Differential Diagnosis of Acute Meningitis

An Analysis of the Predictive Value of Initial Observations

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We analyzed data from the records of 422 patients with acute bacterial or viral meningitis. A cerebrospinal fluid (CSF) glucose level less than 1.9 mmol/L, a CSF-blood glucose ratio less than 0.23, a CSF protein level greater than 2.2 g/L, more than 2000×10^6/L CSF leukocytes, or more than 1180×10^6/L CSF polymorphonuclear leukocytes were individual predictors of bacterial infection with 99% certainty or better. Although any one of these tests could rule in bacterial meningitis with high probability, none could rule it out. To better predict whether a patient has bacterial vs viral infection, we developed a logistic multiple regression model using CSF-blood glucose ratio, total polymorphonuclear leukocyte count in CSF, age, and month of onset. This proved highly reliable when validated in an independent test sample, with an area under receiver operating characteristic curve of 0.97. The model should allow physicians to differentiate between acute viral and acute bacterial meningitis with greater accuracy.

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ACCURATE diagnosis is essential for patients with acute bacterial meningitis (ABM). Examination of the cerebrospinal fluid (CSF) often provides immediate confirmation of ABM, but in a sizable number of cases "classic" CSF findings are not present. In about one fourth of cases of ABM no bacteria are seen in the initial gram-stained CSF smear,[1] and in 30% to 40% of these cases the other CSF parameters are not diagnostic.[2] Conversely, in some cases of acute viral meningitis (AVM) the CSF and blood findings are consistent with bacterial disease.

Authorities have cited various ranges of blood and CSF findings as being typical of either ABM or AVM.[1-4] However, mathematically rigorous analysis of the ability of various laboratory values to distinguish between these diagnoses has not been performed. Therefore, we examined initial data from a large number of cases of both ABM and AVM. Our aims were (1) to establish distributions of CSF and blood cell count parameters in both conditions; (2) to assess the relative diagnostic value of each, independently and together; and (3) to assess whether the final diagnosis could be predicted accurately by means of a statistical model based on a combination of parameters.

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METHODS

We reviewed the charts of all patients with a final diagnosis of acute meningitis who were hospitalized at Duke University Medical Center, Durham, NC, between January 1969 and July 1980. The following cases were excluded: those presenting in the first month of life; those associated with neurosurgical procedures, including CSF shunt infections; cases in immunosuppressed patients; cases of aseptic meningitis in patients with noninfectious diseases that can themselves cause aseptic meningitis with negative viral cultures; and those with all CSF and blood test data missing from the chart. Cases also were excluded if no etiology was confirmed but antibiotics were given for 2 or more days after admission. Patients were not excluded if outpatient antibiotic treatment was given prior to admission, for two reasons: (1) this is a common feature at presentation, so we wished to make our findings relevant to clinical practice, and (2) we intended to compare findings in patients who had received some antibiotic treatment with those who had not. Results of one or more laboratory tests sometimes were missing from the records; we included partial cases for producing descriptions of individual variables, but cases missing any independently important data were excluded from the joint analyses of factors.

Cases of meningitis were sought out by the coded diagnoses assigned to each patient file and also by the independent records of both the pediatric and adult infectious diseases services. For this study, cases were categorized as ABM if an appropriate etiologic bacterium was cultured from CSF or blood or if bacterial antigen was demonstrated in CSF, blood, or urine by counterimmunoelectrophoresis. Cases were excluded if the CSF gram-stained smear was thought to show bacteria but cultures and coun-

terimmunoelectrophoresis were negative because CSF gram stains are not always reliable (see later herein). Cases were categorized as AVM if virus was isolated from blood, stool, or CSF or if the patient's discharge diagnosis was "aseptic" or "viral" meningitis and no cause of meningitis other than viral infection was found.

Laboratory findings were obtained from the patients' case records. During the early part of the study period, most CSF cell counts and smears and many of the blood differential leukocyte counts were made by house staff. By 1974, most of these tests were performed by microbiology technicians. In those cases where results obtained by house staff and by technicians were both recorded, only the technicians' reports were used in this study. For purposes of analysis, the CSF-blood glucose ratio was defined as follows: (CSF glucose + 0.1 mmol/L)/(blood glucose + 0.1 mmol/L).

The Pearson χ^2 test was used for assessing the significance of the difference in two proportions. The two-sample Wilcoxon Rank-Sum Test was used to test for the difference in medians of continuous variables. Spearman's Rank Correlation Coefficient was used to examine the association between two continuous variables. To quantify the association between individual continuous variables and the final diagnosis, Somer's D Rank Correlation Coefficient was used, in which D is a linear transformation of the area under a receiver operating characteristic curve.[5,6] The logistic multiple regression model[6,7] was used to combine multiple measurements for a differential diagnosis of ABM, that is, to predict the probability of ABM (pABM) given a patient with either ABM or AVM. The data set was divided at random into a training sample of 214 patients (106 having ABM) and a test or model validation sample of 208 patients (111 having ABM). By assessing predictive accuracy only in the test sample, we avoid inflation of apparent predictive accuracy caused by fitting noise or spurious patterns in a given sample.

The relationship between pABM and a single continuous variable was estimated by fitting either a logistic model with the variable or an appropriate transformation of it as a covariate, a piecewise linear logistic model, or a piecewise cubic spline logistic model[8] according to the fit required. Fits were checked by plotting proportions of ABM calculated after dividing patients into equal-sized groups on the basis of the variable of interest.[9]

In what follows we define a *predictor of ABM* to be a range of a parameter for which the proportion of patients in the sample having ABM exceeds 99%. A *predictor of AVM* is defined likewise.

RESULTS

Table 1 shows the breakdown of cases into categories just defined as well as the number of cases of ABM due to each of the three leading bacterial pathogens.

Date of Onset

The relationship between date of onset and probability of ABM vs AVM is shown in Fig 1. The fitted curve is a piecewise linear logistic model having a minimum incidence for ABM on August 1. The curve falls steadily from a peak in January and February to a low point in late July. The striking difference observed for likelihood of ABM in winter vs summer presumably reflects the fact that the seasonal curves for viral and bacterial infection of the meninges are oriented in opposite directions. Bacterial meningitis occurs throughout the year but is relatively more common in winter. Viral meningitis is a disease of midsummer. When the two curves are combined, as in this plot, the importance of date of onset in the differential diagnosis of ABM vs AVM becomes clear. The magnitude of this factor is greater than most clinicians appreciate.

Patient Age at Onset

The relationship between age at onset and likelihood of ABM vs AVM, modeled with a piecewise linear logistic model, yielded a complicated curve (Fig 2). However, this curve fits known clinical observations. The data demonstrate a striking increase in incidence of ABM from 1 month to 1 year of age, a sharp decrease from 1 to 2 years, then a gradual decline to a nadir at age 22 years followed by a gradual increase through adult life into old age.

Gram-Stained Smear of CSF

A positive gram stain of CSF easily met the criteria given previously herein for a predictor of ABM. The smear was positive in 71% of cases of ABM but in only 1% of cases of AVM (see later herein). In 10 cases (7%) with positive smears, the findings were misleading. For instance, in 3 cases where CSF culture revealed *Haemophilus influenzae*, the smear had been reported as showing gram-positive rods, and in 2 cases of pneumococcal meningitis the smear report was gram-negative cocci.

There were only two cases of AVM in which a false-positive report of bacteria in the CSF smear was issued by microbiology laboratory staff. The true diagnosis in these cases was confirmed by culture of an enterovirus from the CSF, with negative bacterial cultures. In several instances, smears were interpreted as positive by house staff but reported as negative by microbiology staff.

Cerebrospinal fluid findings in gram stain–positive and gram stain–negative cases are compared in Table 2. Among

Table 1.—Blood and Cerebrospinal Fluid (CSF) Glucose Concentrations, in Quartiles, by Etiology of Meningitis*

	No. of Cases	Blood Glucose Level, mmol/L*	CSF Glucose Level, mmol/L	CSF-Blood Glucose Ratio
Acute bacterial meningitis	217	6.4/**8.2**/10.3	0.8/**2.0**/3.6	0.14/**0.29**/0.44
Haemophilus influenzae	122	6.1/**7.8**/9.1	0.8/**2.0**/3.1	0.19/**0.33**/0.44
Streptococcus pneumoniae	49	7.4/**9.1**/11.3	0.5/**1.7**/3.6	0.09/**0.19**/0.33
Neisseria meningitidis	21	8.6/**10.3**/11.4	0.9/**3.6**/4.7	0.10/**0.22**/0.49
Others	25	6.4/**8.1**/12.8	1.1/**2.1**/4.2	0.19/**0.35**/0.55
Acute viral meningitis	205	5.7/**6.4**/7.2	3.4/**3.9**/4.7	0.54/**0.61**/0.68

*Twenty-fifth percentile/**median**/75th percentile.

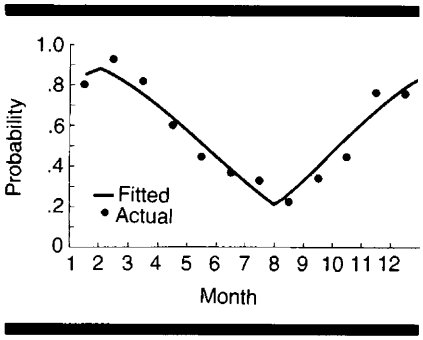

Fig 1.—Probability of bacterial vs viral meningitis as a function of month of presentation.

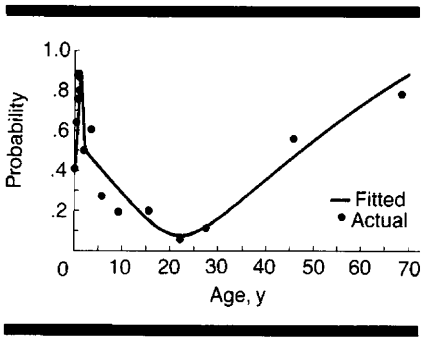

Fig 2.—Probability of bacterial vs viral meningitis as a function of age at onset.

gram stain–negative cases, the proportion in which antimicrobials had been given in the week before hospitalization was higher (49%) than among gram stain–positive cases (32%; $P = .04$). Peripheral white blood cell and differential counts were almost identical for the two groups (data not shown), but spinal fluid findings were different. Most patients with negative smears had glucose concentrations well within the normal range (median, 3.4 mmol/L), whereas in most gram stain–positive cases the CSF glucose level was low (median, 1.7 mmol/L; $P < .001$). Protein concentrations were higher in gram stain–positive cases ($P = .02$). The median leukocyte count in the CSF was three times higher in gram stain–positive than in gram stain–negative cases ($P = .001$). The CSF red blood cell counts also differed in the two groups: the median value was more than eight times higher in gram stain–positive than in gram stain–negative cases ($P = .03$).

Table 2.—Laboratory Findings in 189 Cases of Bacterial Meningitis With and Without Gram Stain–Positive Cerebrospinal Fluid (CSF) Smears*

	Gram Stain Positive (n = 134)	Gram Stain Negative (n = 55)	P†
No. (%) pretreated with antibiotics	43 (32)	27 (49)	.04
CSF protein level, g/L‡	1.18/**1.80**/3.04	4.80/**1.28**/2.50	.02
CSF glucose level, mmol/L‡	0.8/**1.7**/2.8	1.4/**3.4**/4.5	<.001
CSF-blood glucose ratio‡	0.12/**0.23**/0.35	0.33/**0.45**/0.55	<.001
CSF red blood cell count, $\times 10^6$/L‡	19/**257**/1500	8/**30**/260	.03
CSF white blood cell count, $\times 10^6$/L	450/**1520**/4825	148/**512**/1646	.001

*Gram stain report was missing for 28 cases.
†Two-sample Wilcoxon Rank-Sum Test except for pretreatment (χ^2 test).
‡Twenty-fifth percentile/**median**/75th percentile.

CSF Glucose and CSF-Blood Glucose Ratio

Table 1 summarizes the distribution of CSF glucose levels and CSF-blood glucose ratios in ABM and AVM. Figure 3 depicts their relationships with pABM. A CSF glucose value below 1.9 mmol/L or a CSF-blood glucose ratio below 0.23 both qualified as predictors of ABM, according to the definition given previously herein.

The initial blood glucose concentration was higher in ABM (median, 8.2 mmol/L) than in AVM (median, 6.4 mmol/L). Because of this, the CSF-blood glucose ratio was often low in ABM, even though the absolute level of glucose in the CSF was within normal limits. Of the 117 cases for which initial blood as well as CSF glucose values are available, CSF glucose was "normal" (>2.8 mmol/L) in 45 cases, but in 13 of these the CSF-blood glucose ratio was less than 0.4.

The strong predictive value of a low CSF glucose level for ABM is apparent from the data. No patients with AVM had values below 1.7 mmol/L, but 81 (43%) with ABM had CSF glucose concentrations below this figure. A CSF-blood glucose ratio below 0.25 was present in only 1 patient (0.7%) with AVM but in 51 patients (44%) with ABM.

Table 1 also shows blood and CSF glucose concentrations according to causative organism. Blood glucose levels were significantly higher in pneumococcal and meningococcal disease than in *H influenzae* meningitis ($P = .02$ and $P = .03$, respectively). Although the CSF glucose level was often normal in meningococcal meningitis (median, 3.6 mmol/L), blood glucose concentrations were often elevated, resulting in a median glucose ratio of only 0.22. This observation supports use of glucose ratio rather than CSF glucose level for clinical assessments.

In some cases, glucose measurements were the only items of laboratory data that strongly suggested the correct diagnosis. Of 81 cases of ABM with a very low CSF glucose level (<1.7 mmol/L), the CSF leukocyte count and gram stain results were known in 67; of these, the smear was negative in 11 (16%) and the CSF leukocyte count was less than 1000×10^6/L in 25 (37%), and in 6 cases (9%) both findings were present. Conversely, ABM was by no means ruled out by normal or even high levels of glucose in the CSF. In 26 cases of ABM, the CSF glucose level was greater than 4.4 mmol/L; in only 1 of these, a patient with diabetes, could the high level be attributed to coincident hyperglycemia.

Neither did a high initial CSF glucose value predict a good outcome. On the contrary, both very high and very low glucose levels were associated with increased mortality. Three of 10 patients with CSF glucose levels above the 95th percentile died, as did 3 of 10 patients with levels below the 5th percentile (combined mortality, 30%). On the other hand, only 15 (9%) of 176 patients with CSF glucose concentrations between the 5th and the 95th percentile died ($P = .002$).

CSF Protein

In Table 3, the distributions of CSF protein values are summarized, while Fig 4 describes pABM as a function of CSF protein. A value greater than 2.20 g/L was a predictor of ABM. Half the patients with ABM had CSF protein levels greater than 1.72 g/L. By contrast, only 2 patients with AVM (1%) had levels in this range. On the other hand, ABM could not be excluded by low protein levels; in 13 patients (10%) it was in the normal range, below 0.45 g/L.

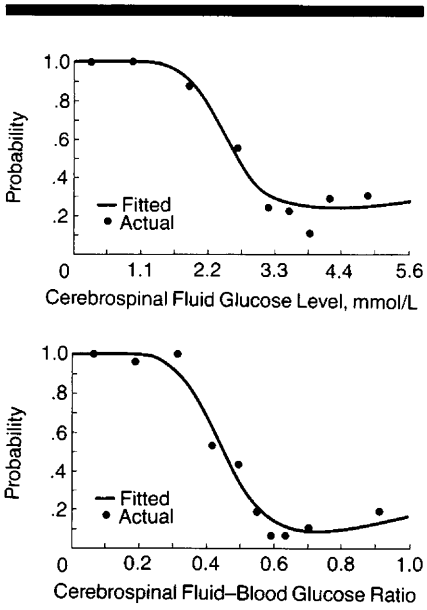

Fig 3.—Probability of bacterial vs viral meningitis as a function of cerebrospinal fluid glucose (top) and cerebrospinal fluid–blood glucose ratio (bottom).

As expected, *Streptococcus pneumoniae* infection was associated with very high CSF protein levels more often than were other organisms. Of the seven cases with protein values greater than 10 g/L, five were due to *S pneumoniae*, one to an enterococcus, and one to group A streptococcus. Unusually high protein levels were not associated with an increased incidence of complications or with increased mortality.

CSF Leukocyte Count

Basic distribution properties of total leukocyte counts and percentage of polymorphonuclear leukocytes (PMNs) in the initial CSF sample are displayed in Table 3; relationships with pABM are depicted in Fig 5. A CSF total leukocyte count of more than 2000×10^6/L was a predictor of ABM, and was present in

Table 3.—Blood and Cerebrospinal Fluid Findings in AVM Compared With ABM and the Effects of Pretreatment of ABM With Antibiotics*

	AVM† (n=205)	P‡	ABM Total (N=217)	ABM Untreated§ (n=135)	ABM P‡	ABM Pretreated§ (n=82)
Blood						
Leukocyte count, ×10⁹/L	7400/**9600**/12 100	.0001	9600/**14 600**/19 600	12 000	.0001	17 000
PMNs, %	54/**70**/79	.04	50/**66**/76	66	.71	67
Bands (% of PMNs)	0/**0**/2	.0001	2/**6**/17	8	.004	4
Glucose level, mmol/L	5.7/**6.4**/7.2	.0001	6.4/**8.2**/10.3	8.3	.46	7.9
Cerebrospinal fluid						
Leukocyte count, ×10⁶/L	37/**100**/250	.0001	330/**1195**/4400	1350	.57	1090
PMNs, %	3/**33**/75	.0001	70/**86**/97	90	.04	82
Glucose level, mmol/L	3.4/**3.9**/4.7	.0001	0.8/**2.0**/3.6	2.2	.03	1.4
Protein level, g/L	0.30/**0.45**/0.75	.0001	0.99/**1.72**/3.00	2	.009	1.31

*AVM indicates acute viral meningitis; ABM, acute bacterial meningitis; and PMNs, polymorphonuclear leukocytes.
†Twenty-fifth percentile/**median**/75th percentile.
‡Two-sample Wilcoxon Rank-Sum Test.
§Median.

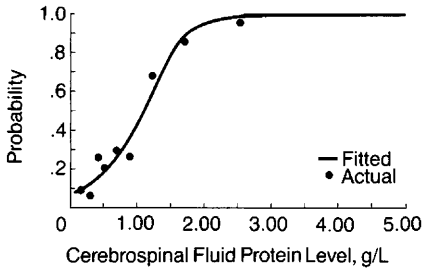

Fig 4.—Probability of bacterial vs viral meningitis as a function of cerebrospinal fluid protein.

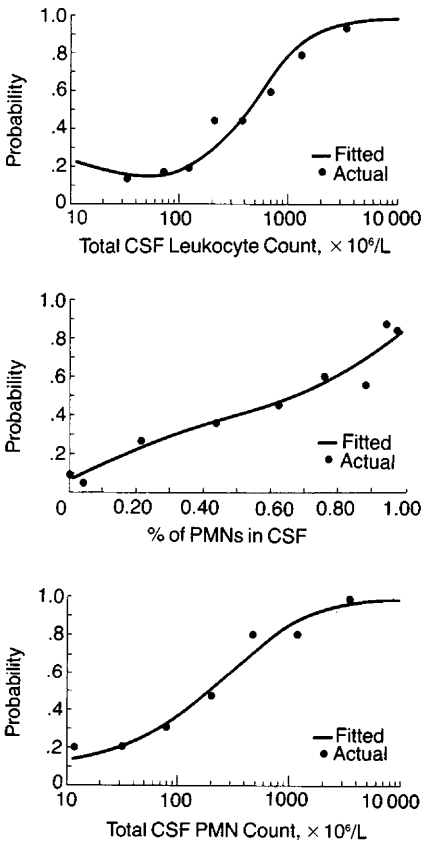

Fig 5.—Probability of bacterial vs viral meningitis as a function of total cerebrospinal fluid (CSF) leukocyte count (top), percentage of polymorphonuclear leukocytes (PMNs) in CSF (center), and total CSF PMN count (bottom).

38% of cases of ABM. A CSF PMN count greater than 1180×10^6/L also predicted ABM. However, low cell counts did not rule out ABM. The CSF leukocyte count was below 1000×10^6/L in 45% of the cases of ABM and below 250×10^6/L in 21%.

The percentage of PMNs in the initial CSF sample was higher in ABM (median, 86%) than in AVM (median, 33%). However, the belief that ABM can be distinguished from AVM by a predominance of PMNs in the CSF was not borne out in this series. In AVM, PMNs predominated in the first spinal fluid sample in 75 cases (40%). Conversely, in ABM, lymphocytes predominated in 28 cases (15%). The shallowness of the relationship depicted in Fig 5, center, indicates that the percentage of PMNs has too much overlap between ABM and AVM to be a useful diagnostic marker. However, a predictor of ABM was provided by the total CSF PMN count (that is, [CSF leukocyte count × %PMNs]/100); 99% of patients with total PMN counts exceeding 1180×10^6/L had ABM. Figure 5, bottom, depicts the diagnostic value of total PMN count in CSF.

In AVM, changes in CSF leukocyte counts during the first two days of hospitalization were highly variable. The median change was +11%, with 25th and 75th percentiles of 0% and +49%. A fall in the proportion of PMNs, which is regarded widely as a regular finding in AVM, was seen in 70% of cases.

The chance of detecting a fall in the percentage of CSF PMNs increased only slightly with the time interval between spinal taps. In a subset of 30 patients whose second lumbar puncture was known to be done within 12 hours of the first, the percentage of PMNs decreased in 19 (63%); in the remaining 78, whose second taps were done between 13 and 48 hours after the first, the PMN percentage fell in 55 cases (71%).

In ABM, the CSF glucose level, protein level, and differential leukocyte count were all correlated with the total CSF leukocyte count. Glucose depression and protein elevation were less marked when the total cell count was low, and in these cases the differential count was also less likely to show a predominance of PMNs. These tendencies are illustrated in Table 4, which compares CSF glucose levels, protein levels, and PMN percentages in two groups distinguished by having total CSF leukocyte counts above or below 500×10^6/L.

Cases of ABM in which the initial spinal tap revealed a predominance of lymphocytes were compared with those in which PMNs were in the majority. The two groups did not differ significantly in blood leukocyte count, blood PMN percentage, or left shift; in the incidence of prior antimicrobial treatment; in the incidence of positive CSF gram stains; or in mortality. However, abnormalities in CSF glucose and protein levels were smaller in the group with lymphocyte predominance. In the latter group, the median CSF glucose level was 3.3 mmol/L, whereas in cases where PMNs predominated, the value was 1.9 mmol/L ($P = .09$). Median CSF protein levels were 1.12 and 1.76 g/L, respectively ($P = .04$). Thus, in those cases of ABM in which the CSF cell count and differential were nondiagnostic, the predictive value of the CSF protein and glucose levels as individual tests also was poor.

For AVM, in contrast to ABM, there

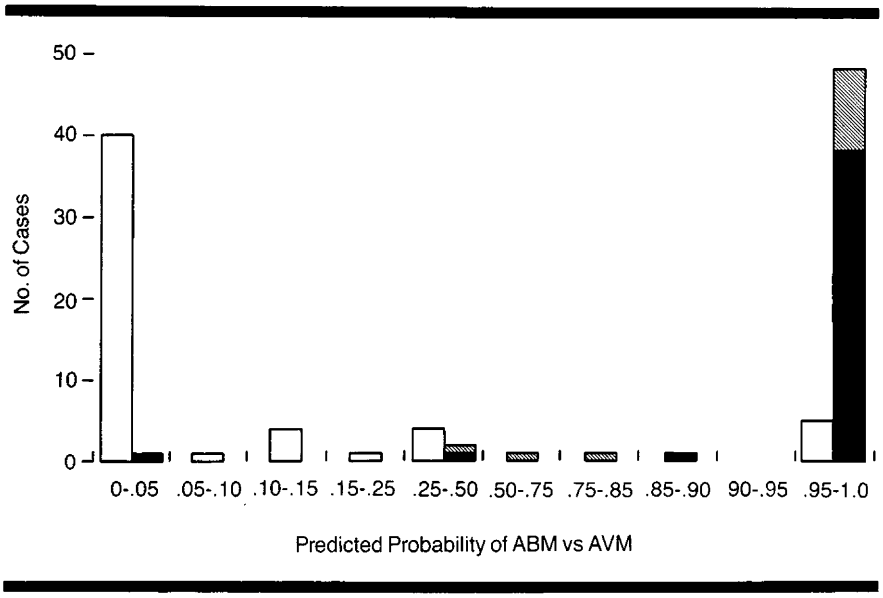

Fig 6.—Validation of the model for probability of bacterial (ABM) vs viral (AVM) acute meningitis in the test sample. The predicted probability from .0 to 1.0 is broken into 5% intervals and the number of cases of ABM and AVM that fell into each interval is shown. Open bars indicate AVM; closed bars, gram stain–positive ABM; and slashed bars, gram stain–negative ABM.

Table 4.—Cerebrospinal Fluid (CSF) Leukocyte Counts Related to Other Parameters in Acute Bacterial Meningitis

CSF Leukocyte Count, $\times 10^6$/L	No. of Cases	CSF Glucose Level, mmol/L*	CSF Protein Level, g/L*	CSF Polymorphonuclear Leukocytes, %*
≥500	139	0.8/**1.7**/3.0	1.18/**1.78**/3.04	78/**90**/98
<500	66	0.9/**2.9**/4.5	0.53/**1.10**/2.28	40/**75**/90
P†	...	.001	.003	<.001

*Twenty-fifth percentile/**median**/75th percentile.
†Spearman's Rank Correlation Test.

was no relation between the total CSF white blood cell count and its differential. Also, in cases with low white blood cell counts ($<500 \times 10^6$/L) the CSF glucose level was no higher than in the rest. However, low total cell counts were associated with lower CSF protein levels, as for ABM. For cases with a total leukocyte count less than 500×10^6/L, the median value was 2.5 mmol/L, compared with 3.5 mmol/L in cases with a leukocyte count greater than 500×10^6/L ($P = .0004$, Spearman's Test).

For AVM, low PMN percentages were not associated with lower protein levels. For cases with less than 50% PMNs, the median CSF glucose level was marginally higher than for those with an excess of PMNs (4.1 vs 3.8 mmol/L, $P = .06$).

Peripheral Blood Leukocyte Count

Table 3 summarizes the distributions of blood leukocyte counts and PMN percentages in ABM and AVM. Most patients with either disease had leukocyte counts between 5000 and $20\,000 \times 10^6$/L; counts in this range were of no help in the differential diagnosis. Very high values for the total leukocyte count, total PMN count, and total immature leukocyte count were not seen in AVM but were found in only a small number of cases of ABM. Extremely high leukocyte ($>27\,200 \times 10^6$/L) and total PMN ($>21\,000 \times 10^6$/L) counts were predictive of ABM, but these occurred in only a small fraction of patients.

Subnormal peripheral blood leukocyte counts were more common in bacterial than in viral disease. In ABM, leukopenia ($<4000 \times 10^6$/L) occurred only in infants and the elderly and was associated with a mortality of 50%. Very high leukocyte counts were not associated with increased mortality, but very high PMN percentages were. Of the 10 cases with PMN percentages above the 95th percentile, ie, 92% PMNs, 5 died. Most of the 10 patients were adults (median age, 43 years). They included only 1 case of disease due to *H influenzae*, 3 to *S pneumoniae*, 2 to *Escherichia coli*, 1 each to *Listeria* and *Salmonella*, and 1 to mixed infection involving α-hemolytic streptococci and *Pseudomonas aeruginosa*.

Low PMN percentages were not associated with poor outcome. Of the 10 patients below the lower 95th percentile, ie, 24% PMNs, all were younger than 1 year, 7 were due to *H influenzae*, and only 1 died.

Proportions of immature PMNs (band forms) were not diagnostically useful unless the value was at least 15%. Values from only 4% of cases of AVM were above this level. The total number of immature cells was more helpful. A value at or above 3000×10^6/L was found in only 1% of cases of AVM and in 18% of cases of ABM.

Detection of Bacterial Antigens in CSF

During the last few years various tests have become available for identifying antigens of *S pneumoniae*, *H influenzae*, and some strains of *Neisseria meningitidis* in body fluids. Counterimmunoelectrophoresis was introduced part way through the period when these patients were admitted. Because this test was not routinely used, our data cannot determine its overall sensitivity. However, in the 53 cases of proved ABM in which the test was done, results were positive in 38 (72%). In 4 cases (8%), cultures of blood and CSF were negative so that counterimmunoelectrophoresis was the only test that provided certain identification of the pathogen. In 1 case of disease due to *H influenzae*, counterimmunoelectrophoresis was positive in urine although it was negative in CSF.

Effects of Pretreatment

Table 3 shows laboratory findings in patients with ABM who had or had not been given antimicrobial agents in the week before their first lumbar puncture. The median blood leukocyte count was 36% higher in those who were pretreated than in the rest. However, there was no significant difference in the percentage of PMNs in each group, and the proportion of immature white blood cells was lower in the pretreated than in the untreated group. Spinal fluid glucose and protein levels were significantly lower in the pretreated group. The percentage of PMNs was slightly reduced by pretreatment ($P = .04$) (Table 3).

Pretreated patients were slightly less likely to have a positive CSF gram stain than were untreated patients (64% vs 80% positive, respectively; $P = .01$). Antibiotic pretreatment seemed to alter the expected link between smear positivity and lowered CSF glucose level: in pretreated patients, glucose levels tended to be lower even though gram stains of CSF were positive less often.

Multivariable Diagnostic Model

The results given previously herein show that for eight CSF parameters, a range could be defined that met our criterion for a predictor of ABM. These predictors (except for gram stain–positive CSF smear) are listed in Table 5, along with measures of the strength of association of each laboratory parameter with the diagnosis. However, no single value for any parameter provided such a predictor of AVM. For each parameter, the distribution for ABM overlapped the entire range of values found in AVM.

A new analysis was then performed to assess whether a better prediction of the final diagnosis could be made by using combinations of initial data rather than single values. We developed a logistic regression model that could use the independent information provided by many parameters, discard parameters not needed for diagnosis because of either low predictive value or high correlation with other predictors, and assimilate the parameters into one predictive value. In addition, other potentially important factors were examined: age, sex, race, and the month of the year in which the case presented.

Certain parameters were found to be related nonlinearly to the logarithm of the odds of ABM. The following coding schemes were found to best represent such parameters in logistic models:

- Month: number of months from the estimated peak incidence of AVM (August 1).
- Age: piecewise linear with change points at 1, 2, and 22 years.
- Glucose ratio: (CSF glucose + 0.1 mmol/L)/(blood glucose + 0.1 mmol/L), truncated at 0.6.
- Total leukocytes in CSF: (count $\times 10^6$/L)$^{0.6}$.
- Total CSF PMN count: (count $\times 10^6$/L)$^{0.333}$.

One disadvantage of using a regression model to address the simultaneous contribution of many parameters is that all parameters must be measured on a patient for that patient's data to be used in the analysis. Only 72 AVM and 48 ABM cases could be used for modeling in the training sample. The glucose ratio was the parameter most often missing. We examined the prevalence of ABM in patients with and without glucose ratio determined to check for possible sampling bias. No significant difference in the prevalence was found.

The CSF gram-stained smear was not used as a predictor because its positivity indicates virtually 100% likelihood of ABM. The regression model was developed without using the gram stain result to utilize the overall information provided by the other parameters. When the result of the gram stain is positive, the predicted probability of ABM can be set at 0.99, overriding the model prediction.

Table 5.—Strength of Association of Laboratory Parameters With Final Diagnosis of ABM or AVM and Predictors of ABM*

Parameter	Indicator of ABM	Patients With Indicator, %	D
Blood			
Leukocyte count, $\times 10^6$/L	>27 200	4.9	.42
PMNs, %	. . .	. . .	−.12
Total PMN count, $\times 10^6$/L	<1900 or >21 000	10.0	.32
Red blood cell count, $\times 10^{12}$/L	. . .	. . .	.40
Glucose level, mmol/L	. . .	. . .	.45
Cerebrospinal fluid			
Leukocyte count, $\times 10^6$/L	>2000	19.3	.68
PMNs, %	. . .	. . .	.61
Total PMN count, $\times 10^6$/L	>1180	23.6	.79
Glucose level, mmol/L	<1.9	23.7	−.58
Protein level, g/L	2.20	17.0	.76
Cerebrospinal fluid–blood glucose ratio	<.23	19.3	−.78

*ABM indicates acute bacterial meningitis; AVM, acute viral meningitis; predictor, range for which the probability of ABM is greater than 0.99; . . ., no such range exists; D, Somer's Rank Correlation Coefficient; and PMNs, polymorphonuclear leukocytes.

A stepwise selection of parameters using the algorithm described by Harrell[6] identified four independently significant parameters for predicting the likelihood of ABM: total PMN count in CSF, glucose ratio, age, and months from August 1. The model predicted the probability of ABM accurately on the first patient sample and also was able to "rule out" or "rule in" ABM in many patients. However, the real test of the model rests in its ability to predict ABM or AVM in the independent test sample, without any refitting of the model. In this sample, 55 AVM and 56 ABM cases had the four variables determined. The predictions were excellent in the test sample, as demonstrated in Fig 6. Without using gram stain results, the 32 cases with the lowest predicted probability of ABM all had AVM. When results of gram stain are incorporated into the predictions, the 48 cases with the lowest predicted probability of ABM all had AVM. The worst prediction was a probability of .33 in a gram stain–negative case of ABM, although 2 gram stain–positive cases of ABM had predicted probabilities of .006. All of the 42 cases with the highest predicted probabilities of ABM actually had ABM. The 6 gram stain–negative cases with the highest predicted probabilities also had ABM.

The value of the model is reflected in the area under its receiver operating characteristic curve,[9] which is 0.968 for our test sample (0.985 in the training sample) without using gram stain results. A perfect diagnostic method, one that correctly rules in or excludes disease for all patients, has an area of 1.0.

Thus, the logistic regression model is useful in combining the information contained in PMNs, glucose ratio, age, and month of onset. Such combined information is best represented as a single new parameter, the predicted pABM. The diagnostic usefulness of pABM is depicted in Fig 6.

Once the accuracy of the model has been determined in an independent sample, both samples of patients can be combined so that more accurate estimates can be computed. The final model is as follows:

$$\text{pABM} = 1/(1 + e^{-L})$$

where L is equal to $+2.29 \times \text{age} + 2.79$ if age is 1 year or younger; $-2.71 \times \text{age} + 7.79$ if older than 1 year but younger than or equal to 2 years; $-0.159 \times \text{age} + 2.69$ if older than 2 years but younger than or equal to 22 years; $+0.100 \times \text{age} - 3.01$ if older than 22 years; $+0.52 \times$ number of months from August 1; $-12.76 \times$ CSF-blood glucose ratio (use 0.6 if ratio exceeds 0.6); and $+0.341 \times (\text{PMNs in CSF} \times 10^6\text{/L})^{0.333}$.

If the gram stain was positive, a probability of .99 would be assumed.

To minimize calculation and to make the predictive model easily usable, a nomogram for calculating the probability of bacterial meningitis has been constructed (Fig 7). Use the nomogram as follows:

1. Place one point of a ruler at the "reading line" by the patient's age.
2. Place another point of the ruler on the reading line by the date of admission.
3. Mark the point where the ruler intersects the vertical line ("A") between these two scales.
4. Place one point of the ruler on the value for glucose ratio. Note that the

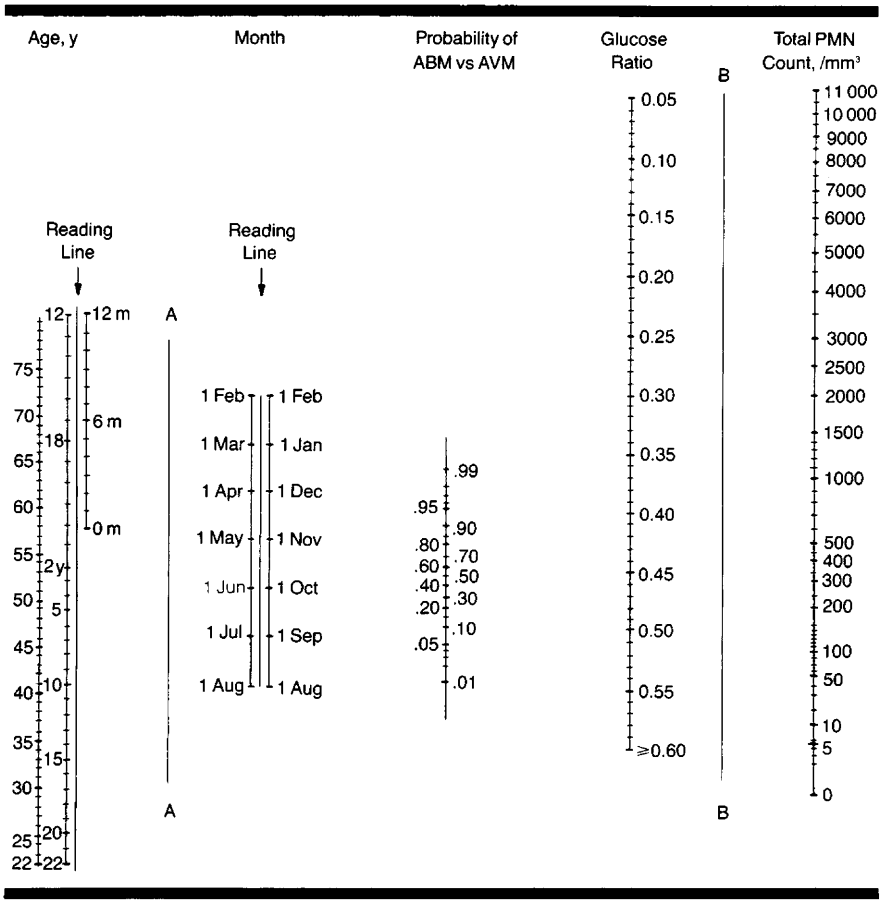

Fig 7.—Nomogram for estimating probability of bacterial (ABM) vs viral (AVM) meningitis. Step 1, place ruler on reading lines for patient's age and month of presentation and mark intersection with line A; step 2, place ruler on values for glucose ratio and total polymorphonuclear leukocyte (PMN) count in cerebrospinal fluid and mark intersection with line B; step 3, use ruler to join marks on lines A and B, then read off the probability of ABM vs AVM.

glucose ratio is defined as (CSF glucose + 0.1 mmol/L)/(blood glucose + 0.1 mmol/L). However, the + 0.1 mmol/L in the numerator and denominator can be ignored for glucose levels not near zero.

5. Place another point on the total PMN count scale.

6. Mark the point of intersection of a line between these two points and the vertical line ("B") between them.

7. Join your marks on lines A and B with a straight line and read the probability of ABM vs AVM from where the ruler intersects the central probability scale.

The following illustrative case shows how to use the nomogram. An 18-year-old man presented on May 15 with fever, headache, and stiff neck. The total CSF leukocyte count is 290×10^6/L, with 27% PMNs, ie, the total PMN count is 78×10^6/L. The CSF glucose level is 3.5 mmol/L, with a blood glucose level of 5.7 mmol/L (ratio, 0.62). The CSF protein level is 0.86 g/L, and the gram-stained smear of CSF is negative for bacteria. For this case, the calculated pABM is .006, and the nomogram yields a probability of less than .01. The patient has AVM.

COMMENT

In current practice, most patients with acute meningitis are treated, at least initially, for ABM. This reflects clinicians' natural reluctance to rule out this grave but treatable disease from the differential diagnosis on the basis of initial laboratory data alone. Our chief aim in this study was to better quantitate the predictive value of commonly performed laboratory tests in the differential diagnosis of acute meningitis by more rigorous analysis. We began by describing and comparing the frequency distributions of clinical data in ABM and AVM, to find out what weight particular values carried in making the differential diagnosis, and hence developed a mathematical model that would be useful in practice. Our contribution is to make use of the full range of each factor and to assimilate multiple factors in the diagnosis of ABM vs AVM.

Certain inevitable weaknesses in a large retrospective review such as this, spanning more than 10 years of hospital records, should be recognized. These include changing habits in recording results, prescribing antibiotics, frequency and choice of laboratory tests, and who performs tests. For example, some blood and CSF cell counts were done by house staff rather than by technicians, especially in the earlier years. These problems cannot be corrected in retrospect. Nevertheless, the present review had provided some clear-cut observations and, we hope, will guide prospective follow-up studies. Such studies should be able to control factors such as timing of blood tests in relation to intravenous glucose administration (which could confound the CSF-blood glucose ratio) and antibiotic administration during the first day in the hospital.

Table 3 shows the stiking frequency with which viral infection elicits a neutrophil leukocytosis in blood and CSF. More than 15 years ago, Portnoy et al[10] challenged "the currently held concept that leukocytosis is characteristic of bacterial disease, and leukopenia or a normal WBC is characteristic of viral disease." They showed that in viral infection of the lower respiratory tract, clinical disease tended to cause leukocytosis, but asymptomatic infection did not, and emphasized that "the classic descriptions of leukopenia associated with viral disease should be considered individually, and conclusions should be based upon the known pathogenesis in these illnesses." In a study of 200 acute febrile illnesses in children, Stein[11] found that "a high neutrophil count, even with a significant number of immature forms, may commonly be seen in a variety of viral infections and is not a dependable indicator of the cause of the illness." In a study in which human subjects were inoculated experimentally with various common viral pathogens, Douglas et al[12] found neutrophilia to be a characteristic early response to infection by rhinoviruses, influenza, and coxsackieviruses. In AVM, the frequent occurrence of an early neutrophil response in the CSF is well-known. Despite these writings, a widespread impression persists that leukocytosis and neutrophilia with left shift characterize bacterial but not viral infection.

Our results show that only extreme peripheral blood leukocytosis ($>27\,200 \times 10^6$/L) and major left shifts (>15% band cells) should be regarded as evidence favoring bacterial meningitis. In a patient under observation with acute meningitis, if other evidence points increasingly away from ABM, this diagnosis should not be adhered to

solely because of a moderate neutrophil leukocytosis in the blood or in early CSF samples.

Cerebrospinal fluid protein and glucose findings are much more distinctive than are leukocyte responses. Our observations underscore the importance of reviewing these values with great care in making an initial diagnosis. In some cases, these were the only initial laboratory findings suggesting bacterial infection (which was later proved by culture). Our results also give clear support for the importance of the CSF-blood glucose ratio as a valuable test, beyond being merely a refinement of the CSF glucose level. The latter may be within normal limits when the ratio is low because of the hyperglycemia often found in ABM.

Because of the statistical limitations imposed by our sample size, the indicators of ABM in Table 5 should be regarded only as estimates of the zones in which these parameters have diagnostic value. Nevertheless, our analysis of initial laboratory values generated some useful information. The fact that we found no single predictor of AVM leads to an important conclusion: laboratory data often can exclude viral in favor of bacterial meningitis, but the reverse is impossible. Cases of ABM do occur in which not one of the initial laboratory values, taken individually, points to bacterial rather than viral infection. This seems to vindicate the common practice of initially treating most patients with acute meningitis for bacterial infection.

However, when four parameters were combined in a predictive model, a much better separation of AVM from ABM was obtained. Using the new parameter generated by the model, ABM could be excluded with at least 95% confidence in 40 cases in the test sample (36% of patients) with no false negatives among patients whose gram stains were negative. Although our model for pABM should be validated in other hospitals to be certain of its accuracy, the model has been validated independently in our own series.

Can meaningful use be made of such a parameter, based as it is on an arcane formula and using such disparate data as CSF chemistry and the month of the year? We suggest it can. The combination of four separate pieces of data that taken singly are of marginal value provides an excellent predictive test. The parameter pABM should best be regarded as one of many pieces of evidence to be factored into the assessment of an individual case. A probability is only a probability, not the final answer; therefore, we advocate that pABM should be treated in the same way as a laboratory report—one piece of diagnostic information among others. Used in this way, it should be of value in many doubtful cases, especially when the physician feels intuitively that he is dealing with aseptic meningitis but also feels the need for a firmer criterion on which to base his management. The value pABM may provide him with such a criterion. When the individual tests are equivocal, an extremely low value for pABM might support a decision not to treat for bacterial meningitis. A somewhat higher probability might indicate the need to treat the patient for possible bacterial meningitis, at least until further information is available. We cannot fix the threshold for treatment, but we can quantitate the chance of an error in diagnosis of ABM vs AVM. Once given pABM, individual physicians can select their own therapeutic threshold in each case. Furthermore, pABM would be an appropriate component of future cost-benefit assessments using decision analysis.

Determination of pABM by means of the nomogram is immediate and costs nothing. Apart from its practical diagnostic value, this parameter is of interest as an example of how thorough statistical analysis of routine laboratory data may reveal diagnostic utility that was hitherto underutilized or even unsuspected. The computing facilities needed to undertake such analyses are now widely available. Use of statistical modeling to improve the diagnostic value of existing tests often may prove more fruitful than the pursuit of new ones. Measurement of CSF pH and lactic acid levels in meningitis provide examples of "valuable new tests" that actually add nothing of diagnostic value to old ones, so long as these are utilized fully.

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