ORIGINAL ARTICLE

Cerebrospinal Fluid Glucose in Bacterial Meningitis

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Abstract

Introduction: Normal cerebrospinal glucose (> 50 mg/dL) is approx. 70%-75% of blood glucose but it can be severely decreased due to bacterial consumption in meningitis. Although it is commonly compared to blood glucose, absolute cerebrospinal fluid glucose may accurately reflect intrinsic changes in cerebrospinal fluid. The objectives were to compare the cerebrospinal fluid/blood glucose ratio and absolute cerebrospinal fluid glucose as tools for diagnosing bacterial meningitis.
Methods: We retrospectively analyzed all of the lumbar punctures performed in the department of pediatrics of a university-affiliated hospital from 1 January 2010 to 31 December 2015. The data included cerebrospinal fluid cytochemical parameters, macroscopic examination, microbial culture, blood glucose, and blood C-reactive protein. Absolute glycorrhachia and cerebrospinal fluid/blood glucose ratio were tested as diagnostic tools.
Discussion: A total of 777 lumbar punctures were performed, wherein 239 met all of the criteria. There were 31 cases of bacterial meningitis. Among the children with bacterial meningitis, 19% had a normal cerebrospinal fluid/blood glucose ratio (> 0.5) and 29% had a normal cerebrospinal fluid glucose level (> 36 mg/dL). On the other hand, 94% of the children with low glycorrhachia had bacterial meningitis, as did 82% of the children with a low cerebrospinal fluid/blood glucose ratio. Decreased absolute glycorrhachia virtually diagnosis bacterial meningitis but a low cerebrospinal fluid/blood glucose ratio can be a clue when the former is normal.

Keywords: Blood Glucose; Child; Glucose/cerebrospinal fluid; Meningitis, Bacterial/diagnosis; Meningitis, Bacterial/blood; Meningitis, Bacterial/cerebrospinal fluid

Introduction

Diagnosing bacterial meningitis requires strong clinical suspicion. Still, laboratorial tests play an important role, especially in newborns and young infants, whose clinical presentation may be less obvious. Performing a lumbar puncture is standard care in these situations and provides valuable information, through the macroscopic and cytochemical examination of cerebrospinal fluid (CSF) as well as its microbial culture. The latter confirms the diagnosis but the former two are quicker and promptly give us crucial clues, such as the number and type of cells present in the CSF, proteins, and glucose. Evaluation of these parameters may support the diagnosis and even suggest its etiology. For instance, a severe decrease in CSF glucose suggests bacterial glucose consumption, while a modest decrease or even a normal CSF glucose may be present in viral meningitis.[1]

Glycorrhachia (CSF glucose) is regulated by brain-blood-barrier transporters[2] that maintain it above 50 mg/dL and about 70%-75% of blood glucose[3-5] and a decrease in the CSF/blood glucose ratio has been established as a sign of bacterial meningitis.[5,6] However, extreme changes in blood glucose,[7] impairments in glucose transportation[2] or simply blood and CSF samples drawn some hours apart compromise this ratio reliability.[8] Absolute CSF glucose does not reflect blood glucose, but it may accurately reflect CSF intrinsic changes, such as bacterial CSF glucose consumption.

Time is crucial in the treatment of bacterial meningitis. Promptly starting adequate antibiotics is lifesaving and we must look for quick, yet accurate, evidence supporting our decision. In this study, we aimed to assess which parameter is more helpful for either supporting or excluding the diagnosis of bacterial meningitis, CSF/blood glucose ratio or absolute CSF glucose.

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Methods

In order to compare the CSF/blood glucose ratio and absolute glycorrhachia as bacterial meningitis diagnostic tools, we retrospectively retrieved data from all lumbar punctures performed in the department of pediatrics of a university-affiliated hospital, from 1 January 2010 to 31 December 2015.

From lumbar puncture results, we retrieved macroscopic examination, cytochemical parameters (glucose, proteins, cell number and predominant cell type, presence of blood elements), and microbial culture. As for the blood tests, glucose was the only mandatory parameter. C-reactive protein was registered whenever CSF cytochemical parameters were altered.

Any patients not found in our clinical database, patients from the neonatal intensive care unit, and patients with no blood glucose measurement, no CSF microbial culture, no CSF glucose measurement, incomplete CSF cytochemical evaluation, or blood glucose measured more than two hours apart from CSF glucose were excluded. [9] We also excluded repeated lumbar puncture performed on patients after the confirmation of bacterial meningitis, to avoid falsely increasing the number of meningitis.

Confirmed bacterial meningitis was established as a positive CSF microbial culture with a known pathogenic organism in a clinically suggestive scenario. Probable bacterial meningitis was established as altered CSF chemistry (CSF cells > 100/mL, polymorphonuclear cells predominance, CSF proteins > 100 mg/dL)[1] and high blood C-reactive protein (> 5 mg/dL),[10] presenting in children with age-adjusted symptoms and/or signs of meningitis (fever, headache, photophobia, and/or nuchal rigidity). In order to prevent overdiagnosis, only patients with suggestive clinical findings and meeting at least two laboratorial criteria were considered to have bacterial meningitis in the absence of microbial confirmation. We reviewed the full patient file from each of these children and included them in the probable bacterial meningitis group only if the physicians who managed their case had considered that they had bacterial meningitis and treated them accordingly.

The absolute CSF glucose and CSF/blood glucose ratio were tested as tools for diagnosing bacterial meningitis. The cut-off value for CSF/blood glucose ratio was 0.5 and it was based on literature.[4,5,8,9] For absolute glycorrhachia, there is no consensual cut-off value,[8] with some authors considering it normal when > 40-50 mg/dL,[3,4] and so we chose it according to the results of the receiver operating characteristic curve analysis. The statistical analysis was performed by a statistician using IBM® SPSS® statistics version 21 and it included both diagnostic tests.

Results

A total of 777 lumbar punctures were performed in the pediatrics department during the time interval of our study (Fig. 1). Of those, 538 were excluded and 239 met all of the inclusion criteria (Fig. 1, Table 1).

There were 46 lumbar punctures performed before the blood glucose measurement (on average 46 minutes before) and 125 were performed after blood glucose measurement (on average 47 minutes after). The remaining 67 lumbar punctures were performed almost at the same time as the blood glucose was measured. The samples were carried to the laboratory together.

Among those 239 lumbar punctures, there were 14 positive CSF microbial cultures confirming bacterial meningitis (Table 2). Streptococcus pneumoniae and Neisseria meningitidis were the most isolated microorganisms (43%). In children less than 2 months old, the isolated microorganisms were Escherichia coli, Group B Streptococcus, and Enterobacter cloacae. According to our predefined criteria, there were 17 patients with probable bacterial meningitis and one of those simultaneously had a positive blood culture (Group B Streptococcus). As shown in Fig. 2, most lumbar punctures were performed in children aged 2-10 years, but most bacterial meningitis was found in children less than 2 years old and this age group also had the highest positive CSF culture rate (10/16 vs. 14/31).

Out of the 31 children with bacterial meningitis, at least 10 had already started antibiotic therapy by the time the lumbar puncture was performed, at least three had not and no precise information was available about the remaining 18.

There were 12 children with extremely low CSF glucose (< 25 mg/dL) and they all had bacterial meningitis, nine of them with positive CSF culture (75%). On average, their CSF glucose was 7.5 mg/dL and their CSF/blood glucose ratio was 0.09. Therefore, it seems extremely likely that low CSF glucose levels are almost pathognomonic of bacterial meningitis. Their mean age was also lower compared to all children with bacterial meningitis (10 *vs.* 19 months).

We set the cut-off for absolute CSF glucose at 36 mg/dL, based on the highest specificity and predictive values. According to the area under the receiver operating characteristic (AUROC) analysis, 0.5 was the optimal cut-off value for CSF/blood glucose, the same as it has been described in the literature. AUROC slightly favored the ratio over the absolute value, both having high values (0.81 *vs.* 0.75) (Figs. 3 and 4). Low CSF glucose had 52% sensitivity, 98% specificity, 80% positive predictive value and 93% negative predictive value. CSF/blood

glucose ratio had 74% sensitivity, 88% specificity, 48% positive predictive value and 96% negative predictive value. According to the chi-square test, both also have significant predictive power.

Statistics for absolute value were chi-square = 21.3 (p < 0.001), phi-coefficient = 0.573 (p < 0.001), odds ratio = 38.85. Statistics for CSF/blood glucose were chi-square = 25.636 (p < 0.001), phi-coefficient = 0.628 (p < 0.001), odds ratio = 19.71.

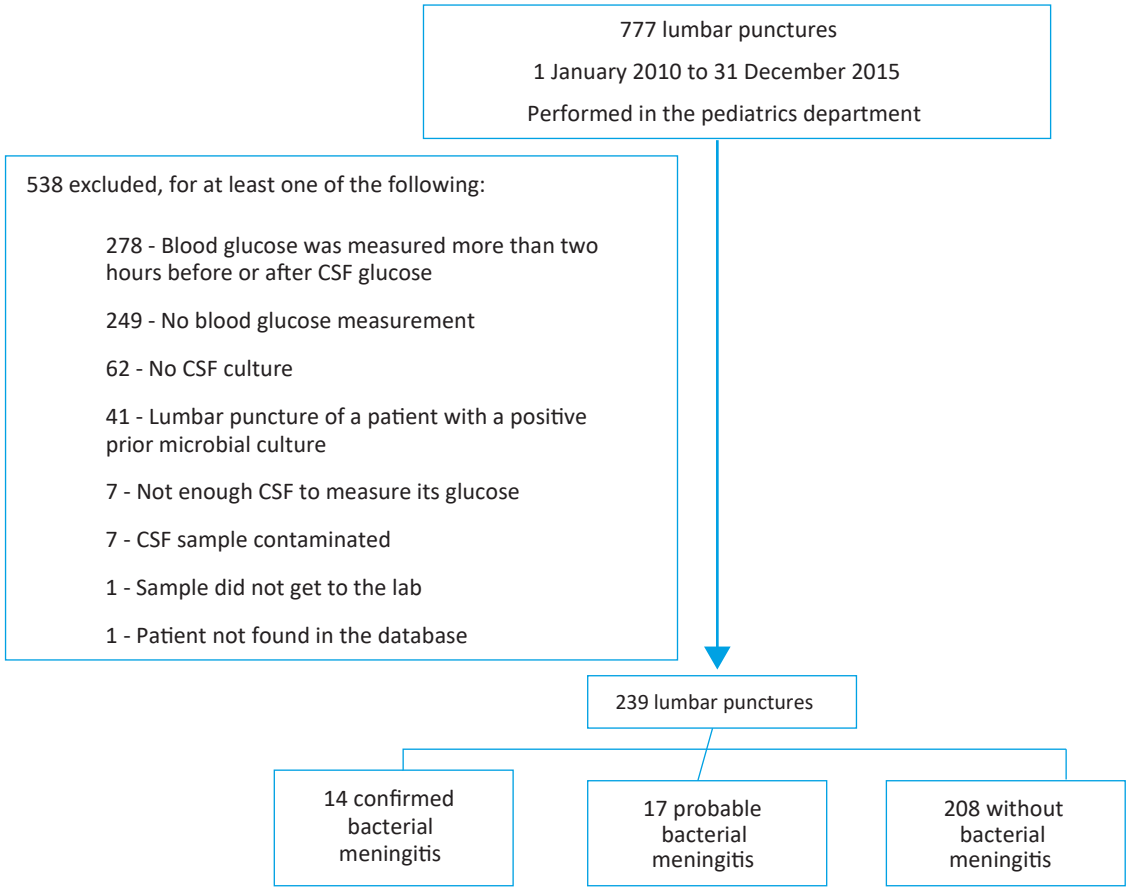
Discussion

Low CSF glucose (< 36 mg/dL) increases the odds of having bacterial meningitis almost 39 times, so children with low CSF glucose should be considered to have bacterial meningitis until proven otherwise. This is also reflected by the high positive predictive value of 80%. Although a decreased CSF/blood glucose ratio also increases the odds of having meningitis by 20 times, it has a lower positive predictive value. In our population, less than half of the patients who test positive had meningitis (positive predictive value of 48%).

As clinicians, if bacterial meningitis is suspected, we look for a test that confirms it and having a low CSF glucose level does it. However, due to its lower sensitivity, it has a higher percentage of false negatives (29% *vs.* 19%), compared to the CSF/blood glucose ratio. Therefore, one should be careful when ruling out bacterial meningitis based solely on a normal CSF glucose, especially if there is a decrease in CSF/blood glucose. According to these results, future guidelines[11] should take into consideration that absolute CSF glucose may have a diagnostic value regardless of the CSF/blood glucose ratio.

Chances are we are still going to determine the blood glucose because blood sampling is one of the most common workup tests in any clinical situation and it does provide valuable information. However, according to our results, there is no point in submitting children to another blood draw just to determine it, especially if the CSF glucose level is so low that we can be sure of the diagnosis.

In addition to having an independent diagnostic value, low CSF glucose may also be more helpful if there is a traumatic lumbar puncture. A blood-stained CSF sample limits cytochemical evaluation, due to the presence of



CSF - cerebrospinal fluid.

Figure 1. Eligibility.

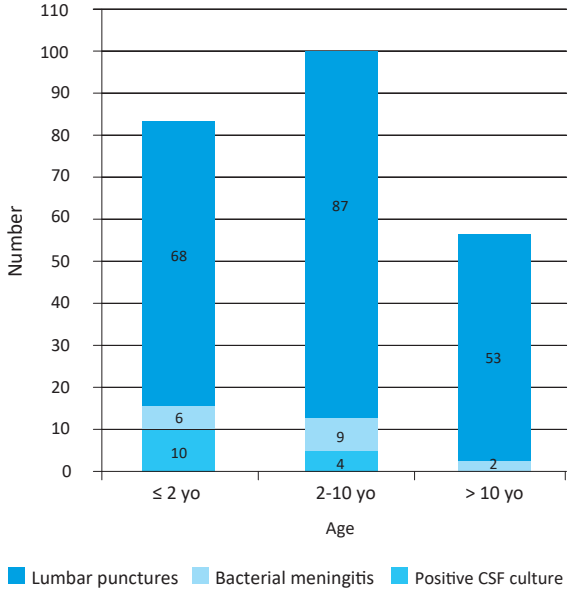
blood cells, proteins, and glucose. However, extreme hypoglycorrhachia would still require CSF glucose consumption, allowing us to suspect bacterial meningitis even in cases of traumatic lumbar puncture when other parameters may not be reliable.[12] In fact, all 12 patients with severely low CSF glucose (< 25 mg/dL) had bacterial meningitis.

Table 1. Demographics

Unit
Emergency room - 129 (54%)
Infectiology - 16 (7%)
Intensive care - 68 (28%)
Others - 26 (11%)

Table 2. Etiology of confirmed bacterial meningitis

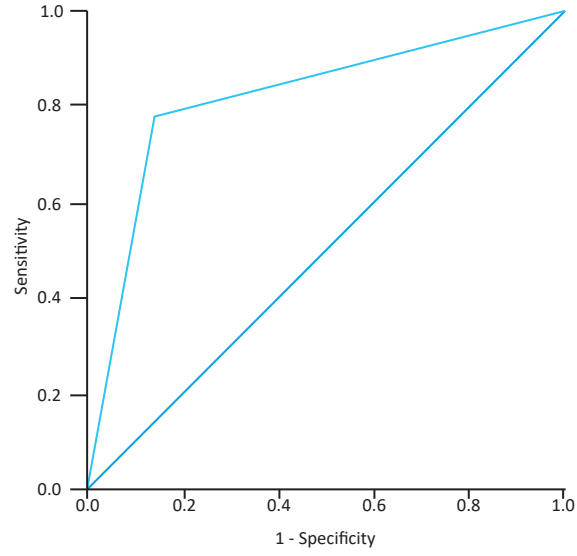
Isolated microorganism	Number of cases	Children age
Streptococcus pneumoniae	3	5 months, 7 months, 7 months
Neisseria meningitidis	3	4 months, 3 years, 3 years
Staphylococcus epidermidis	1	2 years
Escherichia coli	1	37 days
Group B Streptococcus	2	31 days, 50 days
Klebsiella pneumoniae	1	3 years
Enterobacter cloacae	1	26 days
Streptococcus mitis	1	16 months
Mycobacterium tuberculosis	1	8 years
	Total: 14	Average: ≈ 19 months



CSF - cerebrospinal fluid, yo - years old

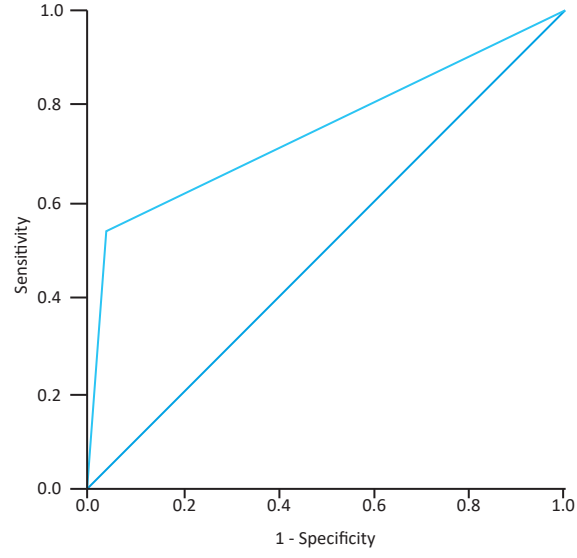
Figure 2. Age distribution.

There were some limitations to our study, including a small sample size. It was a retrospective study and inevitably some data could not be found. In addition, due to our strict case definitions, we may have missed some cases of bacterial meningitis. Our study solely took place at a tertiary care facility and so that may increase the prevalence of lumbar puncture performed in children with diseases that alter CSF glucose. There were many false negatives in the CSF culture. Out of the 31 meningitis cases, over 50% had negative microbial cultures, which is a higher percentage than what has been described in the



Diagonal segments are produced by ties.

Figure 3. Receiver operating characteristic (ROC) curve. Cerebrospinal fluid/blood glucose ratio < 0.5 - area under receiver operating characteristic (AUROC) = 0.812.



Diagonal segments are produced by ties.

Figure 4. Receiver operating characteristic (ROC) curve. Cerebrospinal fluid glucose < 0.36 mg/dL - area under receiver operating characteristic (AUROC) = 0.752.

literature (10%-33%).[1,4,9] This could be due to the lumbar puncture performed in partially treated meningitis, that is, after starting antibiotics, which happened in at least 10 cases (> 30%). In a severely ill child, microbiologic cultures (blood, urine, CSF, sputum) are drawn first only if there is clinical stability and it does not delay starting the appropriate therapy.[13]

Neither the CSF/blood glucose ratio nor absolute CSF glucose are accurate enough or even essential to diagnose bacterial meningitis. Evaluating the other lumbar puncture cytochemical parameters and, most of all, assessing the child's clinical condition is crucial.

Still, the absolute value of CSF glucose has a stronger predictive power, a positive test virtually confirms the diagnosis, which makes it a relevant parameter in bacterial meningitis diagnosis, regardless of the CSF/blood glucose ratio. However, it should be kept in mind that some children with bacterial meningitis will have a falsely negative test and a low CSF/blood glucose ratio could be a clue to the underlying condition.

WHAT THIS STUDY ADDS

- Cerebrospinal fluid/blood glucose ratio is commonly calculated when bacterial meningitis is suspected. Due to its high sensitivity, it is useful for excluding this diagnosis.
- Absolute cerebrospinal fluid glucose yields a higher positive predictive value than the cerebrospinal fluid/blood glucose ratio. A positive test virtually confirms bacterial meningitis.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Glucose no Líquido Cefalorraquidiano na Meningite Bacteriana

Resumo:

Introdução: A relação entre glicorráquia e glicemia é comumente utilizada no diagnóstico de meningite bacteriana. Em situações fisiológicas, a glicorráquia é 70%-75% da glicemia, mas pode estar drasticamente diminuída em situações de meningite bacteriana, por consumo pelos microrganismos. Apesar de habitualmente a glicorráquia ser valorizada por comparação à glicemia, a glicorráquia absoluta pode representar com precisão as alterações a nível do líquido cefalorraquidiano. O objetivo do estudo foi avaliar o valor diagnóstico da glicorráquia absoluta por comparação com a glicorráquia relativa (glicorráquia / glicemia) na suspeita de meningite bacteriana.

Métodos: Foi feita a análise retrospetiva dos resultados de todas as punções lombares realizadas no departamento de pediatria de um hospital nível III entre 1 janeiro 2010 e 31 dezembro 2015. Foram recolhidos os dados dos exames citoquímicos e bacteriológicos do líquido cefalorraquidiano bem como a glicemia e a proteína C reativa. Foi testado o valor da glicorráquia absoluta e da glicorráquia relativa no diagnóstico de meningite bacteriana da glicorráquia absoluta e da glicorráquia relativa.

Discussão: Foram feitas no total 777 punções lombares, 239 das quais cumpriram os critérios de inclusão. Houve 31 casos de meningite bacteriana, 19% dos quais com glicorráquia relativa normal (> 0,5) e 29% com glicorráquia absoluta normal (> 36 mg/dL); 94% das crianças com hipoglicorráquia absoluta e 82% das crianças com hipoglicorráquia relativa tinham meningite bacteriana. Hipoglicorráquia absoluta é virtualmente diagnóstica de meningite bacteriana. A hipoglicorráquia relativa é um sinal de alerta em casos de forte suspeita em que o valor absoluto esteja normal.

Palavras-Chave: Criança; Glicemia; Glucose/líquido cefalorraquidiano; Meningites Bacteriana/diagnóstico; Meningites Bacterianas/líquido cefalorraquidiano; Meningites Bacterianas/sangue