity was detected in 12 (7%) of the 172 patients examined. Drug toxicity was accepted as a more than a 3-fold increase in AST, ALT levels, increase in bilirubin levels, jaundice, nausea, and vomiting. medications were discontinued. In these patients, re-treatment was continued after the AST and ALT levels of the drugs returned to normal. Of 172 patients, 24

Table 3. Cranial CT results of the patients

CT findings	n	%
Hydrocephalus	149	94.9
Meningeal/parenchymal involvement	49	31.2
Subdural effusion	16	10.2
Cerebral atrophy	12	7.6
Tuberculoma	12	7.6
Cerebral infarction/embolism	11	7.0
Brain edema	7	4.5
Hematoma	3	1.9
Ischemia	2	1.3
Normal	12	7.6

(%14) died. On average, the hospital stay of the patients was 23.5 ± 14.5 days.

Of the cases that resulted in death, 19 (79.1%) were within the first 5 years of age, and 5 (20.9%) were above 5 years of age. Of the deceased patients, 3 (12.5%) were in stage I, 12 (50%) were in stage II, and 9 (37.5%) were in stage III.

DISCUSSION

Tuberculous meningitis, which is the most serious complication of tuberculosis in childhood and the most common cause of death from tuberculosis, is most common in children aged 6 months to 4 years, accounting for approximately 10% of tuberculosis cases. In our study, the ages of our patients were found to be between 4 months and 15 years. The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the 172 cases in our study, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1). The mean age of our patients was 59.7 ± 45.6 months.

Recent studies on the BCG vaccine show that the protective effect of the BCG vaccine is 50% against pulmonary tuberculosis in children and adults, and 50-80% against tuberculous meningitis and other disseminated tuberculosis types.[6, 8-11] It is widely believed that the main effect of the vaccine prevents the development of life-threatening forms such as miliary and central nervous system tuberculosis. A dose between 0-3 months in endemic populations as the age of vaccination is a second dose to be given at the beginning of school. Considering the results of our patients' vaccination with BCG vaccine, the low vaccination rate of 20.1% shows the importance of maintaining BCG vaccination for our region in preventing disease with serious morbidity and mortality, such as tuberculosis and, more importantly, tuberculous meningitis, one of the disseminated forms of tuberculosis. It can be thought that this low vaccination rate is due to social, cultural, and traditional reasons, lack of education, the inadequacy of health services, the problem of access to services, effectiveness of vaccination, inadequacy of basic and preventive health services.

In various studies, the rate of having a person with tuberculosis in the family or in the immediate environment was found to be 30-80%. The recent diagnosis of tuberculosis in 47 (27.3%) of our patients from family members or close relatives is consistent with previous studies. Despite these family histories, it was observed that most of our patients did not have family screening. Therefore, it was concluded that the deficiencies in the reporting of the disease with such serious consequences and in family screening should be reviewed. Screening the family members of adults with active tuberculosis and administering antibiotic prophylaxis to children under 5 years of age and other PPD positive individuals are of vital importance in preventing the spread of the disease.[6, 12]

PPD test maintains its importance in diagnosing tuberculosis. it has been reported in various sources that 50% of patients with tuberculous meningitis may have a positive PPD test.[6, 10, 11, 13] It may be negative in miliary spread, immunosuppression, viral infections, especially in infants and young children. In some cases, it may be positive after starting tuberculosis treatment. In tuberculous meningitis, both PPD and pulmonary findings may be negative. In our study, 115 (80.4%) of our patients had negative PPD results and 28 (19.6%) had positive PPD results. In their study consisting of 214 patients, Yaramış *et al*. found PPD positive in 64 (30%) patients.14 Nguyen *et al*. stated that PPD may be negative at a rate of 50-70% in patients.15 In previous studies, the tuberculin test performed with 100 U PPD in patients with tuberculous meningitis was found to be 20% negative.16 The PPD solution applied in our study was 5 U tuberculin test solution. In recent studies, the tuberculin test performed with 10-100 U PPD has been shown to be 75% positive.17

TB meningitis is the most serious form of tuberculosis, usually fatal if left untreated. Symptoms are similar to other forms of meningitis, with an onset that lasts days or weeks. It is clear that early diagnosis and treatment have a significant impact on mortality and morbidity. atypical onset; It may also be in the form of bronchopneumonia, findings suggestive of intracranial mass, GIS symptoms, typhoid or epilepsy. Therefore, the possibility of TBM should be considered in patients presenting with these tables. In their study consisting of 497 male and 360 female cases, Girgis *et al*. reported fever in 90% of the cases, headache in 63%, vomiting in 49%, and lethargy in 32%.18 In their study consisting of 214 cases, Yaramış *et al* found fever in 91%, vomiting in 87%, altered consciousness in 63%, seizures in 62%, and headache in 58%.14

Studies have reported that patients present with nonspecific symptoms such as restlessness, weakness, fever, fatigue, and headache.[19-21] Fever was the most common in 71% of the patients, vomiting in 60%, convulsions in 38%, headache in 31%, diarrhea in

16%, confusion in 14%, cough in 69%, cough in 8%. Neurological deficit, nausea and abdominal pain were the most common symptoms. When compared with the literature data, symptoms were found to be similar.

Diagnosis of tuberculous meningitis is still a problem, although the disease may start acutely in 50% of infants, it can be subacute in children and adults. History and laboratory tests are often nonspecific and rarely pathognomonic. Therefore, radiological imaging, especially cranial imaging, is of great importance in the early diagnosis and treatment of tuberculous meningitis, which has serious morbidity and mortality consequences.

In patients with suspected tuberculous meningitis, showing hydrocephalus, infarction, tuberculoma, edema, ventricular dilatation, involvement of the meninges and especially the basilar region, which may vary according to the degree of cranial CT disease, is important for diagnosis. Hydrocephalus is the most common complication seen in tuberculous meningitis and occurs in the acute period with obstruction of the basal systems and is usually of the communicative type.4 It is reported that the most frequently reported data in cranial CT is hydrocephalus, and it constitutes a greater majority in children than in adults.

In our study, cranial CT results of 157 patients were evaluated retrospectively, 149 (94.9%) of patients had hydrocephalus, 49 (31.2%) had meningeal/parenchymal involvement. and 12 (7.6%) patients had normal results. Hydrocephalus was the most common complication.

Doer *et al*. In their study of 31 tuberculous meningitis patients aged between 3 months and 15 years, had at least one cranial imaging performed in all of the patients. They found abnormalities in 26 (87%) of the patients. They detected hydrocephalus in 17 (57%) patients, meningeal involvement in 12 (40%) patients, tuberculoma in 8 (27%) patients, cerebral infarction in 3 (10%) patients, and multiple abnormal findings in some patients. They found normal imaging in four patients. [22]

In tuberculous meningitis, cranial tomography is useful in monitoring the disease, early diagnosis and treatment of complications, and determining the prognosis as well as in the diagnosis 23. It has been shown that there is a relationship between the symptoms of the disease in terms of onset, prognosis, and sequelae. [20]

Tuberculous meningitis usually has an insidious and chronic onset, so diagnosis can be difficult, mostly in stage II. or III. diagnosis is made. When examining the period in which the 172 cases included in the study came; it is seen that 32 (18.6%) of the patients came to stage I, 82 (47.7%) to stage II, 58 (33.7%) to stage III. Girgis *et al*. reported that 4% of patients were in stage I, 34% were in stage II, and 62% were in stage III. [18]

Chest radiography findings were recorded in 92 of 172 patients included in the study. Pathological chest radiography findings were found in 56 (60.9%) of 92 patients. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP (3 (17%) unilateral, 6 There were bilateral (3.5%) bilateral LAP), 2 (12%) atelectasis, 1 (0.6%) pleural effusion, and 1 (0.6%) LAP + consolidation. Chest X-ray of 36 (39.1%) patients was normal. Girgis *et al*. showed that lung grammar was normal in 169 (40%) of 423 cases. In the same study, perihilar nodular infiltration in the lung grammar of 125 (29.5%) patients, lower lobe infiltration in 50 (11.8%), upper lobe infiltration in 40 (9.4%) and 9 (2%) patients. They determined that there is miliary involvement.18

It was determined that 51% of the patients resided in city centers and 49% resided in districts or villages. In their study, Yaramış *et al*. showed that 14% of the patients came from the city centers, 34% from the districts, and 52% from the villages.14 CSF of our cases was evaluated in terms of protein, glucose, and white blood cell. The presence of M Tuberculosis was demonstrated by PCR in the CSF of 3 patients. CSF glucose levels were below 10 mg/dL in 15 (8.7%) patients, between 11-40 mg/dL in 99 (57.6%), 41-80 mg/dL in 51 (29.7%) patients. 7 (4.1%) were found to be above 80 mg/dL. When the CSF protein of the patients was biochemically examined, it was between 0-50 mg/dL in 44 (32.9%) patients, between 51-100 mg/dL in 19 (14.1%) and 101-200 in 53 (39.6%) patients. It was found to be between mg/dl, 201-500 mg/dL in 13 (9.7%) and over 500 mg/dL in 5 (3.7%) patients.

Lymphocyte dominance was observed in 143 (83.1%) patients, while PNL dominance was observed in CSF in 29 (6.9%). The number of cells in CSF of these patients was between 0-10/mm3 in 7 (4%) patients, between 11-100/mm3 in 55 (32%) and 101-500/mm3 in 84 (48.8%) patients and 500/mm3 and above were found to in the 26 (15.2%) patients.

Girgis *et al*. investigated CSF glucose, protein amount, and leukocyte count in cases with tuberculous meningitis. In their study, they found the average CSF glucose 22 ± 15 mg/dL, CSF protein 220 ± 20 mg/dL, and CSF leukocyte count 437 ± 347/mm3. [18]

In their study, Yaramış *et al*. found CSF glucose

below 10 mg/dL in 12% of the cases, between 10-40 mg/dL in 71% and between 40-80 mg/dL in 17%. They found CSF protein below 100 mg/dL in 23% of the patients, between 100-200 mg/dL in 62% and over 200 mg/dL in 15%.14 In the same study, the CSF leukocyte count was below 500 /mm^3 in 85% of the cases and over 500/mm^3 in 15%. And they stated that 83% of the leukocytes seen in CSF are lymphocytes and 17% are fragmented. In the CSF examination, which is the most important laboratory test, it has been reported that the leukocyte count varies between 500/mm^3 (compartmental lymphocyte dominance in the early period, lymphocyte dominance in the early period), the glucose level is low in the early period or is always low in the normal late period, and the protein level is usually high. [24] The mean white blood cell count was found to be 13.325/mm^3. Girgis et al found the mean peripheral white blood cell count of cases with tuberculous meningitis to be 11.600/mm^3. When compared with the literature data, it was seen that the patients with tuberculous meningitis who had similar leukocyte counts presented with mild leukocytosis. [19] While other laboratory results (urea, creatine, and transaminase elevation) were found to be high in approximately 20% of patients by Girgis colleagues, they were found to be high only in 10 patients who were evaluated as toxicity by Yaramış et al. [14,18]

CONCLUSION

TBM should be detected in the early period and their contagious feature should be eliminated, and uninfected people should be vaccinated. People with a high risk of infection should be protected from the disease by giving preventive antituberculosis drugs, and society and families should be educated and sensitized about the disease.

Authors' Contribution

Study Conception: YDY,; Study Design: YDY,; Supervision: YDY,; Materials: YDY,; Data Collection and/or Processing: YDY,; Funding: EY,; Statistical Analysis and/or Data Interpretation: YDY,; Literature Review: YDY,; Manuscript Preparation: YDY and Critical Review: YDY.

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