

Clinical Features of *B. Cereus* Sepsis in Premature Neonates

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Research

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Abstract

Background: To analyze the clinical characteristics and prognosis of bacillus cereus sepsis in premature neonates.

Method: Retrospectively analyze the data of 8 premature neonates of bacillus cereus sepsis in Shanghai Children's Hospital from January 2015 to December 2019, where clinical information is collected from patients' medical records and charts, information of neurodevelopment is collected for patients from follow-up visits at corrected age of 6 months and 12 months.

Results: 8 premature neonates of bacillus cereus sepsis were identified, among which 5 cases developed meningitis, abnormal Cerebral MRI images were seen in 5 cases. After empirical antibiotic treatment with Meropenem and Vancomycin, 1 patient died, 7 patients survived to discharge. Follow-up visits discovered that 1 patient developed hydrocephalus and showed severely delayed neurodevelopment, 2 patients had mild neurodevelopmental delay, and neurodevelopment was basically normal in other 4 patients.

Conclusions: Bacillus cereus infection can cause severe nervous system complications, and affect neurodevelopmental outcome. Empirical antibiotic treatment with Meropenem and Vancomycin is proven effective.

Background

Neonatal sepsis is a serious disease which threatens life of neonates. Its incidence among survived neonates is 4.5‰~9.7‰^[1]. It is a major risk factor in late-onset sepsis among term and/or premature neonates. Incidence rate increases as gestational age and body weight decreases^[2]. Common pathogens for late-onset sepsis in China are Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, etc. The Bacillus cereus group is comprised of eight closely related species: B. cereus, B. cytotoxicus, B. mycoides, B. pseudomycooides, B. thuringiensis, B. weihenstephanensis, B. toyonensis, and B. anthracis^[3-5].

Bacillus Cereus is a type of gram positive, aerobic facultative bacillus which is widely distributed in the environment^[6]. Besides food poisoning^[7], Bacillus Cereus can cause focal or systemic infection, including sepsis, endophthalmitis, pneumonia, meningitis and encephalitis, especially among immunosuppressed patients. Mortality of neonatal Bacillus Cereus infection is approximately 10%. However, as B. cereus is mainly considered as an environmental contaminant, delays in treatment may compromise the clinical outcome.

Method

Eight premature neonates of bacillus cereus sepsis were identified in Department of Neonatology, Shanghai Children's Hospital from January 2015 to December 2019, and the clinical features and treatments were analyzed.

Result

2.1 General data: Among the 8 cases, 6 were male, 2 were female. 4 cases were delivered by Cesarean section, other 4 were spontaneous vaginal delivered; gestational age at birth: 29–35⁺ 4 weeks; birth weight: 1,060 – 2,330 g; Apgar score at 5 minutes: 8'-10'; Age at onset: 4–31 days; 5 cases had history of PPRM (premature prolonged rupture of membrane, PPRM); 1 case was recorded with maternal cervical incompetence; 2 cases were SGA (smaller than gestational age, SGA)

2.2 Clinical manifestations: 6 cases had fever, highest temperature was 38.2–38.8°C; none of the cases developed hypothermia; 1 case presented with convulsions; 4 cases developed apnea; 2 cases had abdominal distension and feeding intolerance; 1 case refuse feeding; 1 case was on NPO due to suspicion of necrotizing enterocolitis (NEC); 2 cases were fed with expressed breast milk; 4 cases were fed with formula; 4 cases had PICC line; 3 cases had peripheral venous catheter; 1 case had no peripheral venous catheter.

2.3 Treatment: Upon change in condition, 5 cases needed respiratory support; 2 cases were intubated and put on mechanical ventilation, 3 cases were on non-invasive ventilation; 2 cases developed septic shock, and received fluid resuscitation and inotropes; 5 cases received immune support with IVIG. Based on blood culture results, we changed antibiotics to Vancomycin, 6

cases saw their condition improve after being administered with Vancomycin; 1 case was administered with Meropenem and Ampicillin to fight infection before its condition improved; 1 case was initially administered with Benzylpenicillin and Ceftazidime before the therapy was changed into Meropenem which showed no effect and neonate died. Among those whose condition improved, anti-infection treatment lasted 14–49 days. See Table 1.

2.4 Laboratory examination. Increased WBC and increased neutrophil ratio were seen in 2 cases; Leukocytopenia was seen in 5 cases; 2 cases developed thrombocytopenia; all the 8 cases had various degrees of increased CRP and increased PCT. All *Bacillus cereus* strains were resistant to penicillin and compound trimethoprim, sensitive to erythromycin, Clindamycin, Gentamicin, Vancomycin and Levofloxacin; All 8 cases received lumbar puncture; 5 cases had combined meningitis (Table 2).

2.5 Cerebral MRI: Cerebral MRI was performed on 6 patients. 1 patient had normal result; 5 patients had presentations of intracranial hemorrhage or leukomalacia; 1 patient had meningeal enhancement; 1 case developed hydrocephalus during follow-ups, ventricular-peritoneal shunt (VP shunt) was performed. See Fig. 1

2.6 Outcome: 1 patient died, 7 patients survived to discharge. All the survived patients have regular outpatient follow-ups to evaluate the development of nervous system and to have early intervention; 4 of the patients completed Gesell Developmental Schedules at six months of corrected age; 7 of the patients completed ASQ-3(Ages & Stages Questionnaires, Third Edition)at 12 months of corrected age. 1 patient had severe neurodevelopmental delay and underwent rehabilitation treatment, 2 patients had mild neurodevelopmental delay, and neurodevelopment was basically normal in other 4 patients.

Discussion

Bacillus cereus is a spore forming and ubiquitous bacterium presents in soil, foods, insect larvae, almost all surfaces and human skin^[8–9]. *B. cereus* has been found in environmental reservoirs such as ventilator equipment, intravascular catheters, and linen. In addition to food poisoning, *B. cereus* causes a number of systemic and focal infections in both immunologically compromised and immunocompetent individuals. Among those most commonly infected are neonates, especially with indwelling catheters. The spectrum of infections includes fulminant bacteremia, central nervous system(CNS) involvement(meningitis and brain abscesses), to name a few^[6]. Research found that a majority of strains(41%) were isolated in newborns, among which 3/4 were premature infants with low birth weight^[10]. And, with virulence test of bacterial strain, it is found that the average production of bacterial strain toxin from newborns is low, this suggests that newborn may be particularly sensitive to *B. cereus* strains, even those with low toxin production, or that other unknown factors may be responsible for newborn infection. The pathogenicity of *Bacillus cereus* is closely related to the production of tissue damaging/reactive exoenzymes. The secretin includes four kinds of hemolysins, three distinct phospholipases, an emesis-inducing toxin, and three pore-forming enterotoxin: hemolysin BL (HBL), nonhemolytic enterotoxins (NHE) and cytotoxin K.

Besides, *B. cereus* can cause severe late-onset hemorrhagic meningoencephalitis in preterm infants. In this study, 7/8 infants had signs and symptoms of meningitis (CSF showed leukocytosis, low glucose, and increased protein), among which 6 patients have shown abnormal expressions in cerebral MRIs. Early and continuous brain sonography is very important for neonates, especially for premature infants who are suspected of septicemia or having convulsions. Some research states^[11], Serial brain sonography showed that the hemorrhagic meningoencephalitis affects first the white matter and later the basal ganglia and cortex.

According to past research, most *Bacillus cereus* are resistant to penicillin and cephalosporin, but sensitive to aminoglycoside, carbapenem, vancomycin and chloramphenicol^[12]. The cases in this research are all responsive to meropenem and vancomycin treatments.

In short, the clinical symptoms of *Bacillus cereus* sepsis in preterm neonates are non-specific, with increased CRP in lab tests, meningitis expressions in CSF examinations, and hemorrhagic meningoencephalitis in cerebral MRI. Meropenem and vancomycin are proven effective in treatment. The limit of the study is the small sample size, therefore more clinical and lab test features cannot be summarized.

Conclusion

Positive blood culture of bacillus cereus in premature neonates should not be deemed as contamination. Bacillus cereus infection can cause severe nervous system complications. Lumbar puncture should be completed and anti-infection treatment should be given. Meropenem and vancomycin are effective in treatment.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Na Li and Yunlin Shen conceived and designed the study, analysed the data, and drafted the manuscript. Xiaohui Gong helped design the study, Juan Li and Hongzhan Zhang helped analysed the data. All authors read and approved the final manuscript.

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Tables

Table 1
Characteristics of patients with *Bacillus cereus* bloodstream infection

Case	gestational age(weeks)	birth weight(g)	gender	Delivery mode	clinical feature	treatment	outcome
1	29	1060	male	SVD	fever∩apnea∩ abdominal distension	intubation,meropenem∩ vancomycin	Survived
2	30 ⁺⁴	1590	female	SVD	apnea	CPAP∩meropenem∩ vancomycin	Survived
3	34 ⁺¹	2330	male	SVD	fever∩convulsion∩ hypotension∩ metabolic acidosis	intubation,meropenem∩IVIG∩ fluid resuscitation∩dopamine∩ dobutamine	Deceased
4	30 ⁺⁵	1660	male	Cesarean section	apnea∩abdominal distension	CPAP∩meropenem∩IVIG	Survived
5	35 ⁺³	1470	male	Cesarean section	fever	meropenem∩vancomycin∩ IVIG	Survived
6	32 ⁺⁴	1630	male	SVD	fever∩apnea	meropenem∩vancomycin∩ IVIG∩dopamine∩CPAP	Survived
7	34	1500	male	Cesarean section	fever	meropenem∩vancomycin∩ IVIG	Survived
8	35 ⁺⁴	2030	female	Cesarean section	fever	meropenem∩vancomycin∩ IVIG	Survived

SVD: spontaneous vaginal delivery, IVIG: intravenous immunoglobulin; CPAP: continuous positive airway pressure

Table 2
Lab Results

Case	Blood			CSF			MRI
	WBC(*10 ⁹ /L)	PLT(*10 ⁹ /L)	CRP(mg/dL)	WBC	glucose(mmol/L)	protein(mg/dl)	
1	5.42	180	139	2700	0.6	5510	hydrocephalus
2	34.76	209	26	2	2.9	1490	-
3	2.69	39	18	48000	12.1	62500	-
4	4.11	450	9	147	2.8	1760	Abnormal white matter signal
5	4.62	111	29	19	2	1610	normal
6	4.08	443	8	153	1.9	2600	Abnormal signals in the lateral ventricles
7	8.1	65	40	98	1.8	2480	cerebromalacia
8	18.11	304	28	18	2.3	1480	Meningeal enhancement

Table 3
Prognosis of Nervous System

Case	Gesell Developmental Schedules(6month)					ASQ3(12month)				
	Social skill	Adaptability	Language	Gross motor	Fine motor	Communication	Gross motor	Fine motor	Problem solving	Personal-social
1	77	78	85	76	82	5	10	15	10	10
2	101	93	96	97	94	25	30	50	45	35
3	/	/	/	/	/	/	/	/	/	/
4	/	/	/	/	/	25	45	60	50	35
5	96	97	103	100	115	30	35	60	50	50
6	90	82	96	106	90	15	30	55	25	20
7	96	116	107	88	107	25	35	30	50	30
8	/	/	/	/	/	35	45	35	40	30
Gesell Developmental Schedules: DQ(Developmental quotient)≤85 means abnormal										
ASQ3 Critical value: Communication 15.64, Gross motor 21.49, fine motor 34.50, Problem solving 27.32,Personal-social 21.73										

Figures

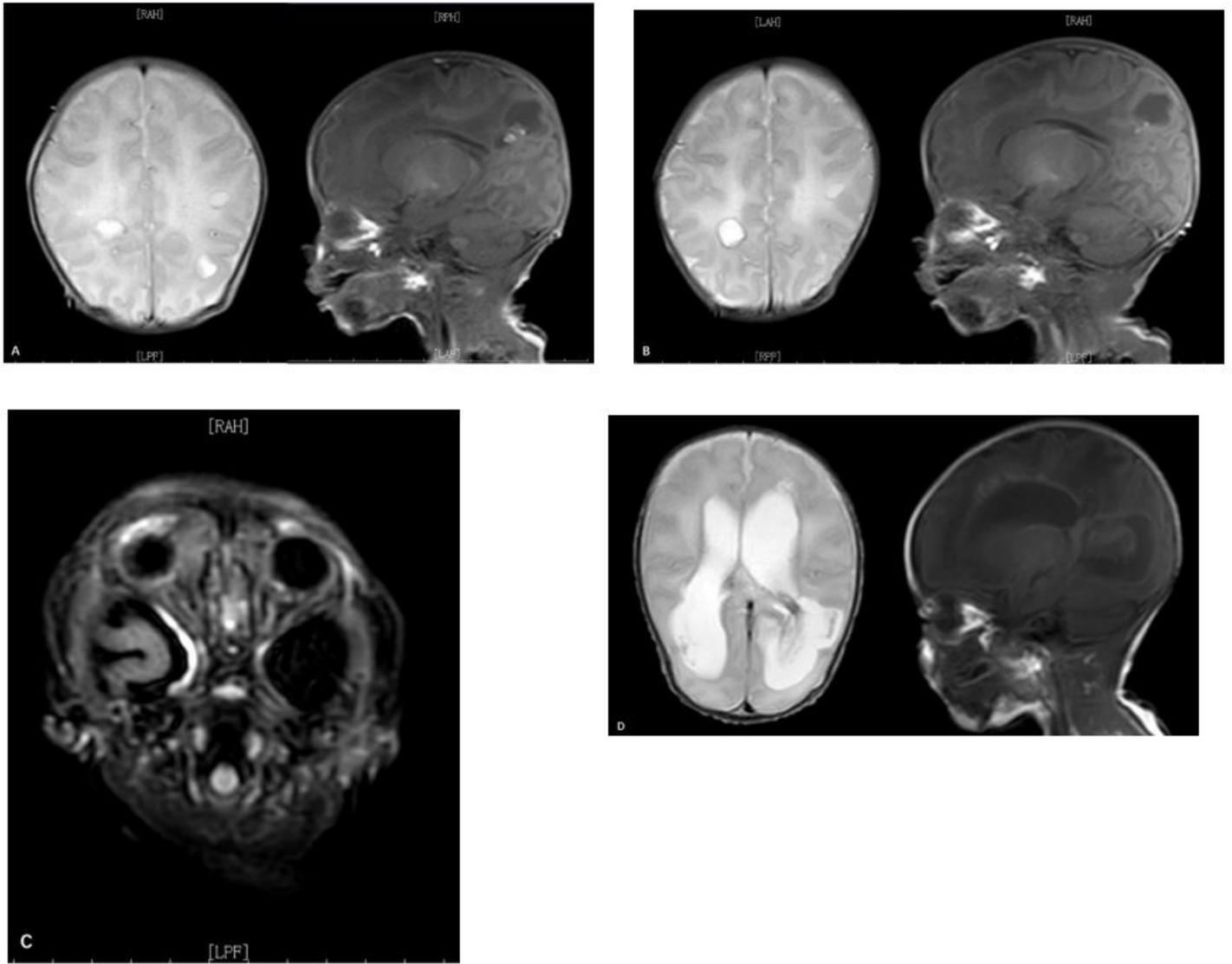


Figure 1

A, B show hemorrhagic liquefactive necrosis of the left hemisphere. Figure A shows abnormal high signal at frontoparietal temporal lobes on both sides, T1WI sagittal view mixed low point high signal, T2WI shows high signal. Figure B shows the reexamination after two weeks of treatment: it shows multiple patchy abnormal high signal at frontoparietal temporal lobes on both sides, with similar range of that of Figure A, spotted signals of high signals of both T1WI, T2WI decrease; while there is no obvious change where T2WI has high signal, T1WI has low signal (softening lesions). C shows T2-flair enhancement. Right temporal meningeal enhancement. Figure C: T2-flair after enhanced, obvious enhancement of about 2.8 cm is seen on the right temporal meninx, right temporal meninx enhances. D encephalocoele and parietal lobe on both sides show platy low T1 signal, high T2 signal, with ill-defined borders, partially connected to the rear corners of encephalocoele on both sides, encephalocoele on both sides are enlarged, while diocoele and epicoele do not show obvious enlargement.