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Group B Streptococcal Meningitis: Cerebrospinal Fluid Parameters in the Era of Intrapartum Antibiotic Prophylaxis

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Abstract

Objective—Describe cerebrospinal fluid parameters in infants with culture-proven Group B streptococcal meningitis in the era of intrapartum antibiotic prophylaxis.

Study Design—Cohort study of the first lumbar puncture from 13,495 infants cared for at 150 neonatal intensive care units. We compared cerebrospinal fluid parameters [white blood cell count, red blood cell count, glucose, and protein], demographics, and outcomes between infants with and without Group B streptococcal meningitis.

Results—We identified 46 infants with Group B streptococcal meningitis. The median cerebrospinal fluid white blood cell count was 271 cells/mm^3 for infants with Group B streptococcal meningitis and 6 cells/mm^3 for infants without meningitis (p=0.0001). Of the infants with Group B streptococcal meningitis, 9/46 (20%) had negative blood cultures. Meningitis complicated 22/145 (15%) of episodes of early onset Group B streptococcal sepsis and 13/23 (57%) of episodes of late onset Group B streptococcal sepsis.

Conclusions—Group B streptococcal meningitis occurs in the presence of negative blood cultures. In hospitalized infants who undergo a lumbar puncture, Group B streptococcal sepsis is frequently complicated by GBS meningitis.

Keywords

Group B streptococcus; intrapartum antibiotic prophylaxis; meningitis

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Introduction

Group B streptococcus (GBS) is the most common cause of neonatal meningitis[1,2]. Mortality of GBS meningitis approaches 30%, and 50% of survivors have significant neurological sequelae including: hydrocephalus, deafness, blindness, and developmental disabilities.[3] Although the institution of intrapartum antibiotic prophylaxis (IAP) in the late 1990s has decreased the burden of GBS disease, neonatal exposure to IAP and empirical antibiotics prior to lumbar puncture (LP) often compromises the diagnosis of meningitis based on culture of the cerebrospinal fluid (CSF).[4,7] In these situations, clinicians must often rely on the analysis of CSF white blood cell (WBC) count, red blood cell (RBC) count, glucose, and protein for the diagnosis of meningitis.

Because descriptions of CSF parameters in infants with GBS meningitis occurred prior to IAP, the purpose of this study is to compare the CSF parameters, demographics, and outcome of infants with culture proven GBS meningitis to infants with negative CSF cultures in the era of IAP.[8]

Methods

We examined the results of the first LP from infants discharged from 150 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group, Inc. from 1997 to 2004. Samples were processed in the local clinical microbiology laboratories according to the local hospital standards. GBS meningitis was defined by a positive CSF culture. We excluded neonates with CSF reservoirs/shunts, and CSF results from infants positive for viral pathogens and bacterial species other than GBS. The Duke University Institutional Review Board provided permission to conduct this investigation. The study used an administrative database for which data were collected in a manner described previously.[2]

Normal CSF parameters for premature infants (< 37 weeks) were defined as white blood cell (WBC) count < 26 cells/mm^3, glucose level > 23 mg/dL and protein < 151 mg/dL.[9] Normal CSF parameters for term infants (≥ 37 weeks) were defined as WBC count < 23 cells/mm^3, glucose level > 33 mg/dL and protein < 171 mg/dL.[9] We also examined the blood culture results in patients with GBS meningitis and the rate of meningitis complicating early and late-onset GBS sepsis. Early-onset infections were defined as positive cultures in the first week of life.

Demographics were compared using Kruskall-Wallis for continuous variables or Fisher's exact tests for categorical variables. CSF parameters were compared using median linear regression. [10] Sensitivity, specificity, positive predictive values, negative predictive values, positive likelihood ratios and negative likelihood ratios were calculated for each CSF parameters as defined above for predicting culture proven meningitis. STATA 10 (College Station, TX) and SAS (Cary, NC) were used for statistical analysis. All P values were two-tailed and statistical significance was defined as a $P \leq 0.05$.

Results

Of 13,495 infants that underwent at least one LP, 46 (0.3%) infants had positive CSF cultures for GBS. Of the 46 infants with GBS meningitis, 33 (72%) were born at term, and 7 (16%) were < 1000 g birth weight. The proportion of infants with GBS meningitis, GBS bacteremia and culture-negative CSF, and negative blood and CSF cultures exposed to IAP were 7/46 (15%), 34/133 (26%), and 4186 (38%), respectively, p=0.001 (Table 1). In the group of infants with GBS meningitis, 3/26 (12%) of the mothers were GBS positive. In the group of infants with GBS bacteremia but negative CSF, 16/90 (18%) of the mothers were GBS positive. In the group negative for GBS meningitis and bacteremia, 1693/6419 (26%) of the mothers were

GBS positive. Calculated p-values found that significant demographic variables were gestational age (p=0.0001), birth weight (p=0.0001), delivery (p=0.02), and IAP use (p=0.001).

The median WBC count for the infants with GBS meningitis, 271/mm^3 [69, 1624], was higher than the infants with GBS bacteremia and culture-negative CSF, 7/mm^3 [2, 14], and infants with negative CSF and blood cultures, 6 /mm^3 [2, 16], p<0.0001. The median CSF glucose for the infants with GBS meningitis, 13 mg/dL [2, 44], was lower than infants who had GBS bacteremia and culture-negative CSF, 52 mg/dL [43, 58], and the infants who had both negative blood and CSF cultures, 49 mg/dL [42, 58], p<0.0001. The median CSF protein for the infants with GBS meningitis, 322 mg/dL [268, 852], was significantly higher than the infants with GBS bacteremia but negative CSF, 98 mg/dL [78, 127] and the infants with both negative CSF and blood cultures, 114 mg/dL [84, 155], p<0.0001.

Out of the 46 infants with culture proven GBS meningitis, 29 (63%) had early-onset disease and 17 (37%) had late-onset infection. The median CSF WBC count in the early-onset group was 1529 /mm^3 [163, 6120] and 102 /mm^3 [57, 276] in the late-onset group, p=0.01. The median CSF glucose in the early-onset group was 6 mg/dl [2, 30] and 36 mg/dL [6, 53] in the late-onset group, p=0.12. The median CSF protein in the early-onset group was 404 mg/dl [273, 852] and 291 mg/dL [178, 822] in the late-onset group, p=0.38.

Nine of the 46 infants (20%) with GBS meningitis had negative blood cultures. Meningitis complicated 22/155 (14%) of episodes of early-onset GBS sepsis and 13/24 (54%) of episodes of late-onset GBS sepsis, p<0.01.

An elevated CSF protein was the most sensitive CSF parameter for detecting culture proven GBS meningitis (92.6%) and a low CSF glucose was the most specific (95.7%), Table 2. An infant with all 3 CSF parameters in the abnormal range had a 32 fold increase in the odds of having a CSF culture positive for GBS.

Discussion

Prior to the introduction of IAP for maternal GBS colonization, the incidence of early-onset sepsis from GBS was approximately 1.5 cases per 1000 live births.[5] In 1996 the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists recommended a screening-based or a risk-based approach for identifying women that should receive IAP as a means of preventing neonatal GBS infection.[5] These efforts resulted in a 65% decrease in early-onset GBS infection between 1993 and 1998.[4] In 2002 a population-based study comparing the screening-based approach to the risk-based approach found that the screening-based approach was 50% more effective at preventing perinatal GBS disease. The findings of this study led to revised CDC recommendations in 2002 that called for universal GBS screening of all pregnant women at 35–37 weeks gestation. The incidence of GBS disease in infants dropped to 0.32 cases per 1000 live births in 2003, the lowest ever recorded in the United States.[5,6]

Because diagnosis of GBS meningitis may be complicated by prior exposure of the infant to antibiotics, we decided to evaluate the CSF parameters under current care practices including IAP. We observed an elevated CSF WBC count and protein and a decrease in glucose in the CSF of our infants with GBS meningitis compared to infants with negative CSF cultures.[9] Infants with GBS bacteremia and meningitis were also less likely to have been exposed to IAP (Table 1). IAP may have decreased the sensitivity of the blood and CSF cultures and increased the likelihood of false negative results in those infants classified as being free of GBS disease.

Although GBS disease occurred among infants exposed to IAP, this should not be construed as failed therapy. The doses and frequency of IAP was not known in this study and may be a

limiting factor in our results. Nevertheless, physicians should not automatically assume that the risk of GBS is eliminated when a mother is given IAP or is culture negative for GBS.[11]

Historically, early-onset GBS disease typically presents as fulminant sepsis in the first week of life, while late onset disease presents as a focal infection (e.g., meningitis) after the first week of life.[5] Our study was consistent with previous reports of higher rates of meningitis complicating late-onset GBS sepsis.[12]

Although a low CSF glucose is associated with the highest positive predictive value (5.4%) of any of the 3 CSF parameters, it has the lowest sensitivity (60.7%). Fifty-eight percent of infants with GBS meningitis had an abnormal CSF WBC count, glucose and protein in contrast to only 18% of premature infants from the same cohort with meningitis caused by any pathogen (Gram-negative, Gram-positive, or *Candida*).[13] Nearly all (96.7%) infants with GBS meningitis have at least 1 abnormal CSF value. Among infants from the same cohort with *Candida* meningitis only 4/7 (57%) had an abnormal CSF glucose, protein or WBC count.[14]

Clinicians often defer the LP until after the blood culture becomes positive. This practice has been questioned by several investigators.[1,2,16] In this cohort, 20% of infants with GBS meningitis had negative blood cultures. Future work with GBS meningitis should also include prospective studies of survival and neurodevelopmental follow-up to assess the utility of CSF parameters in diagnosing meningitis. This data supports the conclusion that the LP is important in the initial sepsis evaluations of infants provided that the patient has sufficient clinical stability to undergo the procedure.

Abbreviations

GBS, Group B Streptococcus; CSF, cerebrospinal fluid; IAP, intrapartum; LP, lumbar puncture; WBC, white blood cell; RBC, red blood cell; NICU, neonatal intensive care units; IQR, interquartile range.

References

1. Wiswell TE, Baumgart S, Gannon CM, Spitzer AR. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed? Pediatrics 1995;95(6):803–6. [PubMed: 7761203]
2. Garges HP, Moody MA, Cotten CM, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics 2006;117 (4):1094–1100. [PubMed: 16585303]
3. Leib SL, Kim YS, Chow LL, et al. Reactive oxygen intermediates contribute to necrotic and apoptotic neuronal injury in an infant rat model of bacterial meningitis due to Group B streptococci. J Clin Invest 1996;98(11):2632–9. [PubMed: 8958228]
4. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med 2000;342(1):15–20. [PubMed: 10620644]
5. Schrag SJ, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease (Revised guidelines from CDC). MMWR Recomm Rep 2002;51(RR11):1–22. [PubMed: 12211284]
6. Brooks S, Apostol M, Nadle J, et al. Diminishing racial disparities in early-onset neonatal group B streptococcal disease-United States, 2000–2003. MMWR Weekly 2004;53(23):502–505.
7. Wendel GD Jr. Leveno KJ, Sanchez PJ, et al. Prevention of neonatal group B streptococcal disease: a combined intrapartum and neonatal protocol. Am J Obstet Gynecol 2002;186(4):618–26. [PubMed: 11967482]
8. Sarff LD, Platt LH, McCracken GH. Cerebrospinal fluid evaluation in neonates: comparison of high risk infants with and without meningitis. J Pediatr 1976;88(3):473–7. [PubMed: 1245961]
9. Custer, JW. Blood chemistries and body fluids. In: Custer, JW.; Rau, RE., editors. The Harriet Lane Handbook. Elsevier Mosby; Philadelphia: 2008. p. 686-688.

10. Kottas A, Gelfand AE. Bayesian semiparametric median regression modeling. J American Statistical Assn 2001;96(456):1458–1468.

11. Puopolo KM, Madoff LM, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005;115(5):1240–6. [PubMed: 15867030]

12. Edwards, MS.; Nizet, V.; Baker, CJ. Group B streptococcal infections. In: Remington, JS.; Klein, JO.; Wilson, CB.; Baker, CJ., editors. Infectious diseases of the fetus and newborn infant. Elsevier Saunders; Philadelphia: 2006. p. 403-464.

13. Smith PB, Garges HP, Cotton CM, et al. Meningitis in preterm neonates: importance of cerebrospinal fluid parameters. Am J Perin 2008;25(7):421–426.

14. Cohen-Wolkowiez M, Smith PB, Mangum B, et al. Neonatal candida meningitis: significance of cerebrospinal fluid parameters and blood cultures. J of Perin 2007;27:97–100.

15. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics 2004;113(5):1181–6. [PubMed: 15121927]

Table 1

Demographics

	GBS meningitis (%)	GBS bacteremia, culture negative CSF (%)	Negative Blood and CSF Culture (%)
N	46	133	13,316
Gestational age (weeks) - median [IQR]	38 [36, 39]	38 [35, 40]	37 [31, 39]
Birth weight (g) - median [IQR]	3122 [2735, 3570]	3301 [2696, 3625]	2740 [1825,3425]
Delivery - N (%)			
Caesarian-section	12 (28)	47 (35)	5746 (43)
Maternal GBS status			
Positive	3 (12)	16 (18)	1938 (25)
Negative	17 (65)	50 (56)	3438 (44)
Unknown	6 (23)	24 (27)	2381 (31)
Intrapartum antibiotic prophylaxis - N (%)			
Yes	7 (15)	34 (26)	5203 (39)
Race/ethnicity - N (%)			
Black	6 (14)	24 (18)	2462 (19)
Hispanic	13 (31)	28 (22)	3890 (30)
White	23 (55)	75 (58)	5923 (46)
Other	0 (0)	3 (2)	595 (5)
Sex - N (%)			
Male	20 (43)	68 (51)	7498 (56)
Death-N(%)			
Yes	2 (5)	1 (1)	218 (2)

Table 2

CSF parameter comparison

	Sensitivity	Specificity	PPV	NPV	+ LR	− LR
Elevated WBC	89.3	81.7	1.8	99.9	4.9	0.1
Elevated protein	92.6	75.7	1.5	100.0	3.8	0.1
Low glucose	60.7	95.7	5.4	99.8	14.0	0.4
Any abnormal value	96.7	67.2	1.1	100.0	3.0	0.1
All values abnormal	58.3	98.2	11.1	99.8	32.0	0.4

PPV (positive predictive value), NPV (negative predictive value), +LR (positive likelihood ratio), −LR (negative likelihood ratio)