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CASE SERIES

Neonatal Late-Onset Meningitis Caused by Serotype III CC17 Group B *Streptococci* Aggregating in Two Families from Southern China

Lei Yue, Haiying Liu

Clinical Laboratory, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, Guangdong, People's Republic of China

Correspondence: Haiying Liu, Clinical Laboratory, The Affiliated Brain Hospital of Guangzhou Medical University, No. 36 Mingxin Road, Guangzhou, Guangdong Province, 510370, People's Republic of China, Email xiangliuhaiying@aliyun.com; liuhaiying@gzhmu.edu.cn

Background: Late-onset meningitis infected by group B *Streptococcus* (GBS) continues to be a major cause of perinatal mortality, morbidity and long-term neurodevelopmental sequelae despite the implementation of universal screening, but its risk factors are not fully understood.

Case Presentation: We reported a set of dizygotic twins and a pair of compatriot siblings diagnosed with late-onset GBS meningitis aggregating in two Chinese families. All of GBS strains were identified as serotype III CC17 with high homology between the strains within the same family, and the isolates from the compatriots identical to their mother's carriage. The siblings in the two families presented clinical signs several days after close contact with their index cases having a fever at home, and obtained prompt diagnosis and anti-infective therapy. The two index patients had obvious brain damage before effective treatment and severe sequelae compared to their siblings with complete healing.

Conclusion: The dramatic difference in outcomes between the index cases and their siblings brings attention to prevent and control familial aggregation of neonatal late-onset GBS infection which never reported in China.

Keywords: group B *Streptococcus*, neonate, meningitis, twins, compatriots

Background

Group B *Streptococcus* (GBS) is the most frequent cause of neonatal serious infection.[1,2] Most cases occur in the first week of life (early-onset) and present with fever and septicemia. Conversely, late-onset disease (LOD, from day 7 to 89) often presents with meningitis and remains a devastating disease, with a mortality rate of 10% to 15% and permanent neurologic morbidity in 20% to 50% of the survivors. GBS-LOD cannot be prevented by intrapartum antibiotic prophylaxis and continues to be a major cause of perinatal mortality, morbidity and long term neurodevelopmental sequelae.[3] Familial aggregation of such cases exposing to the same environment may provide further clues to elucidate the risk factors and transmission of GBS. Here we reported four cases, a set of twins and a pair of compatriots synchronously with LOD meningitis caused by serotype III CC17 GBS in two families from Southern China. The dramatic difference in outcomes between the index cases and their siblings enhances the importance of early diagnosis and timely treatment of the late-onset GBS meningitis. It also calls attention to familial aggregation of neonatal GBS infection in view of two-children policy that was recently encouraged in China.

Case Presentation

Family 1

Compatriot A

The elder sister, weighing 3.06 kg was delivered by cesarean section at 38 weeks gestation (G1P1). Thirty-six days after birth, she had a fever (peak of 39.0°C) and was consequently admitted to the hospital due to seizures, confusion, and poor

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response. Counts of blood cells (CBC) revealed WBC 5.5*10^9/L with 52.0% neutrophils and CRP 83.1mg/L, shown as Table 1. GBS was isolated from both cerebrospinal fluid (CSF) and blood. WBC of 825*10^6/L, glucose of 0.11mmol/L, and protein levels of 7.5g/L were found in the CSF. A diagnosis of meningitis was made. On 42 day of hospital stay, MRI revealed increased subdural effusion (Figure 1a). On hospital day 80, she continued to have a unilateral limb twitch and convulsions, and was diagnosed with symptomatic epilepsy. On hospital day 167, she was discharged and was prescribed oral linezolid. She had been followed-up once every two weeks; however, her CSF parameters remained abnormal. Seven months after discharge, she was readmitted to the hospital for a fever and convulsions with no obvious cause. No bacterium was cultured in blood and CSF, but the CSF parameters were still abnormal. The patient received linezolid as an anti-infective drug. She was discharged after another 3 months of hospitalization. She continued to suffer from secondary epilepsy throughout the first year of routine outpatient follow-ups and her condition improved later on.

Compatriot B

One-year younger brother, weighing 4.27 kg was delivered by cesarean section at 36+3 weeks gestation. Twenty-one days after birth, he developed increased auscultation and increased heart rate 48 hours after his sister had a relapse fever at home. CBC revealed WBC of 7.8*10^9/L with 70.5% neutrophils and CRP 5.6mg/L. High-dose penicillin was administered after blood sampling for culture. WBC of 59*10^6/L, glucose of 1.67mmol/L, and protein levels of 0.95g/L were found in the CSF. Next day, GBS was isolated from initial blood and CSF. Meropenem and penicillin were subsequently administered. Occipital arachnoid cyst was found in the head MRI (Figure 1b). CSF parameters fluctuated

Table 1 Laboratory Test Results of GBS Infection in Two Families After Admission

	Family 1		Family 2	
	Compatriot A	**Compatriot B**	**Twin A**	**Twin B**
Blood culture	GBS+	GBS+	GBS-	GBS+
CSF culture	GBS-	GBS+	GBS+	GBS-
CSF WBC (10^6/L)	330*	130*	825*	246*
CSF glucose (mmol/L)	0.02#	2.70*	0.11#	1.67#
CSF protein (g/L)	6.21*	0.86*	7.5*	0.95*
Granules percentage in CSF	80%*	80%*	28%*	22%*
Blood routine WBC (10^9/L)	2.3#	5	5.5	7.8
Neutrophil (10^9/L)	1.13#	4.01	2.86	5.5
CRP (mg/L)	>200*	126*	83.10*	5.6
Abnormal count of T cells	563.40	1495.18	786.42	/
Abnormal count of B cells	25.77	574.06	1055.56	/
Neutrophil burst experiment (Stimulus index)	/	102.21	64.28	/
Serum immunoglobulin G (g/L)	4.53	4.45	2.99	3.17
Serum immunoglobulin A (g/L)	<0.07	<0.07	0.14	0.10
Serum immunoglobulin M (g/L)	0.17	0.16	0.42	0.33
Serum complement C3 (g/L)	0.63	0.58	0.81	0.47
Serum complement C4 (g/L)	0.15	0.12	0.13	0.05

Notes: *High than the normal range; #Low than the normal range.
Abbreviations: CRP, C-reactive protein; WBC, white blood cell count.

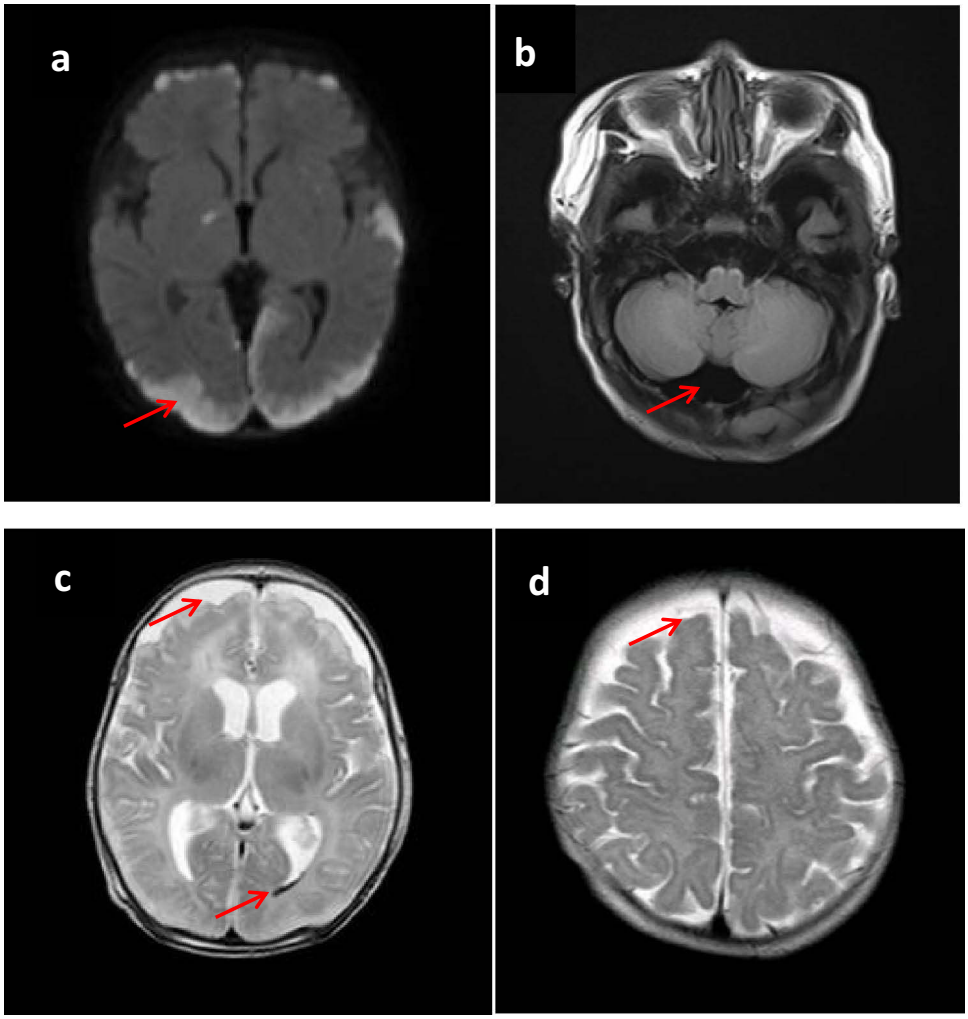

Figure 1 Head magnetic resonance imaging of late-onset GBS meningitis in the twins and the compatriots after admission. (**a**): Increased subdural effusion and meningoencephalitis were revealed in compatriot A. (**b**): Formation of occipital arachnoid cyst was found in compatriot B. (**c**): Bilateral frontal subdural empyema and hemorrhage was indicated in twin A. (**d**): Suppurative meningitis was diagnosed in twin B. The red arrow points to the focal area.

until penicillin was replaced with linezolid. He was discharged after 37 days spent in the hospital. There was no any sequelae observed during 2 years of follow-ups.

Family 2

Twin A

The younger dizygotic twin, G4P2, weighing 2.6 kg was born at 37+2 weeks gestation by cesarean delivery. Seventeen days after birth, neonatal sepsis was diagnosed due to fever with a peak of 39.2°C. Blood routine revealed WBC of $2.3*10^9$/L with 49.1% neutrophils and CRP >200 mg/L. Next, imipenem-cilastatin sodium was administered for 7 days. His blood culture was negative. However, his parents refused the doctor's suggestion to perform lumbar puncture for CSF examination, so the baby was released home. On 48 days of age, he was readmitted to neonatal intensive care unit due to high fever, convulsions, cyanosis and severe diarrhea. Meropenem and linezolid were initially administered. Head MRI indicated bilateral frontal subdural empyema and hemorrhage (Figure 1c). He was diagnosed with septic shock and purulent meningitis. GBS was identified from blood and CSF cultures at the second day after admission. CSF analysis showed WBC of $330*10^6$/L, glucose of 0.02mmol/L, and protein levels of 6.21g/L. High-dose penicillin combined with linezolid were then administered.

On the 23 day of hospitalization, neurosurgery was performed by bilateral frontal subdural effusion and catheter drainage. Oral sodium valproate was added to antiepileptic treatment. The patient developed recurrent fever and frequent paroxysmal binocular up gaze. Considering severe neurological sequelae and economic reasons, his parents decided to give up treatment and the patient was discharged from the hospital. He has been raised alone by his grandparents living in countryside and continued to suffer from dysplasia and secondary epilepsy throughout the two years of telephone follow-up.

Twin B

At 48 days of age, the elder twin sister (weighing 2.6 kg at birth) was admitted to the hospital with a fever only 3 days after her younger brother developed fever again. CBC revealed WBC of $5.0*10^9$/L with 80.2% neutrophils and CRP of 126mg/L. She had positive blood culture for GBS and negative CSF culture; her CSF parameters were abnormal with WBC $130*10^6$/L, glucose 2.70mmol/L, and protein levels of 0.86g/L. Purulent meningitis (Figure 1d) and acute upper respiratory infection were diagnosed with description of meropenem and vancomycin. On the 10^{th} day of the hospitalization, CSF parameters improved and body temperature returned to normal. Consequently, the patient was prescribed meropenem and linezolid. On the 62^{nd} day of the hospitalization, CSF analysis was normal. The patient was discharged home and was prescribed with linezolid. She remained healthy during outpatient follow-ups.

Etiology and Strain Analysis

Both of the mothers showed no abnormalities during pregnancies and no GBS screenings were performed in late pregnancy, thus the status of GBS remained unknown at delivery. Cefuroxime or cefazolin were intravenously administered as routine anti-infective before cesarean surgery. Both families used formula instead of breast milk. After neonatal GBS disease was diagnosed, GBS cultures were performed from urine, throat swabs, and vaginal-rectal swabs collected from the mothers. GBS was positive in vaginal-rectal sample from the compatriots' mother, while GBS was not found in mother of the twins and the samples were not accessible from their grandmother as the caregiver.

Bacterial phenotypic and genetic analysis were performed with GBS strains isolated from CSF from twin A, blood from twin B, CSF of the compatriots and their mother who carried strain. All the isolates were identified as belonging to serotype III, ST17 and CC17 by Latex® agglutination and multi-locus sequence typing. They all expressed hypervirulent GBS adhesin gene (*HvgA*) detected by PCR. MALDI-TOF mass spectrometry (Vitek MS, bioMeriuex, France) showed a homology of >85% for the two GBS strains from family 1, while homology higher than 90% was found in the strains from the compatriots and their mother in family 2 (shown as Figure 2). All the patients and their mothers showed no abnormalities in peripheral immune functions including lymphocyte subsets, neutrophil burst experiment and concentration of immunoglobulin isotypes (IgG, IgA, IgM) and complements (C3, C4).

Discussion

Up to date, there are no more than thirty twins reported to suffer from neonatal GBS diseases, and both twins can develop EOD and/or LOD GBS infection.[4] Familial aggregation of neonatal GBS disease usually occurred in twins and the relative risk of invasive GBS infection in a twin sibling of an affected infant has been estimated to be as high as 25-fold.[4] The possible explanations for this increased risk in twins include the fact that twins are similar in their genetic heritage, exposure to the same maternal genital bacteria and the same maternal immune status, ie low concentrations of protective antibodies.

Vertical transmission, breast milk, and environmental sources have been suggested as a possible source of GBS LOD.[3] A fraternal twins, each of whom had 2 episodes of late-onset sepsis and cellulitis caused by identical serotype Ia/c despite appropriate therapy.[5] Doran et al described although exhibiting similar signs and symptoms at presentation and genetically identical GBS isolates, the index case of twins developed late-onset fulminant fatal meningitis while his sibling without CNS involvement recovered completely.[6] Arora et al reported LOD sepsis in twins caused by indistinguishable GBS with Pulsed field gel electrophoresis, indicating a common source of exposure in both twins.[7] Late-onset and recurrent neonatal GBS disease in a set of twin associated with breast-milk transmission with a case died from meningitis and the other survived sepsis.[8] Similarly, a case of late-onset meningitis and recurrent infection in newborn twins resulting from ingestion of maternal breast milk infected with genetically identical serotype III GBS, also affording evidence for maternal milk as the source of neonatal GBS infection.[9] Indeed, maternal breast milk has been occasionally

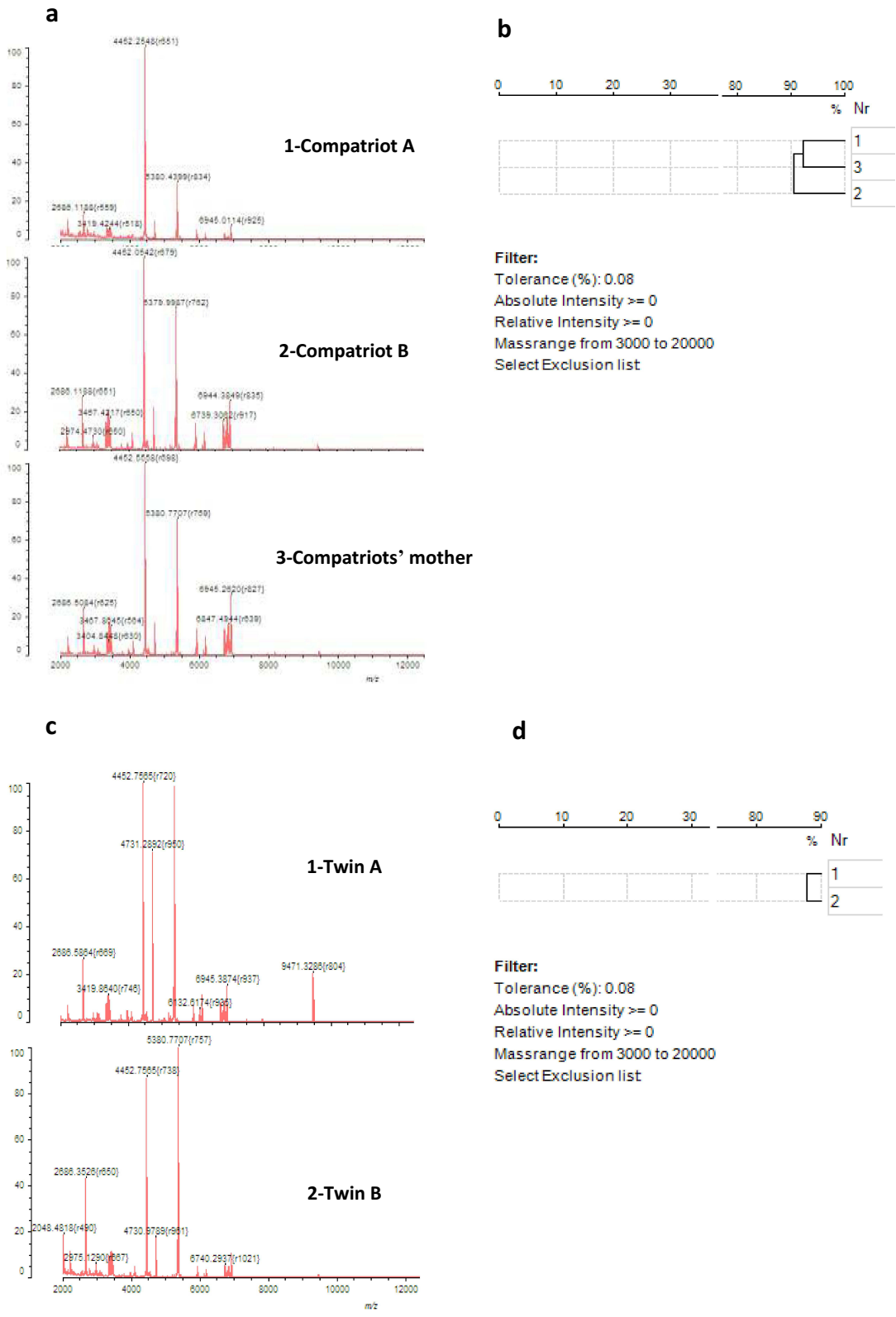

Figure 2 Comparison of peptide mass fingerprint and homology analysis for GBS strains from the two families by MALDI-TOF mass spectrometry. (**a**): Peptide mass fingerprint of GBS strains from family 1. Both strains of compatriot A and B were isolated from CSF and the strain of their mother was cultured with vaginal-rectal swab. (**b**): Homology analysis for the three GBS strains from the compatriots and their mother in family 1. (**c**): Peptide mass fingerprint of GBS strains from family 2. The strains of twin A and twin B were respectively isolated from CSF and blood. (**d**): Homology analysis for two GBS strains from the twins in family 2.

reported as a potential source of late-onset neonatal sepsis from both GBS and other viral and bacterial pathogenic organisms, especially in preterm infants and in the case of recurrent infection or simultaneous sepsis in siblings.[10] Therefore, GBS transmission through breast milk should be considered in late-onset GBS sepsis. Furthermore, synchronous recurrence of GBS late-onset sepsis in a dizygotic premature twins were caused by serotype III ST17 clones which were identical to their mother's rectovaginal carriage and GBS DNA also were detected in the mother's breast milk.[11] A recent nationwide surveillance study in Japan found four sets of both twins developed LOD GBS bacteremia and culture of human milk from one mother was positive for GBS whose serotype (Ia) was the same as that in blood cultures from both twins.[12] The patients in the two Chinese families were fed by the same formula, hereby breast milk could be excluded as the risk factor. However, the source of pathogens in family 1 seemed to be much clear because the GBS strains isolated from the compatriots were highly homologous with their mother's vaginal-rectal carried strain. The serologically, genetically and phenotypically identical strains from the twins suggested they were caught by the same GBS clones. Nevertheless, it was not possible to define the source of the disease in the twins since their mother was not a GBS positive carrier and we failed to do the screening for their grandmother who had helped nursing the babies after birth. The latest study further confirms that high incidence of CC17 GBS in LOD is likely due to an enhanced post-delivery mother-to-infant transmission.[13] The above-mentioned reports in twins manifest that maternal transmission, including rectovaginal carriage and/or contaminated breast milk, is an important source for familial aggregation of neonatal GBS disease, despite it is controversial in dealing with maternal carriage and infected milk.

It is worth noting that most of apparently well siblings of the twins would develop GBS disease often within 24–48 hours of onset in the index cases diagnosed.[4] The situation was the same as the later sick siblings in the two Chinese families presented clinical signs only several days after close contact with their index cases having a fever at home. Taken together with the identical GBS strains detected by MALDI-TOF mass spectrometry, the findings strongly implied the index sick sibling be considered as the exact transmission source leading to familial aggregation of neonatal GBS disease. Since stronger virulence and persistence in human bloodstream invasion than mucosal commensal colonization has been identified by a recent study.[14] Virulence of the microorganism is also linked to neonatal GBS infection. In Edwards'series, 1 of 6 sets of twins of index cases developed late-onset meningitis infected with same GBS serotype III as their index cases, and both of these infants had subdural effusions and abnormal findings at neurological examinations at the time of discharge from the hospital.[4] Among the limited number of previously reported twins with LOD GBS disease, most isolates have been identified as serotype III. The cases we reported are no exception, and identical CC17 clones possessing *hvg*A, which not only facilitate destroying and penetrating the intestinal and blood–brain barriers, but also mediate the migration of bacteria into the bloodstream and the central nervous system leading to infections, were found to be responsible for this familial aggregation.

Neonatal immunodeficiency in genetics and physiological development (low concentrations of maternal IgG) may theoretically predispose to invasive GBS infection in premature infants with low birth weight.[15] Nonetheless, Licciardi et al failed to identify genetic origin in two cases of isolated neonatal GBS sepsis occurring in two infants with an early-onset and a late-onset in two families in a large consanguineous kindred of the Sinti ethnic group exposed to the same environment.[16] Although these reports may be skewed by preferential reporting of concordant cases, neonatal GBS colonization and lack of protective maternal antibody are likely to be the same. Unfortunately, antibodies against GBS could not been evaluated in the patients, which is one of the limitations to this study.

To our knowledge, this is the first report of familial aggregation of late-onset GBS meningitis. Reviewing the medical history of the two families and immune function tests of the mother and children, there were no known obvious immunodeficiency diseases, even for compatriot B who was born preterm but with normal birth weight. All the affected cases developed meningitis, but the dramatic difference in the outcomes for the indexes and their siblings highlighted the importance of early diagnosis and timely treatment, presenting early intervention is likely to improve the outcome. The indexes had obvious brain damage before effective treatment, compared with their siblings. GBS meningitis could occur in the presence of negative blood cultures. Nevertheless, the two siblings received timely anti-infection treatment and the pathogens were identified. Under the special circumstances with an apparently non-affected sibling in twin or multiple births with GBS disease, the sibling who appears not to be infected with invasive infection is at higher risk of developing GBS disease, suggesting that careful long-term observation of the unaffected twin is warranted. The American revised 2010 CDC guidelines for secondary prevention recommend that any newborns with signs of sepsis should receive a full

diagnostic evaluation including a lumbar puncture if the newborn is stable enough to tolerate the procedure, and receive antibiotic therapy pending the results of the evaluation.[17] Empirical evaluation and antibiotic therapy are recommended for suspected systemic infection if any manifestations of illness occur, or even asymptomatic infection in the twin, the triplets, or any multiples index cases with invasive GBS disease.

Conclusions

In summary, we reported neonatal LOD meningitis caused by serotype III CC17 GBS aggregating in two families from southern China. The dramatic difference in outcomes between the index cases and their siblings brings attention to prevent and control familial aggregation of neonatal late-onset GBS infection which never reported in China.

Abbreviations

LOD, late-onset disease; GBS, group B *Streptococcus*; CC, complex clone; CBC, counts of blood cells; WBC, white blood cells; CRP, C-reactive protein; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; HvgA, hypervirulent GBS adhesin; MALDI-TOF, matrix-assisted desorption ionization-time of flight.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available since the medical records and data are the patient's privacy, but are available from the corresponding author on reasonable request under the consent from close relatives of the patient.

Ethics Approval and Clarification

This study was approved by the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University to publish the case details and written informed consents were obtained from the patients' guardians.

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Disclosure

The authors declare that they have no competing interests.

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