Enteroviral Meningitis and the Bacterial Meningitis Score

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Keywords

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Abstract

Objectives

Enteroviral meningitis is currently the most prevalent type of meningitis in the pediatric population. The correct differentiation of bacterial from viral meningitis remains critical in determining appropriate therapy for the child with cerebrospinal fluid (CSF) pleocytosis. This can be challenging, especially in younger children. The Bacterial Meningitis Score (BMS) is a prediction rule developed by Nigrovic et al. to identify children who are at very low risk of bacterial meningitis, based on one clinical and four biochemical parameters.

Case report and literature review

We report a case of enteroviral meningitis in a two-year-old child and review the literature on the age-related differences in clinical presentation and CSF parameters, the use of the BMS in practice, and its impact.

Conclusions

Normative CSF parameters show wide variability, especially in neonates, indicating the need for age-specific reference values. In children older than two months without signs of invasive bacterial infections and without pre-treatment with antibiotics, BMS has been shown to be reliable and may be useful to assist in clinical decision making.

Introduction

As a result of successful vaccination programs against *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and more recently, after introduction of quadrivalent meningococcal conjugate vaccines against serogroups A, C, W and Y (Nimenrix®, Menveo®) and the monovalent recombinant protein vaccines against serogroup B (Bexsero®, Trumenba®), there has been globally a steady decline in the incidence of bacterial meningitis (1).

Aseptic meningitis (i.e. meningitis with negative cerebrospinal fluid (CSF) bacterial cultures, with both infectious and non-infectious causes) is now the most prevalent type of meningitis, with non-polio enterovirus (NPE) as the leading cause, accounting for more than 75% of viral meningitis cases with an identified pathogen (2,3). Nevertheless, there are still cases of meningitis caused by bacterial pathogens, highlighting the importance of prompt and accurate differentiation from its viral counterpart (2,4).

Assessing a pediatric patient for meningitis can be challenging, because of the wide variability in presenting symptoms and cerebrospinal fluid (CSF) parameters across various age groups (5,6). The current safe approach for patients with CSF pleocytosis is to administer empirical antibiotic therapy until either the reverse transcriptase polymerase chain reaction (RT-PCR) identifies the causal viral pathogen and/or the CSF culture remains negative for > 48 hours (3,7).

Immediate initiation of antibiotic therapy is life-saving in the case of bacterial meningitis, but prolonged use in suspected viral meningitis may be questionable given the potential adverse effects of antibiotics (2,8). Same et al. conducted a retrospective cohort study on the prevalence and characteristics of antibiotic-associated adverse effects in the pediatric hospitalized population (9). Of the 400 antibiotic courses studied, 21% had at least one adverse effect, with the most common adverse effects being hematologic (e.g. leukopenia, neutropenia), gastrointestinal (e.g. diarrhea, nausea) and renal (e.g. acute kidney injury), accounting for 31%, 15%, and 11% of adverse effects, respectively. Furthermore, 15% of adverse effects were caused by an unnecessary course of antibiotics (9).

The issue of starting and continuing empiric antibiotics in the setting of a probable viral meningitis in this setting remains controversial, and has led to the creation of several clinical prediction rules to assess whether one is at high risk for bacterial meningitis while also determining the probability of viral meningitis.

The Bacterial Meningitis Score (BMS) is a validated clinical prediction rule, created by Nigrovic et al., to calculate the risk of bacterial meningitis in patients with CSF pleocytosis, based on five variables: positive CSF Gram stain, CSF absolute neutrophil count ≥ 1000 cells/µL, CSF protein ≥ 80 mg/dL, peripheral blood absolute neutrophil count ≥ 10 000 cells/µL and history of seizure before or at the time of presentation (10). With a zero score, the risk of bacterial meningitis is estimated as very low.

We present a case of enteroviral meningitis in a 2-year-old toddler and will provide a brief review of the literature on clinical presentation and CSF parameters. In addition, we will discuss the use of the Bacterial Meningitis Score in the pediatric population and its applicability in clinical practice.

Methods

A thorough literature search on enteroviral meningitis was performed using the PubMed database. The search terms consisted of various combinations of keywords such as “Meningitis”[Mesh], “Enterovirus”[Mesh], “enteroviral”, “children”, “infants”, “neonates”, “Bacterial Meningitis Score”, “cerebrospinal fluid”, “guidelines” and “consensus”. English language restriction was applied. The results were evaluated on the basis of the title and abstract before the remaining parts of the article were analyzed. Relevant studies referenced in these articles were also included. This search yielded a total of 26 articles.

Case report

A 2-year-old male toddler with no relevant medical history presented to the emergency department with symptoms of vomiting, fever of 39 degrees Celsius and somnolence for 1 day. Because of terminal neck stiffness, lumbar puncture was performed. CSF analysis showed a WBC

count of 43 µL (normal range ≤ 5 WBC/µL), a normal erythrocyte count of < 1000/µL, a total protein concentration of 16 mg/dL (normal range 15-40 mg/dL) and a glucose concentration of 68 mg/dL (serum glucose level was 90 mg/dL (normal)). Gram stain was negative. In the peripheral blood sample, there were 14670 WBC/µL (normal range 6000-17000 WBC/µL), with an absolute neutrophil count of 8024 neutrophils/µL (normal range 1500-8500 WBC/µL), and a CRP of 17 mg/L (normal ≤ 5 mg/L). Ceftriaxone (100 mg/kg/day) was given until RT-PCR of the CSF confirmed the diagnosis of enteroviral meningitis. CSF culture remained sterile. The patient showed a complete recovery under symptomatic therapy and was discharged after 3 days.

Discussion

Age-related differences in clinical presentation and CSF parameters in viral meningitis

Non-polio enterovirus is the most prevalent cause of viral meningitis. Although young age is a known predisposing host factor, it can affect a wide range of age groups, from neonates to adults (6). Especially in the (very) young age group, enteroviral infections can be very serious and sometimes fatal due to overwhelming infection.

Regarding the clinical presentation of meningitis, healthcare professionals must always keep in mind that classic symptoms such as photophobia and nuchal rigidity are more typical in adults and older children. Neonates and infants are more likely to present with one or more non-specific findings on clinical examination, such as fever, irritability, lethargy and a bulging fontanelle. In older children, gastrointestinal or respiratory symptoms such as nausea, vomiting, cough, as well as headache and rash, are more common in association with neck stiffness and a positive Kernig sign (6,11,12). Recognizing these features and promptly performing lumbar puncture with subsequent CSF analysis is crucial for the diagnosis of meningitis and initiation of symptomatic and possible causal therapy.

Biochemically, CSF parameters are undoubtedly of paramount importance in the assessment of a child with clinical suspicion of meningitis. The significant age-related difference in the normative range of CSF analysis parameters needs to be addressed. Wong et al. showed that CSF protein levels tend to decrease rapidly in the course of the first few months of life (a phenomenon attributed to the reduced permeability of the blood-brain barrier), reach a minimum at approximately 6 months of age, and remain steady before gradually increasing toward normal adult levels during adolescence (13). A multicenter, cross-sectional study by Thomson et al. in infants ≤ 60 days of age, showed that especially infants ≤ 28 days of age differed in CSF parameters from infants 29 – 60 days of age: WBC counts (upper limit: 15 WBC/µL versus 9 WBC/µL, p<.001) and protein levels (upper limit: 127 mg/dL versus 99 mg/dL, p<.001) were higher, glucose levels (lower limit: 25 mg/dL versus 27 mg/dL, p<.001) were lower in infants ≤ 28 days of age (14).

These findings implicate that the current one-size-fits-all approach where only one normative range is provided for different age groups is not the most appropriate in the pediatric population. It is important to note that the present evidence is based on studies with rather small study populations. Therefore, further research in larger cohorts is warranted to determine the most appropriate age-specific reference values.

Regarding CSF pleocytosis in younger infants with enteroviral meningitis, Tan et al. observed a wide variability (0-4608 WBC/µL in the age group < 90 days, compared to 0-1290 WBC/µL in the age group 90 days-1 year), with some of the outliers having levels even suggestive for bacterial meningitis (5). On the other hand, some studies report a lower CSF pleocytosis in infants compared to older children (15). Furthermore, up to 60% of infants with enteroviral meningitis may have no CSF pleocytosis, which more common in infants younger than 90 days of age, and it is hypothesized that this is due to their immature immune system, which is unable to mount a robust inflammatory response (5,11).

Bacterial Meningitis Score: its use and application to our case

The Bacterial Meningitis Score (BMS) is a validated clinical decision rule developed by Nigrovic et al., to help identify patients at very low risk for bacterial meningitis among patients with CSF pleocytosis, based on one clinical and four biochemical parameters (Table 1) (10,16,17).

Table 1 : Components of Bacterial Meningitis Score. Applicable in infants above the age of 2 months, clinically not ill-appearing, not pretreated with antibiotics. If none of these variables are present (BMS = 0), patient is classified as low risk for bacterial meningitis..

Components of Bacterial Meningitis Score
Positive cerebrospinal Gram stain (2 points)
Cerebrospinal fluid absolute neutrophil count ≥ 1000 cells/µL (1 point)
Cerebrospinal fluid protein ≥ 80 mg/dL (1 point)
Peripheral blood absolute neutrophil count ≥ 10 000 cells/µL (1 point)
History of seizure before or at time of the presentation (1 point)

The initial article was published in 2002, in the 'post-*Haemophilus influenzae* vaccination era', based on meningitis patients from one institution (10). According to their subsequent study in 2007 (in the 'post-Pneumococcus vaccination era'), based on patients from several institutions, the BMS showed a high accuracy and a sensitivity of 100% (95% CI [96.9%;100%]), a specificity of 63.5% (95% CI [61.4%;65.6%]) and a negative predictive value of 100% (95% [99.8%;100%]), under the exclusion criteria that it should not be applied in children younger than 2 months or who were pretreated with antibiotics (16). The BMS had indeed misclassified 2 patients with bacterial meningitis, aged between 1 and 2 months, as low-risk patients (16).

In the later published meta-analysis of all published validation studies, the BMS still showed a very high sensitivity of 99.3% (95% CI [98.7%;99.7%]) (17,18). Compared to the 2007 publication, the authors formulated and emphasized their recommendations for the use of BMS, stating that it should be used only in non-ill-appearing patients over the age of 2 months without physical examination findings suggestive of invasive bacterial infection (e.g. petechiae, purpura) and without prior antibiotic administration, although further specification of signs suggestive of invasive bacterial infection was not formulated (17).

In our case of the 2-year old-child, the application of the BMS yielded zero points and thus can be classified as very low risk for bacterial meningitis according to the BMS.

Besides the BMS, other clinical prediction rules (CPRs) are available, such as the modified BMS, Bonsu score, modified Bonsu score, Oostenbrink score, Meningitest rule and others (19). Each CPR uses its own combination of clinical predictors to assess the possibility of bacterial meningitis. Furthermore, novel biomarkers such as CSF lactate and serum procalcitonin are being investigated (20).

The number of comparative studies for these CPRs is limited, but an European retrospective multicenter cohort study comparing the performance of BMS and Meningitest demonstrated that although the sensitivity of both CPRs are similar, the specificity was higher in the BMS (52%, 95% CI [42%;62%] vs 36%, 95% CI [27%;46%]) (21).

Wu et al. developed a new CPR for bacterial meningitis in infants aged 29-90 days using three predictors resulting a total score of five points: procalcitonin ≥ 3.80 ng/mL (2 points), CSF glucose ≤ 1.86 mmol/L (2points) and CSF protein ≥ 1269 mg/dL (1point) (22). This new model identified bacterial meningitis with 100% sensitivity (95% CI [46.6%;72.9%]) in the study population, while BMS had a sensitivity of 90.9% (95% CI [78.3%-97.4%]). However, the limitations of this study are the limited study population and the lack of timely measurements of CSF glucose concentration (22).

Table 2: Patients with bacterial meningitis with a BMS of 0 from the meta-analysis of the external validation studies.

		Age (years)	CSF ANC (/µL)	CSF protein (mg/dL)	Peripheral blood ANC (/µL)	History of seizures before or at the time of presentation	Petechiae/ purpura	Identified pathogen
Nigrovic et al. (15)	1	0.2	0	31	8100	No	No	*E.Coli*
	2	0.1	497	65	6600	No	No	*E.Coli*
Dubos et al. (24)	3	0.3	≤13	61	7744	No	No	*N.meningitidis* (type B)
	4	0.7	32	25	3600	No	Yes	*N.meningitidis* (type B)
	5	5.4	≤30	30	9400	No	Yes	*N.meningitidis* (type C)
	6	3.4	60	20	1517	No	No	*N.meningitidis* (type C)
	7	0.1	≤8	46	3270	No	No	*S.pneumoniae*
Tuerlinckx et al. (23)	8	2.5	26	21	7683	No	Yes	*N.meningitidis* (unknown subtype)
	9	15	22	46	7689	No	No	*N.meningitidis* (unknown subtype)

Critical appraisal on the Bacterial Meningitis Score: External validation studies

Although the BMS is a highly sensitive scoring system with a high negative predictive value, it is of course not foolproof. It is intended to assist, not to replace, clinical decision making.

In the patient with CSF pleocytosis, we favor an approach in which clinical evaluation and observation, along with correct interpretation of the available laboratory tests, remain crucial.

First, a thorough clinical evaluation should be performed when examining the child. One should be alert for warning signs such as sick or toxic appearance, severe nuchal rigidity, vomiting, photophobia, etc.. However, neonates with bacterial meningitis can often present with atypical signs, and even beyond the neonatal period, there is no clinical sign of bacterial meningitis that is present in all patients (23).

If there is a suspicion of bacterial meningitis, it is imperative that blood cultures and cerebrospinal fluid (CSF) are obtained as soon as possible (7,24). In some cases, a CT scan of the brain prior to lumbar puncture is warranted to exclude intracranial, space-occupying lesions that may lead to increased intracranial pressure (7)

Based on the results of CSF analysis, the BMS can be calculated for the patient, taking into account the exclusion criteria as listed by Nigrovic et al. and as mentioned above. Their meta-analysis with a total of 5312 patients showed that the combined sensitivity and the negative predictive value were high, 99.3% (95% CI [98.7%;99.7%]) and 99.7% (95% CI [99.3%;99.9%]), respectively, although not 100% anymore as it was initially predicted (17).

In this study, we focus on the 9 cases from the external validation studies where the patient had bacterial meningitis and a BMS of 0 (Table 1). The majority of these patients were younger than one year whereof three were younger than 2 months (Table 2). Of the children older than one year (n=4), two had a petechial rash (in which case the use of BMS is contraindicated), and two others were infected with *N. meningitidis* (one with type C, the other unknown).

The epidemiologic landscape of causative pathogens of bacterial meningitis has undergone a considerable transformation since the introduction of vaccines against common pathogens (1). A study in the Netherlands showed a significant decline in the incidence of *H. influenzae* type b and *N. meningitidis* meningitis after the introduction of their respective vaccines in recent decades. On the other hand, the incidence of both non-typeable *H. influenzae* meningitis and pneumococcal meningitis caused by serotypes not covered by PCV7, PCV10 and PCV13 has increased (1,25).

In the light of the ever-evolving epidemiologic background of meningitis, it seems well-advised to re-evaluate BMS in this 'post-vaccination era', in terms of sensitivity and specificity, inclusion/exclusion criteria and the causative pathogens of false negative cases.

Use of Bacterial Meningitis Score in the clinic

The BMS can assist our clinical evaluation and consequently guide our therapeutic management.

In children with BMS of zero, empirical antibiotic therapy could be safely discontinued if the RT-PCR turns out to be positive for enterovirus, without awaiting the results of the bacterial cultures (26). In case of BMS ≥1 and negative culture, bacterial etiology must be excluded by multiplex PCR. Looking carefully at the characteristics of the misclassified patients in Table 2, one could consider an approach where the decision to treat with empiric antibiotics is individualized.

Conclusion

We presented a case of a two-year-old child with enteroviral meningitis, and discussed the age-related differences in clinical presentation and the need for age-specific normative values for CSF analysis. Furthermore, we reviewed the Bacterial Meningitis Score and its potential use in clinical practice. The BMS is able to estimate the risk of bacterial meningitis with high sensitivity and high negative predictive value in non-ill-appearing children without petechial rash or purpura, who are older than 2 months and not pretreated with antibiotics. Although a BMS of zero can be translated into a very low risk of bacterial meningitis, clinical judgment remains imperative.

Conflict of interest

The authors have no conflict of interest to declare.

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