Clinical case series of nine patients with tuberculous meningitis in the Clinical Centre of Vojvodina, Novi Sad, AP Vojvodina, Serbia 2001-2010

Radoslava Doder¹², Grozdana Čanak¹², Sandra Stefan Mikić¹², Siniša Sević¹², Aleksandar Potkonjak³, Dragan Doder⁴, Vuk Vračar⁵

¹School of Medicine, University of Novi Sad, ²Department of Infectious Diseases, Clinical Centre of Vojvodina, ³Department of Veterinary Medicine, Faculty of Agriculture, University of Novi Sad, ⁴Provincial Institute of Sports Medicine and Sports; Novi Sad, Serbia

ABSTRACT

Aim To determine immediate risk factors of developing tuberculous meningitis, to assess the practical importance of clinical signs and findings in the cerebrospinal fluid (CSF) when opting for the specific therapy, and to predict the outcome of disease in relation to the beginning of treatment.

Methods A retrospective clinical case series of nine patients with tuberculous meningitis who were treated from April 2001 until November 2010 at the Department of Infectious Diseases in Novi Sad, Serbia was presented. Data of patients’ medical records and presentation of clinical and laboratory features, neuroradiological findings and outcome were used.

Results The factors of immediate risk/predisposition for the development of tuberculous meningitis were found in two (22.2%) patients. The duration of symptoms prior to admission was 9 days on average (from 3 to 20 days). The most frequent symptoms on admission were headache and fever in eight (88.9%) patients, whereas two patients (22.2%) were presented with stiff neck and photophobia. Consciousness was preserved in six patients (66.7%), two patients were somnolent and one was in coma. Two (22.2%) patients had concurrent pulmonary tuberculosis. Neuroradiological signs of the disease were present in two patients.

Conclusion The duration of symptoms before admission, clinical examination and CSF analysis can be helpful in identifying patients who are at high risk of developing tuberculous meningitis.

Key words: meningitis, tuberculosis, clinical features, complications, outcome
INTRODUCTION

Tuberculosis of the central nervous system (CNS) is expected in about 1% of all patients having active tuberculosis (1). It is caused by hematogenous dissemination of Mycobacterium tuberculosis (MBT) from the primary infection in the lungs and the formation of small andsubependymal foci in the brain or spinal cord (1). Rupture of the tubercula on the surface of the brain leads to the direct penetration of MBT into the subarachnoid space and development of meningitis (2). The process of merging of multiple small foci located deep in the parenchyma of the brain or spinal cord results in tuberculomas (rarely abscess), without meningitis (1).

Early diagnosis and promptly indicated treatment are essential for the favorable course and outcome of tuberculous meningitis (TBM)(2). This disease begins gradually with uncharacteristic symptoms such as headache, fever, vomiting and anorexia. The stiff neck and paralysis of cranial nerves occur in 40-80% and 30-50% of patients, respectively (2). The analysis of cerebrospinal fluid (CSF) is necessary and it usually reveals typical, moderately intensive pleocytosis (10-1000x10³, with the dominance of lymphocytes), elevated protein level (0.5-3.0 g/L) and decreased concentration of glucose (sugar ratio in the CSF: blood sugar <0.5) (3). However, CSF findings may be atypical in immunocompromised patients (e.g. acellular or dominated by neutrophils) (4). Direct microscopic identification of acid resistant bacilli and isolation of MBT from the CSF culture are the fastest and safest ways to confirm the diagnosis (2,3). The latest meta-analysis has shown that the commercial techniques using amplification of DNA fragments in the diagnosis of TBM are 56% sensitive and 96% specific, and that they can be useful in assessing therapeutic response (5). Conventional radiography of the lungs can detect active TB or old specific changes in half of the patients with TBM, and a miliary form of the disease in 10% of patients (2). Computed tomography (CT) of the head can detect hydrocephalus and accumulation of the contrast in the base of the brain (6). Both signs are more often present in children (~80%) than in adults (~40%) and may be absent in older patients (7). Magnetic resonance imaging (MRI) of endocranial cast can help to diagnose infratentorial lesions in relation to early changes in TBM, but the diagnostic sensitivity and specificity of these signs are low. In fact, similar radiological findings are typical for cryptococcal meningitis, cytomegalovirus encephalitis, toxoplasmosis, sarcoidosis, metastases in the meninges and lymphoma (8).

Treatment of all forms of CNS tuberculosis should be initiated by taking four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin) for two months, and then continue with two drugs (isoniazid, rifampicin) for the next eight to ten months (3,5,6). Streptomycin was one of the first major antituberculous drugs, which was replaced by isoniazid as the cornerstone of therapy with less harmful side-effects. Its use is limited by high rates of resistance, parenteral administration, nephrotoxicity, and ototoxicity (1,3,5). Ethambutol induced optic neuropathy, especially when treating comatose patients (1,3,5). According to the latest guidelines, adjuvant corticosteroid therapy (dexamethasone/prednisolone) is recommended in all patients with TBM, regardless of the severity of the disease (9). Hydrocephalus is common in children with TBM (7). Diuretics, repeated lumbar puncture (LP) or CSF diversion through ventriculoperitoneal or atrial shunting can be used in accordance with the increased intracranial pressure (5).

The objective of this study was to determine immediate risk factors for the development of TBM, to assess the practical importance of clinical signs and cytological and biochemical changes in the CSF when opting for a specific therapy, and to predict the outcome of the disease in relation to the beginning of treatment.

PATIENTS AND METHODS

A clinical case series of nine patients, presented in this study, were diagnosed with tuberculous meningitis and treated at the Department of Infectious Diseases in Novi Sad from April 2001 until November 2010. Patients were divided into two subgroups, one having the confirmatory diagnosis of tuberculous meningitis (patient No 1, 6 and 9) and the other group having the presumptive diagnosis of tuberculous meningitis (patient No 2, 3, 4, 5, 7 and 8). The data were obtained from the medical records of all patients. Risk factors, demographic, clinical and diagnostic data on admission and clinical outcome after TBM treatment are hereby
presented. This study was approved by the Ethics Committee of Clinical Centre of Vojvodina.

**Risk factors**

The risk factors included a close contact with the person having a similar disease, previous pulmonary tuberculosis, the use of corticosteroid drugs, malignant disease, head trauma, HIV co-infection as well as the social status.

**Diagnostic criteria**

The definite diagnosis of TBM was made in three patients when MBT was isolated from the CSF, or other body fluids or tissues. In all other patients, the diagnosis of “probable TBM” was based on the clinical features and analysis of changes in the CSF obtained by lumbar puncture on admission, and favorable response to the application of anti-tuberculosis drugs (ATD).

**Clinical data**

Clinical data included the duration of symptoms before admission, presenting symptoms and findings, CSF analysis results, basic hematological analyses and microbiological cultures on admission, additional diagnostic procedures and applied therapy. The following inclusion criteria were used: fever >38.0 ºC, headache, meningeal irritation, and neurological finding (examination of consciousness, cerebral nerves, presence of physiological and/or pathological reflexes and abnormal movements), as well as CSF pleocytosis, protein and glucose level and the reduction in CSF/blood glucose ratio. Cytological-biochemical analysis of CSF was performed at the Laboratory Diagnostics Center, Clinical Center of Vojvodina. Blood culture, CSF culture, urine culture for bacteria and fungi, and microbiological analysis of nasal and throat swabs were carried out at the Department of Microbiology, Institute for Public Health of Vojvodina in Novi Sad. Directmicroscopy and MBT culture in the CSF, sputum and urine samples were performed in the Centre for Microbiology, Virusology and Immunology at the Institute for Pulmonary Diseases of Vojvodina in Sremska Kamenica. All patients underwent lung radiography, CT scan or MRI of the head, electroencephalogram (EEG), and other diagnostic methods as needed (abdominal ultrasonography, chest CT scan, fundus examination).

**Statistical analysis**

The methods of descriptive statistics were used for statistical analysis. Pearson’s Chi square test was applied to determine the statistically significant correlation between the two subgroups (with the confirmatory diagnosis and with a presumptive diagnosis).

**RESULTS**

**Risk factors**

Epidemiological data regarding the contact with a person having a similar disease were negative. No common risk factors for TBM (previous pulmonary tuberculosis, use of corticosteroid drugs, malignant disease, and head trauma) were found. Half of the patients were tested for HIV status, and all of them were seronegative. Two patients (one from each subgroup) had data on alcohol consumption. Eight of nine patients lived in the city area.

**Demographic and clinical characteristics**

The average age of patients was 47.3 years, ranging from 19 to 65 years; females were more prevalent (F:M=66.5%:33.4%). The length of symptoms before admission for treatment was 9 days on average, ranging from 3 to 20 days (8.6 days and 9.1 days in the subgroup with the confirmatory diagnosis and the subgroup with presumptive diagnosis, respectively (p=0.904). On admission, eight (88.9%) patients had headache and fever, stiff neck and photophobia were observed in two (22.2%) patients. Consciousness was preserved in six (66.7%) patients: two patients had preserved consciousness and one female patient was drowsy with dysarthria in the subgroup with the confirmatory diagnosis, whereas in the subgroup with the presumptive diagnosis, four patients were conscious, one patient was somnolent and one was in coma. Nystagmus and hemiparesis were found in one, and tremor in two patients in the subgroup with the presumptive diagnosis (Table 1). The CSF analysis on admission showed white blood cell count of 331.8±193.5 x 10^6 with 61.2% lymphocytes (in the subgroup with the confirmatory diagnosis it was 255.6±166.6 x 10^6 with 74.6% lymphocytes; in the subgroup with the presumptive diagnosis it was 370 ± 208.6 x 10^6 with 54.5% lymphocytes) (p=0.440). The l-
vel of proteins in CSF was 1.9±1.2 g/L (2.2±1.5 and 1.8±1.2 in the subgroup with the confirmatory and presumptive diagnosis, respectively) (p=0.675); the glucose concentration in CSF was 1.9±0.7 mmol/L (1.5±0.5 and 2.1±0.8, in the subgroup with the confirmatory and presumptive diagnosis, respectively) (p=0.291) (Table 2).

**Diagnostic data**

All patients had intracranial meningitis except one female patient who had spinal form of meningitis. Only three patients had positive CSF culture. The active form of tuberculosis was identified in two patients with the confirmatory diagnosis of TBM. In younger patients, the disease had mi-

**Treatment**

Initial antituberculosis therapy with three drugs (isoniazid, rifampicin, pyrazinamide) was administered in four patients; other patients were given four drugs (isoniazid, rifampicin, pyra-

**Outcome**

Seven (77.7%) patients were discharged without any consequences of the disease. One patient with the presumptive diagnosis was discharged with severe neurological deficit, and another one with the confirmatory diagnosis was transferred to another facility due to exacerbated pulmonary infection.

**DISCUSSION**

The duration of symptoms in tuberculous meningitis ranges from a few days to a month. The shorter...
course of illness (<5 days) may lead to the diagnosis of bacterial or viral meningitis (7). Fungal meningitis, similar to the tuberculous meningitis, may have a protracted course (7). The duration of symptoms before admission for the treatment was 9 days in our cases, that in accordance with the data of other authors (10). Difficulties in establishing early and accurate diagnosis based on clinical parameters, changes in the CSF and neuroradiological diagnostic of TBM have been discussed in many clinical studies (4-7). Regardless of etiology, meningeval syndrome presents with similar symptoms such as fever, headache, irritability, stiff neck and vomiting (2,4,5). Drowsiness, cough, weight loss and night sweats may suggest tuberculosis, but they are not specific enough (7). Therefore, it often happens that on admission many patients are already at the advanced stage of the disease and have developed neurological signs such as seizures, different degrees of coma and paralysis of cranial nerves (11). Many studies, which have attempted to correlate headache and neurological deficit with tuberculous meningitis, have shown no diagnostic value (5-8,10,11). In our cases, however, the most common clinical symptoms were headache and fever, followed by the stiff neck and photophobia.

In addition, consciousness was preserved in more than a half of the patients. Neurological signs such as nystagmus, dysarthria and tremor were found in individual cases. The routine analysis of the CSF in many patients with TBM revealed moderate pleocytosis dominated by lymphocytes, elevated protein and decreased glucose concentration (3,5-7,10). Normal or atypical CSF findings were described in HIV-positive patients, cryptococcal meningitis and cytomegalovirus meningitis, as well as in the central nervous system lymphoma (4,7,12). The examination of cerebrospinal fluid of our patients showed the typical finding for tuberculosis meningitis. The diagnostic evaluation can be helped by neuroradiological changes in CT scan: hydrocephalus, basal arachnoiditis, infarcts and tuberculomas (7,8,10,11). Computed tomography of the brain or MRI of the endocranium, along with clinical and laboratory parameters are generally believed to be very important for the diagnosis of tuberculous meningitis (13). In one of our patients, hydrocephalus was diagnosed by CT and in the case of a female patient with post-contrast enhanced nodular lesions in leptomeninges described in the MRI, the previous CT scan was normal. The outcome of the disease was favorable, with no deaths. It is generally believed that coma and delayed initiation of therapy were predictors of poor outcome. Similar experience in relation to outcome has been described in many studies (7,8,10,11-15).

Tuberculous meningitis affected middle-aged people, predominantly women in our cases. The duration of nonspecific symptoms before admission was longer than a week. Common characteristics on admission were headache, fever and stiff neck. Analysis of the CSF is essential, especially if the culture is negative. Magnetic resonance imaging of the brain and head is a diagnostic modality in TBM complications. The outcome of the disease was favorable after 11 months of antituberculous chemotherapy, without fatal outcomes. A delayed treatment of TBM because of missed diagnosis may result in poor outcome and death. A comparison of patients with the confirmatory diagnosis and with presumptive diagnosis of tuberculous meningitis has resulted in the conclusion that simple, noninvasive and practical clinical data and cerebrospinal fluid assessment can be useful to the physicians in diagnosing tuberculous meningitis in adults at an early stage.

**REFERENCES**


**FUNDING**

No specific funding was received for this study.

**TRANSPARENCY DECLARATIONS**

Competing interests: none to declare

Klinička serija slučajeva kod devet bolesnika s tuberkuloznim meningitisom u Kliničkom centru Vojvodine (AP Vojvodina, Srbija) u periodu od 2001. do 2010. godine
Radoslava Doder1,2, Grozdana Čanak1,2, Sandra Stefan Mikić1,2, Siniša Sević1,2, Aleksandar Potkonjak3, Dragan Doder4, Vuk Vračar4
1Medicinski fakultet, Univerzitet u Novom Sadu, 2 Klinika za infektivne bolesti, Klinički centar Vojvodine, 3 Departman za veterinarsku medicinu, Poljoprivredni fakultet, Univerzitet u Novom Sadu; 4 Pokrajinski zavod za sport i medicinu sporta; Novi Sad, Srbija
SAŽETAK
Cilj Utvrditi faktore neposrednog rizika za razvoj tuberkuloznog meningitisa, ispitati praktični značaj kliničkih znakova i nalaza u likvoru u donošenju odluke za otpočinjanje specifične terapije, kao i ustanoviti ishod bolesti u odnosu na početak lečenja.


Rezultati Faktori neposrednog rizika/predispozicije za razvoj tuberkuloznog meningitisa naveni su kod dva (22,2%) bolesnika. Trajanje simptoma bolesti pre prijema na lečenje, iznosi je u proseku 9 dana (od 3 do 20). Najčešći simptomi i znaci pri prijemu na lečenje bili su glavobolja i povišena temperatura kod osam (88,9%), te ukočen vrat i fotofobija kod dva (22,2%) bolesnika. Svest je bila očuvana kod šest (66,7%), dok su dva bolesnika bila somnolentna, a jedan u komi. Nistagmus, dizartrija i tremor registrovani su u pojedinačnim slučajevima. Istovremena plućna tuberkuloza registrisana je kod dva (22,2%) bolesnika. Neuroradiološke znake bolesti imala su dva bolesnika. Kultura likvora bila je pozitivna kod tri (33,3%) pacijenata.

Zaključak Dužina simptoma pre prijema na lečenje, klinička slika i analiza likvora, mogu biti od pomoći u identifikaciji bolesnika koji su u visokom riziku za tuberkuloznu meningitis.

Ključne reči: meningitis, tuberkulozni, klinička slika, komplikacije, ishod