
Article

Prospective Validation of a Diagnosis Model as an Aid to Therapeutic Decision-Making in Acute Meningitis

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Abstract The aim of this study was to validate a diagnosis model that provides pABM, the probability of bacterial versus viral meningitis, based on four parameters collected at the time of first lumbar tap: cerebrospinal fluid protein level, cerebrospinal fluid polymorphonuclear cell count, blood glucose level, and leucocyte count. The model was evaluated prospectively as an aid to therapeutic decision-making in 109 consecutive patients with acute meningitis and negative cerebrospinal fluid Gram stain. In each case pABM was computed before a therapeutic decision and three diagnoses were established successively: (i) clinical evaluation, i.e. before pABM computation (bacterial meningitis, viral meningitis, or meningitis of undetermined origin); (ii) computation of pABM (viral meningitis if $pABM < 0.1$, bacterial meningitis otherwise); and (iii) determination of definitive diagnosis (bacterial meningitis: positive cerebrospinal fluid culture; viral meningitis: negative cerebrospinal fluid culture, no other aetiology and no treatment; meningitis of undetermined origin: cases fitting neither of the first two diagnoses). The computed diagnosis was viral meningitis in 78 of the 80 cases diagnosed definitively as viral meningitis, and bacterial meningitis in four of the five cases diagnosed definitively as bacterial meningitis. Negative and positive predictive values and accuracy of the model were 98.7%, 66.7%, and 96.5%, respectively. The clinical diagnosis was undetermined in 22 cases, 15 of which were diagnosed definitively as viral cases; in all of these 15 cases, the computed diagnosis was viral meningitis, leading the physician to refrain from starting antibiotics in all of them. The results confirm that the model evaluated is reliable and aids in the identification of patients in whom antibiotics can be safely avoided.

Introduction

Accurate and rapid diagnosis of acute bacterial meningitis (ABM) is essential to a favourable outcome [1–2]. Although examination of the cerebrospinal fluid (CSF)

often provides immediate confirmation of ABM, it sometimes fails to differentiate ABM from acute viral meningitis (AVM). Current guidelines recommend starting antibiotics whenever a bacterial aetiology cannot be excluded definitively [2]; however, the cost of antibiotic therapy and its attendant hospitalisation, as well as its potential side effects, have raised concern about giving unnecessary antibiotics in cases of AVM. Until now, no single CSF or blood parameter has been able to discriminate between ABM and AVM, since, for each potential parameter, its distribution for ABM may overlap the entire range of values found in AVM [3].

We previously elaborated a logistic model that proved effective in differentiating ABM from AVM [4]. This model provides pABM, the probability of ABM versus AVM, based on four parameters collected at the time

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of the first lumbar tap: the CSF protein level, the total CSF polymorphonuclear cell count, the blood glucose level, and the leucocyte count. We found that the best pABM cut-off value for discriminating ABM from AVM was 0.1. We implemented in our institution a computerised program that calculates pABM within seconds after entering the parameters necessary for its calculation. We then urged physicians from our team to compute pABM before making a therapeutic decision in all cases of acute meningitis not obviously of bacterial origin. The aim of this study was to prospectively validate the performance of our model as an aid to diagnosis and therapeutic decision-making in consecutive cases of acute meningitis with negative CSF Gram stain.

Patients and Methods

Patients and Setting. All consecutive patients, adults as well as children, who had acute community-acquired meningitis were considered for this validation study. Excluded were patients with clinical evidence of encephalitis and those for whom the diagnosis of ABM was obvious (cloudy CSF and positive CSF Gram stain). All patients were hospitalised in the Department of Infectious Diseases, University Medical Centre of Nancy, Nancy, France, between April 1993 and April 1997.

Validation Process. The patient's physician computed pABM before he/she made his/her therapeutic decision. In each case, three diagnoses were established successively. The clinical diagnosis was the physician's putative diagnosis based on physical examination and interpretation of the available laboratory findings in blood and in CSF at the time of the first lumbar tap. On this basis, the clinical diagnoses were distributed into three categories (bacterial, viral, undetermined aetiology) before pABM computation. The computed diagnosis was determined as the result of pABM computation; pABM was computed using the logistic equation of the previously established model [4], i.e.,

$$\begin{aligned} \text{pABM} &= 1/(1 + e^{-L}), \text{ where} \\ L &= 32.13 \times 10^{-4} \times \text{CSF PMN count (10}^6/\text{l)} \\ &+ 2.365 \times \text{CSF protein (g/l)} \\ &+ 0.6143 \times \text{blood glucose (mmol/l)} \\ &+ 0.2086 \times \text{leucocyte count (10}^9/\text{l)} - 11 \end{aligned}$$

In our former study, we had determined that 0.1 was the best pABM cut-off value for discriminating ABM from AVM since it was associated with a negative predictive value of 0.99. Therefore, the computed diagnosis was distributed into one of two categories: bacterial if $\text{pABM} \geq 0.1$, and viral if $\text{pABM} < 0.1$. The definitive diagnosis was established after the patient's discharge and included three categories that were defined as follows: (i) bacterial meningitis: if an appropriate aetiological bacterium was cultured from CSF or blood or if a bacterial antigen was demonstrated in patient's CSF, blood, or urine by latex agglutination or if seroconversion for *Leptospira* spp. was evident; (ii) viral meningitis: if a virus was isolated from culture of blood, stool, or CSF or if the diagnosis at discharge was viral meningitis and no aetiology other than viral infection was demonstrated and no antibiotics were given for the treatment of meningitis; and (iii) meningitis of undetermined aetiology: in cases fitting neither of the former two definitions. These definitions were those used previously by Spanos et al. [5] as well as by us [4] for model development and validation.

The three indices used to assess the performance of the model were the positive predictive value, the negative predictive value, and accuracy (A). Standard definitions were used for these

Table 1 Definitions of the performance indices used to evaluate the diagnosis model. Negative predictive value (NPV) = $d/c + d$. Positive predictive value (PPV) = $a/a + b$. Accuracy (A) = $a + d/a + b + c + d$

Computed diagnosis	Definitive diagnosis	
	Bacterial meningitis	Viral meningitis
Bacterial meningitis	a	b
Viral meningitis	c	d

indices [6]. These definitions, applied to the current problem, are shown in Table 1.

The evaluation of the model as an aid to therapeutic decision-making was performed by cross-tabulating definitive versus computed diagnoses for each of the three categories of clinical diagnosis.

Results

The model was tested in 109 patients (mean age 30 years, range 1–85). Patients' characteristics and the distribution of blood and CSF parameters within the three categories of acute meningitis are displayed in Table 2. The definitive diagnoses were distributed as follows: bacterial meningitis ($n=5$), viral meningitis ($n=80$), and meningitis of undetermined aetiology ($n=24$). Thirty-one patients had been given antibiotics prior to admission and the diagnosis of meningitis. Although there was a trend towards a higher rate of antibiotic administration prior to admission in patients whose definitive diagnosis was undetermined, the difference was not statistically significant ($P=0.25$). The causative microorganisms are displayed in Table 3.

Definitive diagnoses were first cross-tabulated versus clinical diagnoses (Table 4) and then versus computed diagnoses in the 85 cases of bacterial or viral meningitis (Table 5). The computed diagnosis was viral meningitis in 78 of the 80 cases diagnosed definitively as viral meningitis, and bacterial meningitis in four of the five cases diagnosed definitively as bacterial meningitis. Therefore, the negative and positive predictive values and the accuracy of the model were 98.7%, 66.7%, and 96.5%, respectively.

The only case of definitive bacterial meningitis that was computed as viral by the model was a case of leptospirosis. The corresponding patient was a 46-year-old man whose leucocyte count was 12,500 PMN cells/mm³ and blood glucose level was 6.11 mmol/l. CSF was optically normal and contained 650 leucocytes/mm³ (55% PMNs), 1.94 mmol/l of glucose, and 0.59 g/l of protein. Although the model gave $\text{pABM}=0.04$, the physician started the patient on amoxicillin for presumed leptospirosis. The presumption of leptospirosis was based on

Table 2 Patient characteristics and blood and CSF parameters in 109 cases of acute meningitis. Quantitative variables are expressed as median (range)

Characteristic	Definitive diagnosis		
	Bacterial meningitis (n = 5)	Viral meningitis (n = 80)	Undetermined (n = 24)
Age in years	23 (15–65)	29.5 (0.8–63)	23.5 (1–85)
No. (%) with antibiotics prior to admission	1 (20)	20 (25)	10 (42)
Leucocyte count (10 ⁹ /l)	12.5 (5.8–19.4)	8.0 (2.4–17.6)	10.9 (6.2–21.3)
Blood glucose level (mmol/l)	7.1 (6.1–16.8)	5.49 (1.1–7.9)	5.4 (3.8–9.5)
CSF leucocyte count (10 ⁶ /l)	1930 (320–10 ⁴)	147 (11–1600)	475 (45–2900)
CSF PMN count (10 ⁶ /l)	1835 (176–10 ⁴)	18 (0–525)	35 (2–2755)
CSF protein level (g/l)	1.4 (0.3–6.0)	0.5 (0.1–1.3)	0.6 (0.1–4.0)
CSF glucose level (mmol/l)	2.5 (0.05–3.8)	2.9 (1.9–4.2)	2.9 (0.3–4.4)
CSF/blood glucose ratio	0.4 (0.002–0.5)	0.5 (0.4–3.7)	0.5 (0.05–1.0)
No. (%) of cases with fatal outcome	0	0	1 (4.2)

PMN, polymorphonuclear cell

Table 3 Distribution of the causative microorganisms in 109 cases of acute meningitis

Organism	No. of cases
Definitive bacterial meningitis (n = 5)	
<i>Streptococcus pneumoniae</i>	1
<i>Neisseria meningitidis</i>	1
<i>Listeria monocytogenes</i>	1
<i>Leptospira</i> spp.	2
Definitive viral meningitis (n = 80)	
Enterovirus	19
Herpes zoster virus	3
Herpes simplex virus	2
Mumps virus	2
Lymphocytic choriomeningitis virus	1
Virus not identified	54
Definitive undetermined aetiology (n = 24)	

Table 4 Cross-tabulation of definitive versus clinical diagnoses in the 109 patients studied

Clinical diagnosis	Definitive diagnosis (no. of cases)			
	Bacterial meningitis	Viral meningitis	Undetermined aetiology	Total
Bacterial meningitis	4	0	14	18
Viral meningitis	0	65	4	69
Undetermined aetiology	1	15	6	22
Total	5	80	24	109

Table 5 Cross-tabulation of definitive versus computed diagnoses in the 85 cases of microbiologically defined meningitis. Negative predictive value = 78/79 (98.7%), positive predictive value = 4/6 (66.7%), accuracy = 82/85 (96.5%)

Computed diagnosis	Definitive diagnosis (no. of cases)		
	Bacterial meningitis	Viral meningitis	Total
Bacterial meningitis	4	2	6
Viral meningitis	1	78	79
Total	5	80	85

a history of contact with rodents, a biphasic fever, and concomitant acute renal failure and elevated aminotransferases. The clinical course was favourable, and the diagnosis of leptospirosis was confirmed serologically after the patient's discharge.

To evaluate the aid provided by the model to the clinician for therapeutic decision-making, we cross-tabulated definitive versus computed diagnoses for each of the three categories of clinical diagnosis. Of the 109 patients studied, 22 had an undetermined clinical diagnosis (Table 6, a). In 19 of these, the computed diagnosis was viral meningitis, which helped the physician decide not to start antibiotics in 15 cases, which were definitively determined to be of viral aetiology. In three cases, patients were given antibiotics, and therefore the definitive diagnosis could only be undetermined. The single patient with definitive bacterial and computed viral diagnoses was the formerly described patient with leptospirosis.

Among the 69 patients with a clinical diagnosis of viral meningitis (Table 6, b), only one of the 63 patients with definitive and computed diagnoses of viral meningitis was given antibiotics. The reasons for treating this patient included a 3-day course of amoxicillin prior to hospitalisation and elevated inflammatory blood tests. Eventually, an enterovirus was recovered from stools. Two patients with a definitive diagnosis of viral meningitis were computed as having bacterial meningitis. Nevertheless, neither was given antibiotics, probably because in both cases there was strong clinical evidence that meningitis was of viral aetiology: one case complicated the course of chickenpox and the other occurred 2 weeks after an episode of herpes genitalis. In both cases the pABM value was <0.2, a value associated with a negative predictive value of 98%.

All of the 18 patients with a clinical diagnosis of bacterial meningitis (Table 6, c) were treated with antibiotics, irrespective of the pABM value.

Table 6 Evaluation of the model as an aid to diagnosis and therapeutic decision-making in (a) the 22 patients in whom the clinical diagnosis was undetermined, (b) the 69 patients with a clinical diagnosis of viral meningitis, and (c) the 18 patients with a clinical diagnosis of bacterial meningitis. The number of patients who received antibiotics for meningitis treatment is within parentheses

Computed diagnosis	Definitive diagnosis			
	Bacterial meningitis	Viral meningitis	Undetermined aetiology	Total
a				
Bacterial meningitis	0	0	3 (3)	3
Viral meningitis	1 (1)	15 (0)	3 (3)	19
Total	1	15	6	22
b				
Bacterial meningitis	0	2 (0)	0	2
Viral meningitis	0	63 (1)	4 (4)	67
Total	0	65	4	69
c				
Bacterial meningitis	4 (4)	0	5 (5)	9
Viral meningitis	0	0	9 (9)	9
Total	4	0	14	18

Discussion

Our diagnosis model had been elaborated through a multivariate logistic regression analysis of 500 consecutive cases of acute community-acquired meningitis that had been reviewed retrospectively [4]. That study was primarily intended to validate a similar approach that had been reported by Spanos et al. [5]. Of the 500 meningitis cases we had reviewed, 398 were documented as either AVM ($n=283$) or ABM ($n=115$), and 102 were of undetermined aetiology. Performance indices of this model were quite satisfactory: its area under the receiver operating characteristic (ROC) curve was 0.991, and its negative predictive value was 0.99 for pABM cut-off value of 0.1 [4]. Additionally, the validity of our model and the relevance of pABM=0.1 as a cut-off for therapeutic decision-making were confirmed by independent investigators on a retrospective series of acute meningitis [7, 8]. This prompted us to use it in clinical practice as a diagnostic aid for meningitis care.

The objective of this study was to evaluate whether the use of our model could contribute to the improvement of diagnosis and therapeutic management of meningitis. We confirm that our model can effectively and safely aid in excluding the diagnosis of bacterial meningitis, since we found again that the negative predictive value associated with pABM cut-off value of 0.1 was as high as 0.987, which is very close to the negative predictive value we had found in our first study. The only case of a definitive diagnosis of bacterial meningitis that was computed as viral meningitis by the model was due to leptospirosis. This is not surprising, since *Leptospira* meningitis usually mimics viral meningitis

[9]. Furthermore, leptospirosis is often associated with a spontaneous benign course, so that in many cases patients are not given antibiotics [9]. For these reasons, we could have chosen to exclude cases of leptospirosis from analysis or classify them as viral meningitis. This would have improved the performance indices of our model, resulting in a negative predictive value of 1.

In order to evaluate our model as an aid to therapeutic decision-making, we cross-tabulated definitive versus computed diagnoses for each of the three clinical diagnosis categories. We first looked at the 22 cases with an undetermined clinical diagnosis (Table 6, a), since we deemed this clinical situation to be that in which our model might be most helpful. On the one hand, one can interpret the fact that 15 of 19 patients whose computed diagnosis was viral meningitis were not – and appropriately not – given antibiotics as a result of the clinician's knowledge of the pABM value, since current practice guidelines should have led him/her to start antibiotics, all the more so since 5 of these 15 patients had received antibiotics prior to the diagnosis of meningitis. On the other hand, one can appreciate that, in the only patient whose definitive diagnosis was bacterial meningitis, the attending clinician had remained free to start antibiotics. Likewise, the physician's therapeutic decision was not in agreement with the computed diagnosis in 2 of the 70 patients with a clinical diagnosis of viral meningitis and a computed diagnosis of bacterial meningitis but a definitive diagnosis of viral meningitis: in both cases the physician's decision to withhold antibiotics was consistent with his/her primary clinical judgement and was not altered by the result of pABM computation. In summary, the model appeared to significantly help physicians refrain from starting antibiotics when they were doubtful about the aetiology of meningitis and if the computed diagnosis was viral meningitis; conversely, the therapeutic decision was not altered by a discordant computed diagnosis when the clinician's confidence in his/her clinical diagnosis was strong.

These two conclusions are of utmost importance. First, we would like to re-emphasise that, as previously advocated by Spanos et al. [5] and us [4], pABM should be regarded as one piece of diagnostic information among others and should never be substituted entirely for a careful diagnostic evaluation in each individual case. Secondly, we confirm that, used in this way, our model is of special interest in doubtful cases, when the physician is almost convinced that he/she is facing aseptic meningitis but would appreciate having stronger evidence on which to base his/her therapeutic decision. This would help reduce the inappropriate use of antibiotics that are still used too often and for too long in cases of acute meningitis of undetermined aetiology, as demonstrated by recent studies in adults [10] as well as in children [11]. One could argue that the low rate of bacterial meningitis in our study might be a limitation

to its relevance. We would like to point out, however, that the model was used by physicians specifically in cases of acute meningitis of undetermined aetiology, excluding cases that were obviously bacterial. In addition, recent epidemiologic data showed that the incidence of bacterial meningitis has decreased dramatically [12]. As a result, the proportion of viral meningitis cases among those of undetermined aetiology would likely increase. This makes our model of special interest as an aid to help physicians refrain from starting antibiotics.

Also of importance is that our model has been elaborated and validated regardless of antibiotic administration prior to lumbar puncture. Since the latter has been shown to decrease the yield of Gram stain, patients with acute meningitis and antibiotic treatment prior to lumbar puncture are more prone to receive antibiotics for treatment of meningitis [2, 11]. Therefore, the decision to withhold or to stop antibiotic treatment early could be made according to the result of our model-derived pABM computation, which has now been validated as a consistent clinical criterion for the therapeutic decision-making process.

Finally, another advantage of the model is that it provides valuable clinical information without delay and at no additional expense, which is not the case for other newer laboratory markers that have been recently evaluated in this field, such as procalcitonin or cytokine assays [13, 14].

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