American Journal of Emergency Medicine xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Brief Report

Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis ☆

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ARTICLE INFO

Article history:
Received 20 July 2013
Received in revised form 15 November 2013
Accepted 17 November 2013
Available online xxxx

ABSTRACT

Background: Bacterial meningitis is an emergent disease requiring prompt diagnosis and treatment with appropriate antimicrobials. Although the lumbar puncture is widely used as a diagnostic tool for bacterial meningitis, it remains unclear which value in cerebrospinal fluid (CSF) analysis in emergency laboratory tests precisely predicts the presence of bacterial meningitis.

Methods: This is a single-center, retrospective review of medical records to determine which emergency laboratory CSF test results are useful for predicting bacterial meningitis. The diagnosis of meningitis is made when the white blood cell count in CSF exceeds 5 cells/μL, while the diagnosis of bacterial meningitis additionally requires the growth of a pathogen from a CSF culture or the identification of a pathogen in Gram staining of CSF specimen.

Results: We identified 15 patients with bacterial meningitis and 129 patients with aseptic meningitis. While neutrophil-predominant pleocytosis and a decreased glucose level in CSF can predict the presence of bacterial meningitis, the CSF/blood glucose ratio is more precise (optimal cut-off = 0.36, sensitivity = 92.9%, specificity = 92.9%, area under the curve = .97) even after administration of antimicrobials prior to examination in the emergency department.

Conclusion: This study suggests that the CSF/blood glucose ratio may be a better single indicator for bacterial meningitis. Since the CSF glucose and blood glucose values are promptly and easily obtained from a lumbar puncture, the CSF/blood glucose ratio should be considered as a timely diagnostic indicator of bacterial meningitis. It may also help exclude the diagnosis of bacterial meningitis especially in cases in which no microorganisms can be cultured.

1. Introduction

Bacterial meningitis is an emergent, life-threatening, infectious disease which requires prompt diagnosis and appropriate antimicrobial therapy. Keeping meningitis in mind as a differential diagnosis, the physician should perform a lumbar puncture if none of the clinical findings can adequately rule out this disease [1]. The presence of pleocytosis confirms the diagnosis of meningitis, but it may not always predict the presence of *bacterial* meningitis, which requires treatment with antimicrobials. The use of empiric antimicrobials is justified if the physician suspects bacterial meningitis; however, whenever possible, the physician should refrain from administering antimicrobials without adequate medical grounds for their use.

The association between emergency laboratory examinations of cerebrospinal fluid (CSF) and the diagnosis of bacterial meningitis has rarely been reassessed since the 1980s [2–4]. A recent study reported that CSF lactate concentration is a better, single indicator for predicting bacterial meningitis than conventional markers such as CSF glucose, CSF/blood glucose ratio, CSF protein and CSF total number of leukocytes [5,6]. However, the CSF lactate level is likely to be affected by the administration of antimicrobials [6], and measuring CSF lactate is not routinely performed. Several management guidelines for bacterial meningitis have noted that the measurement of conventional markers in CSF should be considered when assessing the possibility of bacterial meningitis. Given the lack of recent studies examining the utility of emergency laboratory examinations of CSF for predicting the presence of bacterial meningitis, we investigated the diagnostic value of this method for predicting bacterial meningitis at a Japanese tertiary care center.

☆ No support, grants, nor funding were given to the authors.
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http://dx.doi.org/10.1016/j.ajem.2013.11.030

2. Methods

2.1. Study setting

This study was conducted at the Tokyo Metropolitan Tama Medical Center, a 789-bed tertiary care teaching hospital in Tokyo, Japan. The emergency department (ED) at this institution takes in an average of approximately 38,000 patients, including 7,200 ambulances, annually. The study was approved by the institutional review board of Tokyo Metropolitan Tama Medical Center with a waiver of informed consent to review the patient records.

2.2. Study design and participants

The current retrospective study consists of a review of medical records to assess the predictive value of emergency laboratory examinations of CSF for bacterial meningitis. We initially included all ED patients who underwent a lumbar puncture between January 1, 2007 and November 31, 2012, as potential candidates for the study. In addition, patients with confirmed bacterial meningitis who were seen at the hospital between January 1, 2005, and December 31, 2006, were included for analysis of the sensitivity and specificity of emergency laboratory examinations in order to offset the small number of cases for this period. Patients who had received a lumbar puncture for the purpose of primary diagnosis other than meningitis, or those with insufficient data in their medical records, were excluded from the analysis. Since the study focused on bacterial meningitis, patients with confirmed tuberculous, carcinomatous, or fungal meningitis were also excluded. In this study, all patients were older than 15 years of age. There were no pediatric patients due to the proximity of a children's hospital, which receives most of the pediatric patients in the area.

2.3. Criteria

Patients with clinical evidence suggesting meningitis and a total cell count in the CSF of more than 5 cells/μL were, in accordance with previous reports, considered to have meningitis [2,7,8]. Bacterial meningitis was defined as the growth of a pathogen from CSF culture or the identification of a pathogen in a CSF specimen by Gram staining. A patient was considered to have aseptic meningitis if the pleocytosis exceeded 5 cells/μL, and no pathogens could either be grown in the CSF culture, or identified in the CSF by Gram staining.

2.4. History taking and emergent laboratory examinations

All clinical information, including the background of the patients (such as prolonged steroid and/or immunosuppressant use preceding lumbar puncture and a past history of diabetes mellitus or malignancy), was recorded by an emergency physician. The patients underwent a lumbar puncture at the emergency physician's discretion. The emergency laboratory examinations performed for their predictive value for bacterial meningitis are as follows: initial opening pressure, CSF total cell count, CSF mononuclear cell count, CSF polymorphonuclear cell count, CSF polymorphonuclear/total cell ratio, CSF protein, CSF chloride, CSF glucose, CSF/blood glucose ratio, blood cell count with neutrophil fraction, blood electrolytes, and blood C-reactive protein (CRP).

2.5. Data analysis

Statistical analyses were performed using JMP 10 (SAS Institute Inc, Cary, NC). Each receiver operating characteristic (ROC) curve was drawn based on bacterial meningitis and aseptic meningitis. The point of maximal sensitivity plus specificity on the ROC curve was used as the optimal cut-off value.

3. Results

A total of 573 patients who underwent a lumbar puncture between January 1, 2006, and November 31, 2012, were identified. Fifty-two of these patients were excluded because they met the exclusion criteria (hydrocephalus: 11, subarachnoid hemorrhage: 7, traumatic tap: 5, Guillain-Barré syndrome: 5, multiple sclerosis: 3, neurosarcoidosis: 2, central nervous system metastasis: 2, HIV encephalopathy: 1, and incomplete medical record: 6). We subsequently excluded 10 additional cases of meningitis diagnosed as tuberculous (n = 5), carcinomatous (n = 4), or fungal meningitis (n = 1), even though they met the inclusion criteria for meningitis. Among the 521 eligible patients, 129 were diagnosed with meningitis according to the previously described criterion of a CSF cell count >5/μL. Including the 5 bacterial meningitis cases from 2005 and 2006, a final tally of 15 bacterial meningitis cases (2005-2012) and 119 aseptic meningitis cases (2007-2012) were gathered for analysis. Baseline patient characteristics are shown in Table 1 and data from individual cases of bacterial meningitis are shown in Table 2.

The total cell count and polymorphonuclear cell count in CSF were statistically elevated in the bacterial group compared to the aseptic group. The areas under the curve (AUCs) were 0.91 and 0.92, respectively, for the two groups. The AUC of the polymorphonuclear/total cell ratio was 0.85. Importantly, the AUC of the CSF/blood glucose ratio was 0.97 whereas the AUC of CSF glucose alone was 0.90. The sensitivity and specificity figures shown in Table 3 were based on the optimal cut-off.

Other blood tests were also performed but the results were nonspecific. Almost none of the electrolytes and blood chemistries showed any significant difference. The white blood cell count, neutrophil fraction, and CRP showed a significant difference between the bacterial and aseptic groups but their AUCs (0.72, 0.89, and 0.78, respectively) were not as high as in the CSF analysis (Table 3).

We also analyzed whether prior administration of antimicrobials affected the result. Of the total of 134 meningitis cases, 44 cases (6 bacterial and 38 aseptic) had been administered antimicrobials prior to observation at the ED. In the prior administration group, the AUC of the polymorphonuclear cell count, CSF glucose, and the CSF/glucose ratio were 0.96, 0.97, and 0.996, respectively. The other properties in the prior administration group were similar to those for all patients (data not shown).

Table 1
Baseline patient characteristics

Variables	Bacterial N = 15	Aseptic N = 119
Age (median; range)	67; 26-87	37; 16-95
Men	7/15 (46.7%)	62/119 (52.1%)
Current medication		
-Antimicrobial use	6/15 (40%)	38/119 (31.9%)
-Steroid use	2/15 (13.3%)	11/119 (9.2%)
-Immunosuppressant use	0/15 (0%)	1/119 (0.8%)
Diabetes mellitus	3/15 (20.0%)	5/119 (4.2%)
Malignancy	1/15 (6.7%)	8/119 (6.7%)
Signs and symptoms at ED visit		
Glasgow Coma Scale	11.9 (3.2)	14.3 (2.2)
Respiratory rate (breaths/min)	23.7 (7.5)	18.8 (3.7)
Heart rate (in beats/min)	110.2 (17.8)	90.7 (18.1)
Temperature (C)	38.6 (1.4)	37.8 (1.0)
Systolic blood pressure (mmHg)	148.8 (21.9)	123.3 (22.7)
Headache	9/10 (90.0%)	96/101 (95.0%)
Fever (≥38.0°C)	10/14 (71.4%)	49/119 (41.2%)
Altered mental status	12/15 (80.0%)	30/119 (25.2%)
Nuchal rigidity	9/10 (90.0%)	44/93 (47.3%)

Values are presented as positive number/number evaluated (percentage) or as mean (SD).

Please cite this article as: Tamune H, et al, Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis, Am J Emerg Med (2013), http://dx.doi.org/10.1016/j.ajem.2013.11.030

Table 2
Individual data of bacterial meningitis cases

Age	Sex	Prescribed antimicrobials prior to ED visit	CSF culture	Gram staining	Initial opening pressure of LP(cmH2O)	CSF total cell count(/μL)	CSF mononuclear cell count (/μL)	CSF polymorphonuclear cell count(/μL)	CSF polymorphonuclear/total cell ratio (%)	CSF protein (mg/dL)	CSF chloride (mEq/L)	CSF glucose (mg/dL)	CSF/blood glucose ratio	Blood WBC (/μL)	Blood neutrophil fraction (%)	Blood CRP (mg/dL)
26	M	None	CNS		24	128	125	2	1.8	63	118	54	NA	6200	79	0
38	M	Cefcapene	PSSP		35	208	0	195	93.6	281	116	<10	0.06	14800	89	9
40	M	Cefditoren	PSSP		32	4880	320	4560	93.4	322	NA	33	0.19	20100	NA	4
56	M	None	PSSP		NA	4416	569	3947	89.4	234	118	<10	0.07	22900	95	1
56	F	None	*E. coli*		28	95	45	49	52.1	100	114	18	0.29	8100	95	55
61	M	None	*S pyogenes*		NA	6656	875	5781	97.1	323	111	14	0.07	7500	83	1
61	M	Ceftriaxone	Negative	GPC	29	1370	40	1330	86.9	196	117	10	0.06	10500	91	8
67	M	None	PISP		35	1387	1131	253	18.3	982	NA	<10	0.03	9100	NA	36
70	F	Levofloxacin	Negative	GPC	28	531	77	453	85.4	53	NA	40	0.31	10600	NA	7.6
72	F	None	*S pyogenes*		18	520	69	451	86.7	112	121	46	0.46	2300	95	26.29
76	F	None	*S bovis*		33	2448	16	2432	99.3	310	119	62	0.36	12900	84	0.6
77	F	None	*S agalactiae*		NA	5827	530	5297	90.9	304	111	39	0.25	10700	NA	7
80	F	None	*S agalactiae*		12	1323	123	1200	90.7	140	NA	14	0.11	37500	97	23.5
80	M	Ceftriaxone	Negative	GPDC	32	4000	0	4000	100	416	106	<10	0.07	48200	98	23.6
87	F	Fosfomycin	PISP		18	3667	1427	2240	61.1	471	115	<10	0.04	10600	93	38.1

M, male; F, female; LP, lumbar puncture; CNS, coagulase negative staphylococci; PSSP/PISP, penicillin sensitive/intermediate *Streptococcus pneumoniae*; GPC, Gram-positive coccus; GPDC, Gram-positive diplococcus; NA, not assessed.
Total cell count is not necessarily equal to the sum of the mononuclear and polymorphonuclear values because of the presence of other type cells such as red blood cells.

4. Discussion

Although the use of empiric antimicrobials is justified if the physician suspects bacterial meningitis after a comprehensive examination of the patient's medical history and symptoms, the present study suggests that the CSF/blood glucose ratio has demonstrable utility for the diagnosis of bacterial meningitis, and may thus expedite the physician's decision as to whether or not to administer antimicrobials.

The several studies assessing CSF analysis in patients with meningitis were mostly published in the 1980s, while only a few studies discussing CSF analysis as a means of predicting bacterial meningitis were published after the 1990s [2–4]. Despite the recommendation in the Japanese guidelines for the management of meningitis to measure the CSF/blood glucose ratio in patients with suspected meningitis [9], no definitive study was previously published to support this practice in Japan. Patient background in Japan has changed greatly since the 1980s, as seen in the increased incidence of diabetes mellitus, and the more frequent use of steroids, immunosuppressants, and chemotherapeutic agents [10]. Although the causal association between patient background and the properties of bacterial and aseptic meningitis is unknown and needs further research, the present study, at any rate, suggests that the CSF/blood glucose ratio may be the best diagnostic indicator among the conventional markers, given the current medical setting.

In this study, the AUC of the CSF/blood glucose ratio was 0.97. The sensitivity and specificity for the CSF/blood glucose ratio at the optimal cut-off value of 0.36 reached 92.9% and 92.9 %, respectively. Further, the AUC for sensitivity and specificity was 93.3% and 86.6 % at a cut-off of 0.40, and 100% and 57.1% at a cut-off of 0.50, respectively. The cut-off value in the present study was consistent with that used in previous studies by Briem (75% and 99% at a cut-off of 0.40) and Lindquist et al. (70% and 96% at a cut-off of 0.40) [3,4].

However, a previous study demonstrated an inadequate AUC for conventional CSF markers [8]. The study showed that the AUCs were 0.59, 0.79 and 0.11 (0.89) [11] for the CSF leukocyte count, percentage of CSF leukocytes, and the CSF/blood glucose ratio, respectively, whereas the AUCs were 0.81 and 0.98 for blood CRP and blood procalcitonin, respectively [8]. Although it remains unclear why the results varied in the previous studies, differences in the inclusion criteria may have affected the outcome. Moreover, regional differences may also explain the discrepancy since the causative pathogens and the spectrum of antimicrobials used might have differed from one region to the next [12].

In actual practice based on the present study, the prompt administration of antimicrobials is recommended at a cut-off value of 0.50, the optimal screening value for all cases of bacterial meningitis. However, it is also possible that the cut-off value of 0.50 might not be sufficient to include all cases of bacterial meningitis if the number of patients enrolled were greater. Further studies with larger sample sizes may improve our understanding of the relationship between emergency CSF laboratory analysis and the prediction of bacterial meningitis.

As mentioned in the introduction, several studies noted that CSF lactate may be a better single indicator for predicting bacterial meningitis [5,6]. However, the CSF lactate level is likely to be affected by prior administration of antimicrobials [6]. In the present study, the AUC of the CSF/blood glucose ratio was 0.996 in 44 cases (6 bacterial and 38 aseptic) who had been administered antimicrobials prior to observation in the ED. This finding suggested that the CSF/blood glucose ratio may prove reliable even after patients have received antimicrobials prior to a lumbar puncture, and warrants further study with a larger population.

The present study has some limitations. First, it is a single-center review of patient records with only a small number of bacterial meningitis cases. However, we believe that the results are still significant in that this is the first Japanese study to assess the value of the CSF/blood glucose ratio for predicting bacterial meningitis in the current healthcare setting. Second, the bacterial and aseptic meningitis cases in this study were not compared in terms of the duration of

Table 3
Selected values of CSF and blood markers in patients with bacterial or aseptic meningitis

	Bacterial meningitis N = 15	Aseptic meningitis N = 119	AUC	Optimal cut-off	Sensitivity	Specificity
Initial opening pressure of LP (cm H_2O)	28.5; 12-35 [a]	17; 0-33 [a]	0.85*	24	75.0%	87.5%
CSF total cell count (/μL)	1387; 95-6656	59; 6-1699	0.91*	520	80.0%	89.1%
CSF mononuclear cell count (/μL)	123; 0-1427	51; 0-945	0.65	320	40.0%	92.4%
CSF polymorphonuclear (/μL)	1330; 2-5781	6; 0-1504	0.92*	49	93.3%	84.9%
CSF polymorphonuclear/total cell ratio (%)	89.4; 1.8-100	14.8; 0.3-99.7	0.85*	85.4	73.3%	93.3%
CSF protein (mg/dL)	281; 53-982	67; 21-393 [b]	0.88*	100	86.7%	76.9%
CSF chloride (mEq/L)	116; 106-121 [c]	122; 97-132 [c]	0.88*	119	90.9%	80.6%
CSF glucose (mg/dL)	14; <10-62	56; 10-198	0.90*	40	80.0%	92.3%
CSF/blood glucose ratio	0.07; 0.03-0.46 [d]	0.53; 0.12-0.76 [d]	0.97*	0.36	92.9%	92.9%
Blood WBC (×10^3/μL)	10.6; 2.3-48.2	8.0; 1.0-27.9	0.72*	10.5	66.7%	76.3%
Blood neut (%)	93; 79-98 [e]	77; 3-94 [e]	0.89*	83	90.9%	71.6%
Blood CRP (mg/dL)	8.0; 0-55.0	0.8; 0-45.6 [f]	0.78*	4.3	73.3%	78.0%

Values are shown as median; range.
LP, lumbar puncture.
Insufficient data in the medical record:
[a] 20.0% of cases (3/15) in bacterial meningitis and 19.3% (23/119) in aseptic meningitis.
[b] 1.7% of cases (2/119) in aseptic meningitis.
[c] 26.7% of cases (4/15) in bacterial meningitis and 26.9% of cases (32/119) in aseptic meningitis.
[d] 6.7% of cases (1/15) in bacterial meningitis and 4.2% of cases (4/119) in aseptic meningitis.
[e] 26.7% of cases (4/15) in bacterial meningitis and 26.1% of cases (31/119) in aseptic meningitis.
[f] 0.8% of cases (1/119) in aseptic meningitis.
* $P < .05$, bacterial meningitis vs. aseptic meningitis, Wilcoxon test.

the interval between the initiation of antimicrobial therapy and the performance of each emergent laboratory examination, nor was the length of each interval documented. This omission might have affected the results of this study. The third limitation is that some important biomarkers, including the CSF lactate and serum procalcitonin levels, were not measured and, therefore, could not be compared with the CSF/blood glucose ratio. The final limitation resides in the fact that we did not include meningitis cases without pleocytosis, in accordance with previous studies. Further large-scale, multicenter, prospective studies are required to which finding has the greatest utility in predicting bacterial meningitis.

5. Conclusion

This study demonstrates that the CSF/blood glucose ratio may predict the presence of bacterial meningitis more precisely than other routinely measured markers in CSF. Since the CSF glucose levels and blood glucose levels are promptly available, the CSF/blood glucose ratio should be examined as a timely diagnostic indicator for bacterial meningitis. To assess the presence of bacterial meningitis comprehensively, the CSF/blood glucose ratio in combination with other signs, symptoms, and conventional markers, may also help exclude the diagnosis of bacterial meningitis especially in cases with no microbial culture growth.

6. Declaration

We investigated the same cohort in another article [1]. However the subjects of the articles are independent of one another.

Acknowledgments

We thank Dr Hiroyoshi Y. Tanaka for his reading of the manuscript and his suggestions for improving its contents, Dr Keita Tatsuno for his various invaluable suggestions, Mr Keigo Morita for his unflagging diligence in gathering the references, and all of the staff and patients who contributed to this study.

References

[1] Tamune H, Takeya H, Suzuki Y, Tagashira Y, Kuki T, Nakamura M. Absence of jolt accentuation of headache cannot accurately rule out meningitis in adults. Am J Emerg Med 2013;31:1601–4.
[2] Straus SE, Thorpe KE, Holroyd-Leduc J. How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis? JAMA 2006;296:2012–22.
[3] Briem H. Comparison between cerebrospinal fluid concentrations of glucose, total protein, chloride, lactate, and total amino acids for the differential diagnosis of patients with meningitis. Scand J Infect Dis 1983;15:277–84.
[4] Lindquist L, Linné T, Hansson LO, Kalin M, Axelsson G. Value of cerebrospinal fluid analysis in the differential diagnosis of meningitis: a study in 710 patients with suspected central nervous system infection. Eur J Clin Microbiol Infect Dis 1988;7:374–80.
[5] Huy NT, Thao NT, Diep DT, Kikuchi M, Zamora J, Hirayama K. Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systemic review and meta-analysis. Crit Care 2010;14:R240.
[6] Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. J Infect 2011;62:255–62.
[7] van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351:1849–59.
[8] Ray P, Badarou-Acossi G, Viallon A, Boutoille D, Arthaud M, Trystram D, et al. Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative gram-stained smear. Am J Emerg Med 2007;25:179–84.
[9] Guideline from Societas Neurologica Japonica. http://www.neurology-jp.org/guidelinem/zuimaku.html (in Japanese) Last accessed November 15, 2013.
[10] National nutritional assessment. Ministry of Health Labour and Welfare, Japan. http://www.mhlw.go.jp/houdou/2008/12/h1225–5.html (in Japanese). Last accessed November 15, 2013.
[11] Steichen O, Martinez-Almoyna L. Comments on "Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative gram-stained smear". Am J Emerg Med 2008;26:237.
[12] Nguyen THM, Tran THC, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 2007;357:2431–40.

Please cite this article as: Tamune H, et al, Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis, Am J Emerg Med (2013), http://dx.doi.org/10.1016/j.ajem.2013.11.030