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PREDICTIVE FACTORS AND DIAGNOSTIC SCORES APPLYING IN TUBERCULOUS MENINGITIS

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Abstract. Introduction. Tuberculous meningitis represents a severe manifestation of the systemic infection. Clinical and laboratory diagnosis based on classical methods is difficult and delayed. The current rapid diagnostic tests are costly and sometimes inaccessible.
Objectives. We aimed to optimize the diagnostic strategy by establishing the features that are quickly available and have the best predictive value for TBM diagnosis by using two variants of scoring.
Methods: We retrospectively studied 58 non-HIV cases of possible TBM hospitalized in the Cluj-Napoca Clinic of Infectious Diseases during 2000-2007. The inclusion criteria were: meningitis syndrome, non-purulent cerebrospinal fluid with lymphocytes predominance, decreased glucose and increased protein levels. We established the significant clinical, laboratory and imagistic features through univariate analysis. These variables were used in a modified Thwaite's and Kumar's diagnostic scoring (score-1 and-2, respectively). We calculated likelihood ratios for TBM prediction accuracy.
Results. The diagnosis was microbiologically confirmed in 33.3% of all patients after 3 weeks in average. Statistical analysis revealed nine variables significantly predictive for TBM diagnosis: prodrome duration≥7 days or ≥14 days, age<23 years, WBC<9000/mm3, cerebrospinal fluid white-cell count <300/mm3, CSF neutrophils proportion <50% or <22%, paralysis, extrapyramidal signs / ataxia/ myoclonus / tremor. Using the adapted scoring 1, the posttest probability reached 92%. By using score 2 (based on three variables) we found a significant increase of the TBM prognosis (pLR = 5.2, nLR = 0.2, posttest probability =94%).
Conclusions. The confirmatory diagnosis of TBM is delayed and occurs in a small proportion of cases. Early TBM diagnosis may be improved by using Thwaite's and Kumar's diagnostic scoring adapted to our available variables that were significantly found in the study population.
Keywords: tuberculous meningitis, diagnostic scoring, likelihood ratio

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Abbreviation:
TBM – tuberculous meningitis
CSF – cerebrospinal fluid
CNS – central nervous system
pLR – positive likelihood ratio
nLR – negative likelihood ratio

Introduction

In Romania, the prevalence of tuberculosis is higher than in Central Europe, being estimated at 126.4/100.000 persons in 2005. Tuberculous meningitis (TBM) is a severe complication of systemic tuberculous infection, being associated with a fatality rate of 20%-50% and with a neurological sequelae rate of 20%-30% [1]. The inflammatory reaction of subarachnoidian space has two severe consequences: arachnoiditis related to cranial nerves palsy or hydrocephalus, and endarteritis, followed by arterial occlusion and infarctions. The diagnosis is difficult and often delayed due to a variable and nonspecific clinical picture, resembling a chronic infection of the central nervous system. Moreover, biochemical and cytological changes of CSF in TBM could also accompany other central nervous system pathological conditions (infectious and noninfectious). Positive CSF culture for *Mycobacterium tuberculosis* confirms diagnosis but the due diagnosis and treatment requires too much time. The rapid diagnosis tests (PCR, RT-PCR) are not always available, being expensive and requiring well-equipped laboratories. Therefore, a better diagnosis algorithm and early adequate therapy are both necessary for prognostic improvement and decreased TBM fatality rate.

Objectives

In these circumstances, we completed a retrospective study based on a series of meningitis cases with CSF changes suggestive for tuberculous infection. The aim of the study was to find a number of parameters that could be rapidly evaluated and which would have maximal predictive value for the TBM diagnosis. Also, we have proposed variants of diagnostic scoring based on these parameters and on Thwaite's and Kumar's scoring in order to improve the diagnosis algorithm and appropriate treatment.

Methods

We conducted a retrospective study, analyzing possible meningitis cases hospitalized in the Cluj-Napoca University Hospital of Infectious Diseases between 2000 and 2007. The including criteria for a meningitis case comprised epidemiological data, clinical manifestations and CSF changes suggesting tuberculous meningitis: fever; meningeal syndrome; paresis/paralysis or other neuropathological syndromes; clear, opalescent or citrine appearance of CSF; lymphocytic pleocytosis; low CSF glucose level; increased CSF protein level; cerebral CT changes (tuberculomas, hydrocephalus or basilar meningitis findings). Fifty-eight consecutive cases, adults and children, accomplished the above mentioned criteria. The Ziehl-Neelsen staining and CSF harvesting for *Mycobacterium tuberculosis* (using MB/BacT system) were performed. For other bacteria, specific media cultures, Gram stains and agglutination tests for bacterial antigens (*S. pneumoniae, S. agalactiae, N. meningitidis, H. influenzae*) were done. All cases of viral, non-tuberculous, doubtless bacterial meningitis (with either purulent/turbid or clear CSF and positive bacteriologic examination) were excluded. HIV infected patients were also precluded from the study. We created a database which included the variables: age, sex, prodrome duration, white blood cells count, meningeal syndrome, CSF aspects (appearance, leukocytes count, and protein and glucose levels), neuropathological findings (coma, paresis/paralysis, extrapyramidal syndrome, ataxia, seizures), epidemiological and microbiological data. The statistical analysis was performed using EPIINFO 2000 software. We analyzed the significant variables with predictive value for the TBM diagnosis and two different diagnosis scores were evaluated (table I and II):

In the first score, adapted from Thwaites GE

VARIABLE	Cut-off (obtained average value)	COUNT
Age	≥ 23 years	+2
	< 23 years	0
Peripheral white blood cells	≥ 9000/mm^3	+4
	< 9000/mm^3	0
Prodrome duration	≥ 14 days	-5
	< 14 days	0
CSF leukocytes	≥ 300 cells/mm^3	+3
	< 300 cells/mm^3	0
CSF-polymorphonuclear proportion	≥ 22%	+4
	< 22%	0
SCORE		**≤ 4: probably TBM** **>4: consider another diagnosis**

Table I The first score (adapted from Thwaites GE)

VARIABLE	VALUE
Symptomatic period before hospitalization ≥ 7 days	Yes/No
Optical atrophy	Yes/No
Paresis/paralysis	Yes/No
Extrapyramidal syndrome/ataxia/tremor/myoclonus	Yes/No
< 50% polymorphonuclear leukocytes in CSF	Yes/No
First variant of the score	**≥ 2 parameters - probably TBM**
Second variant of the score	**≥ 3 parameters - probably TBM**

Table II The second score (adapted from Kumar R)

[2], we used continuous variables significant for the TBM presumption, the cut-off for each of them was the average value determined in our cases. A score of less or equal to 4 was considered predictive for TBM (table I)

In the second score, adapted from Kumar R [3], we used dichotomic variables. We evaluated two variants of this score: a predictive value for TBM was considered if at least 2 parameters (in the first variant) or at least 3 parameters (in the second variant) have been present (table II).

In order to evaluate the score accuracy for the TBM prediction we used likelihood ratio: pLR = Se/[1-Sp] and nLR = [1 – Se]/Sp (4). According to Bayes' theorem, if pLR >5 and nLR <0.2, then the test has significant predictive value for the diagnosis [5]. The confirmation of the diagnosis, established in agreement with the specialist in pneumology, has been made based on microbiological data, and in absence of these, epidemiological, clinical and imaging data correlated with CSF pathologic changes.

Results

Between 2000 and 2007 58 cases of meningitis were hospitalized in the Cluj-Napoca University Hospital of Infectious Diseases, cases which met the inclusion criteria, namely: clinical picture and CSF changes suggestive for tuberculous meningitis. Forty-five patients (77.6%) have had a definite

Age		Mean: 23 years; Median: 14.5 years; Limits: 6 months-78 years
Past tuberculous infection		8 (14%)
Contact with a patient with tuberculosis		13 (22.4%)
Prodromal duration		Mean: 14 days (2–60), Median: 10 days
Fever		58 (100%)
Coma		17 (29%)
Neuropathological syndromes		40 (69%)
Suggestive cerebral CT (tuberculomas / hydrocephalus /basilary meningitis)		14 (24%)
Pulmonary radiography suggestive for tuberculosis		34 (59.6%)
White blood cells		Mean: 9000/mm^3 (3000-22000/mm^3)
CSF appearance	Clear	43 (74%)
	Citrine	15 (26%)
CSF leukocytes		Mean: 300/mm^3 (3-1000/mm^3)
CSF polymorphonuclear proportion		Mean: 22%, Median: 10% (1-75%)
CSF lymphocytes		Mean: 79% (10-99%)
Glycorrhachia		Mean: 34mg%, Median: 31mg% (5-95mg%)
CSF protein concentration		Mean: 170mg%, Median:144mg%
TBM diagnosis (clinical, paraclinical, epidemiological)		45 (77.6%)
Positive Ziehl–Neelsen smears		2 (4.4%)
Positive *M.tuberculosis* cultures		15 (33.3%)
Non-tuberculous bacterial meningitis diagnosis		13 (22.4%)

Table III Characteristics of the study patients

tuberculous meningitis diagnosis (subsequently established) and 13 patients (22.4%) have had a final diagnosis of non-tuberculous bacterial meningitis. The patients' age ranged between 6 months and 78 years. Patients' significant data are shown in table III.

We analyzed the variables adapted from Thwaites GE and Kumar R [2,3]. Univariate analysis (odds ratio respectively) is shown in table IV. For TBM prediction some of the variables analyzed in the first score and some in the second one, according to the above mentioned method, were used. Applying the first score, adapted from Thwaites GE, the following statistical data were obtained (table V): sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (pLR, nLR).

According to the Bayesian theorem, we obtained the following results: pre-test odds=3.5 (pre-test disease probability 77%) and post-test odds=13 (post-test disease probability 92 %), meaning a significant increase of TBM probability after applying the first score in the studied population. We applied the second score proposed by R. Kumar in two variants: the presence of ≥2 variables or ≥3 variables. The statistical results are shown in table VI. Using the second score (presence of at least 2 variables) we calculated the pre-test odds=3.46 (pre-test disease probability 77%) and the post-test odds=8.6 (post-test disease probability 89%). The results confirm the score's variant value in TBM diagnosis prediction, although other causes of probable meningitis cannot be excluded with certainty. If at least three variables are used, the pre-test odds=3.46 (pre-test disease probability 77 %) and post-test odds=17.9 (post-test disease probability 94%), obtaining an unambiguous rise of the predictive value of the score for TBM diagnosis, also confirmed by pLR and nLR values.

Discussions

Clear or citrine CSF meningitis poses difficult differential diagnosis problems to be quickly solved. An important proportion of central nervous system infections have a rapid progression towards death or neurological sequelae. In the absence of an early diagnosis and etiological treatment, tuberculous meningitis is characterized by high mortality (20-50%) and sequelae probability (20-30%). Clinical findings and CSF modifications in tuberculous meningitis are various and nonspecific. A definite diagnosis presumes using either a classic method, e.g. isolation and identification of *Mycobacterium tuberculosis*, or modern techniques, represented by

VARIABLE	OR ($CL_{95\%}$)	p
Prodrome duration ≥ 7 days	11 (2.6 - 50)	0.000
Prodrome duration ≥ 14 days	16.4 (1.9- 137)	0.0012
Age < 23 years	4.9 (1.3 - 18)	0.01
White blood cells < 9000/mm^3	3.54 (1 - 12)	0.04
CSF pleocytosis < 300/mm^3	3.54 (1 - 12)	0.04
CSF polymorphonuclear leukocytes < 50%	13.4 (2.2 - 81)	0.004
CSF polymorphonuclear leukocytes < 22%	6 (1.6 - 23)	0.007
Paresis/paralysis	4.8 (1.3 - 18)	0.018
Extrapyramidal syndrome/myoclonus /tremors	9 (2.2 - 36)	0.0015

Table IV Univariate analysis of TBM predictive variables

Score-1	Se	Sp	PPV	NPV	pLR	nLR
≤ 4	86%	77%	92%	62%	3.7	0.17

Table V The first TBM predictive score (adapted from Thwaites GE)

Score-2	Se	Sp	PPV	NPV	pLR	nLR
≥ 2 variables	95.5%	61%	89.5%	80%	2.84	0.072
≥ 3 variables	80%	84%	94%	55%	5.2	0.2

Table VI The second TBM predictive score (adapted from Kumar R)

molecular methods (PCR, RT-PCR) or radioimmunoassay (detection of γ-IFN released by stimulated macrophages and Th1-lymphocytes). The classic methods have a wide range of sensitivity (30-80%) but the results are delayed (approximately 2-3 weeks). The modern techniques are faster, providing a higher sensitivity (60-83%) and specificity (98-100%), but are frequently unavailable, being expensive and requiring a well-equipped laboratory. In these circumstances, the clinicians are compelled to use diagnosis algorithms based on CSF changes and clinical aspects.

Therefore, we aimed to evaluate some predictive factors for TBM diagnosis and to apply adapted diagnosis scores (after analyzing the variables considered in bacterial meningitis with clear or citrine CSF). Studied cases revealed an average prodrome duration of 14 days and the following average values of CSF: pleocytosis of 300 cells/mm^3, glucose level of 34 mg/dl and proteins of 177 mg/dl. Also, neuropathological syndromes were present in an important proportion of cases - 69%. Characteristic neuroimaging aspects for CNS tuberculosis (tuberculomas, progressive hydrocephalus, basilary meningitis) were found with a low frequency (24%), in comparison with suggestive pulmonary radiological aspects for tuberculosis (59.6%). Positive CSF culture for *Mycobacterium tuberculosis* confirmed diagnosis in 33.3% of cases but an optimal diagnosis and treatment requires too much time.

This does not respond to the need for effective early diagnosis and treatment [6]. Univariate analysis of variables suggests a clinical and laboratory criteria set which might be a potential discriminator between TBM and other meningitis with clear or citrine CSF. Therefore, the prodrome duration ≥7 or 14 days, age <23 years, white blood cells <9000/mm^3, CSF pleocytosis <300/mm^3, CSF polymorphonuclear leukocytes <50% or <22% have been significantly correlated with TBM diagnosis (odds ratio between 3.54 and 14.9, $p<0.05$). The score proposed by Thwaites GE is based on univariate analysis and multivariate logistic regression of the significant variables associated to tuberculous meningitis diagnosis.

In our study, we have replaced the cut-offs of the variables proposed by Thwaites GE with the average values obtained in our patients, these values proving significant correlations with TBM diagnosis. Therefore, using the first score, we reported similar sensitivity and specificity with those communicated by Thwaites GE (Se was 86% in both studies while Sp was 77% versus 79%). Although pLR was less than 5, we could still observe an important increase of disease post-test probability (pre-test probability=77% and post-test probability=92% or pre-test odds=3.5 and post-test odds=13). We applied the second score adapted from Kumar R using the variables: prodrome duration ≥7 days, optic atrophy, paresis/paralysis, extrapyramidal syndrome/ ataxia/ involuntary movements. The statistical results revealed a rise of TBM prediction depending on the number of parameters used. Thus, for TBM diagnosis, the presence of at least 2 parameters yields a sensitivity of 95.5% and a specificity of 61% with an increase of the disease probability from 77% (pre-test) to 89% (post-test), but without excluding with high certainty other causes of meningitis. When at least 3 parameters were considered compulsory for the diagnosis, the second score sensitivity increased at 80% and specificity at 84%. In addition, pLR (5.2) and nLR (0.2) values allowed us to consider this last option as a good prognostic test for TBM also demonstrated by the clear-cut increase of post-test odds (17.9) and post-test disease probability (94%).

Therefore, using the first score and the three parameters variant of the second score, we obtained an effectiveness of the TBM diagnosis algorithm, employing a set of clinical and accessible laboratory items.

Conclusions

The classical confirmatory diagnosis of TBM is delayed and found just in a small proportion of cases. Early TBM diagnosis may be improved by using Thwaite's and Kumar's diagnostic scoring adapted to our available variables that were significantly found in the study population.

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