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Simultaneous Late, Late-Onset Group B Streptococcal Meningitis in Identical Twins

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Abstract

To our knowledge, late, late-onset group B streptococcal (GBS) meningitis in identical twins has yet to be reported. We describe a case of 14-week-old twins who developed fever hours apart and presented simultaneously to the emergency department 2 days later with seizures. Blood and cerebrospinal fluid (CSF) cultures from both infants were positive for GBS. Their clinical courses were highly similar, with magnetic resonance imaging (MRI) demonstrating ventriculitis and subdural empyema, complicated by clinical and subclinical seizures requiring quadruple antiepileptic treatment. The CSF was sterile for both on follow-up lumbar puncture 48 hours after the initial positive CSF culture. Both showed marked improvement on antimicrobial and antiepileptic therapy, with fever resolving after 5 days of therapy, control of seizures, and slowly improving MRI findings. Twin A received a 6-week course of penicillin, whereas twin B received 6 weeks plus an additional 10 days due to persistent left cochlear enhancement consistent with labyrinthitis. Evaluation for an underlying primary immunodeficiency was negative. Genomic analysis revealed that the patients' CSF GBS isolates were essentially identical and of capsular polysaccharide serotype Ia.

Keywords

group B *Streptococcus*; meningitis; bacteremia; neonate; twins

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: G. Sherman, G. Lamb, M. Nakamura; data collection: G. Sherman; analysis and interpretation of results: all authors; draft manuscript preparation: all authors. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Consideration

Patient consent was obtained. Boston Children's Hospital institutional review board (IRB) waived approval and request was withdrawn (IRB-P0003758).

Group B *Streptococcus* (*Streptococcus agalactiae* or GBS) is a major cause of infections in the neonate and young infant, with clinical manifestations including pneumonia, sepsis, and meningitis. Invasive disease is categorized by age of onset, with early-onset disease (EOD) presenting between days 0 and 6, late-onset disease (LOD) between days 7 and 89, and late, late-onset disease (LLOD) at ≥90 days, usually in very preterm infants requiring prolonged hospitalization.[1]

Twin gestation is a known risk factor for invasive GBS disease, with a relative risk in the twin of an affected infant estimated to be as high as 25-fold.[2] While reported in LOD,[3] to the best of our knowledge, infection in twins has not been described in LLOD. Herein, we describe the simultaneous presentation of identical twin boys with late, late-onset bacteremia and meningitis with essentially identical GBS isolates and similar disease progression and outcome.

Perinatal History

Identical twin boys were born via vaginal delivery at 36 weeks' estimated gestational age, with labor induced due to concern for oligohydramnios. The mother was not screened for GBS but reported receiving perinatal antibiotics. Birth weights reported by their parents were 1.8 kg for twin A and 2.2 kg for twin B. The immediate neonatal course was uneventful, aside from thermal regulation and hyperbilirubinemia requiring phototherapy. The infants were discharged at 1 week of age and gained weight well on initial breastfeeding and formula feeds until their presentation at 14 weeks (twin A 6.78 kg, twin B 7.7 kg).

Twin A

The first twin presented with a 2-day history of fever, vomiting, and diarrhea. He was brought to a local emergency department (ED) after experiencing a 15- to 20-minute seizure for which he was given intramuscular midazolam. Laboratory results showed high C-reactive protein (CRP) (22.4 mg/dL) and elevated lactate (2.8 mmol/L). He was given a dose of ceftriaxone 50 mg/kg and intravenous fluids, and then transferred to our hospital. Upon admission, he was febrile (39.5°C), tachycardic (192 beats per minute [BPM]), and hypertensive (129/86 mm Hg). He was ill-appearing and fussy but with a soft fontanelle and no focal neurological findings. Repeat CRP was 31.9 mg/dL and procalcitonin was 16.8 ng/mL. Head computed tomography (CT) showed bilateral symmetric extra-axial collections. On repeat examination, his fontanelle was found to be full. Cerebrospinal fluid (CSF) was cloudy with 1789 white blood cells (WBC)/mm^3, protein 317 mg/dL, and glucose <2 mg/dL; Gram stain revealed gram-positive cocci in pairs and short chains. He was treated with ceftriaxone 100 mg/kg/day and vancomycin 60 mg/kg/day, but once blood and CSF cultures grew GBS, his regimen was transitioned to penicillin 500 000 U/kg/day.

Twin B

The second twin became ill several hours later, presenting along with his twin to our ED with a 2-day history of fever. On arrival, he was also tachycardic (192 BPM) and hypertensive (131/89 mm Hg) but was afebrile (37°C). He was initially responsive yet

agitated, but after receiving phenobarbital for a focal seizure, he developed decreased respiratory effort with desaturations and required intubation. C-reactive protein was elevated at 20 mg/dL. Head CT showed similar findings to those of his twin with prominent extra-axial spaces, likely a combination of subarachnoid fluid and small subdural fluid collections. The CSF had 40 WBC/mm^3, protein 515 mg/dL, and glucose <2 mg/dL. Gram stain demonstrated gram-positive cocci in pairs and short chains. He was started on ceftriaxone 100 mg/kg/day and vancomycin 60 mg/kg/day. Blood culture was positive at 7 hours for GBS. The CSF culture was also positive for GBS, and he was transitioned to penicillin 500 000 U/kg/day. He was extubated approximately 36 hours after admission.

Hospital Course and Outcome

Both twins had brain magnetic resonance imaging (MRI) evidence of ventriculitis and empyema but did not require surgical intervention. They remained hemodynamically stable without hypoxemia but had ongoing seizures requiring a regimen including fosphenytoin, phenobarbital, levetiracetam, and lacosamide. Both had repeat CSF evaluation at 48 hours with negative cultures and improved indices. Serial MRI studies demonstrated slow improvement. Their clinical improvement was more marked and rapid, with fever resolving after 5 days of therapy and seizure control achieved soon thereafter. Twin B had MRI evidence of labyrinthitis and profound unilateral hearing loss. Twin A received a 6-week course of penicillin. Because twin B had ongoing left cochlear enhancement after 6 weeks of antibiotic treatment, penicillin was continued until repeat MRI 10 days later showed decreased enhancement.

At 1 year of age, twin A had expressive speech delay but normal hearing and no focal neurologic deficits. Twin B continues to have gross motor, speech, and language delays with mildly reduced tone and strength. He remained with left sensorineural hearing loss and had a cochlear implantation at the age of 7 months. Both continue lacosamide monotherapy, with no episodes concerning seizures.

Immunologic Evaluation

Family history was positive for meningitis in multiple relatives, and given this history, evaluation of the patients for a potential immunodeficiency was undertaken. Both infants had appropriately elevated neutrophil counts that normalized quickly. They both had mildly elevated IgG levels for age and mildly elevated or normal IgA and IgM levels. They had normal numbers and subsets of T cells, B cells, and natural killer cells and normal T-cell proliferation. Complement function was normal as assessed by CH50 and AH50 testing. Both had a normal oxidative burst as assessed by dihydrorhodamine flow cytometric assay. No candidate variants were identified by a targeted next-generation sequencing panel that assessed 322 genes associated with inborn errors of immunity (Prevention Genetics).

Genomic Analysis of GBS Isolates

Preliminary genomic analysis was performed on a CSF GBS isolate from each twin by ARUP Laboratories (Salt Lake City, Utah). The isolates had indistinguishable chromosomal

patterns on pulsed-field gel electrophoresis following restriction digest using *Sma*I (Figure 1).

Whole-genome sequencing (WGS) of the 2 isolates was completed at the Centers for Disease Control and Prevention (CDC) *Streptococcus* Laboratory (Atlanta, Georgia).[4] These results from WGS are intended for surveillance purposes only and not provided for diagnosis, treatment, or assessment of patient health or management. Genomic analysis revealed that the 2 isolates were nearly identical, differing by only 4 single nucleotide polymorphisms (SNPs) across the core GBS genome. The isolates belonged to clonal complex (sequence type) 23, and they contained the capsular polysaccharide biosynthetic operon for capsule type Ia.

Discussion

Group B *Streptococcus* commonly colonizes the human gastrointestinal and genitourinary tracts and less often the pharynx. The colonization rate in pregnant women is 15% to 35%.[1] While EOD is usually transmitted shortly before or during delivery, the host and pathogen factors contributing to LOD and LLOD are less well established. The infant presumably acquires the bacteria postnatally from colonized family members or caregivers, infected breastmilk, or nosocomial sources, such as newborn nurseries. Our patients' isolates were essentially genetically identical, differing by only 4 SNPs, indicating a common source such as a colonized family member, although the source remains unknown.

Whereas prenatal screening and intrapartum antibiotic prophylaxis have significantly reduced the incidence of EOD, LOD incidence remains unchanged, surpassing EOD in recent years. During 2006–2015, EOD incidence declined significantly from 0.37 to 0.23 per 1000 live births, whereas LOD rates remained stable (mean 0.31 per 1000 live births).[5]

Underlying immune deficiency has been identified in only a few patients with LLOD, such as HIV infection and the initial presentation of interleukin-1 receptor–associated kinase-4 deficiency.[6,7] For our patients, the family history of meningitis raised the question of an inherited deficiency in immunoglobulin production or the complement system, both of which have been associated with invasive infections due to encapsulated bacteria, but no obvious abnormality was found on evaluation.

Ten GBS capsular polysaccharide serotypes are known, but 6 serotypes (Ia, Ib, II, III, IV, and V) account for 99.3% of EOD cases and 99.7% of LOD cases in the United States.[5] Among infants with EOD, serotypes Ia and III are most common (27.3% and 27.3%, respectively). However, among those with LOD, serotype III is most common (56.2%), increasing between 2006 and 2015 from 0.12 to 0.20 cases per 1000 live births. More recent serotype data from the CDC[8] (Table 1) from 2015 to 2017 demonstrated that 12% of LOD cases were serotype Ia, whereas 69% were serotype III. Among cases in patients aged 90 days to 17 years, 9 (16%) of 56 cases were caused by serotype Ia, as in our patients.

Our GBS isolates were of sequence type 23, which is the dominant genotype of serotype Ia and one of the more prevalent genotypes in EOD. It was previously shown to be as prevalent among colonizing isolates as invasive ones,[9] but a recent study from China[10] examining 298

pregnant women with GBS colonization during late pregnancy and 32 invasive EOD cases found that sequence type 23 was associated with hypervirulence in causing EOD.

The unique aspects of our patients' cases are the simultaneous presentation of such late-onset GBS meningitis in these twin boys, with an almost identical course and no evidence of underlying immunodeficiency. We found no reports in the literature of twins presenting with LLOD, possibly making this the first report of such an occurrence.

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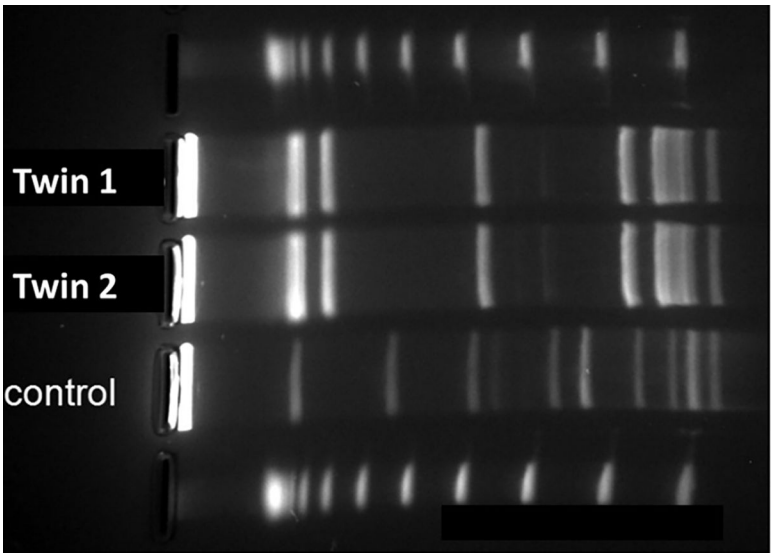

Figure 1.
Genomic analysis of cerebrospinal fluid group B *Streptococcus* isolate from each twin, performed by pulsed-field gel electrophoresis. The 2 isolates had indistinguishable chromosomal patterns.

Table I.

Distribution of Invasive Group B *Streptococcus* Serotypes Among Isolates Recovered From Young Infants and From All Other Ages During 2015–2017 in Centers for Disease Control and Prevention's Active Bacterial Core Surveillance.

Age	Ia	Ib	II	III	IV	V	VI	VII	VIII	IX	NT*	
<7 days (n = 232)	51	24	38	63	27	27	2					
7–89 days (n = 274)	33	20	7	189	17	8						
90 days-17 y (n = 56)	9	12	4	18	3	10						
18–39 y (n = 527)	100	84	105	75	71	83	6		3			
40–64 y (n = 2534)	580	352	464	297	340	457	24	1	6	5	8	
65–79 y (n = 1750)	387	270	302	225	201	336	16	2	4	2	5	
≥80 y (n = 967)	224	157	162	120	89	195	13	2	4	1		
Total	1384	919	1082	987	748	1116	61	5	17	8	13	6340

*NT = non-typeable.

Reproduced from Supplementary Data, Supplement 1, by McGee et al.[8]

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