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Early onset neonatal bacterial meningitis in term infants: the clinical features, perinatal conditions, and in-hospital outcomes

A single center retrospective analysis

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Abstract

To compare clinical features and outcomes between early and late onset of neonatal bacterial meningitis (NBM).

Patients were allocated in 2 groups: early onset neonatal bacterial meningitis (ENBM) and late onset neonatal bacterial meningitis (LNBM). Data analysis includes asphyxia at birth, premature rupture of membranes (PROM), amnionitis, amniotic fluid contamination, maternal age, clinical manifestations of the patients, laboratory findings, radiological results, complications related to meningitis, duration of hospitalization and therapeutic effect.

There was no difference in gender, birth weight, gestational age, and incidence of asphyxia between 2 groups. The incidence of PROM, chorioamnionitis and amniotic fluid contamination, proportion of small-for-gestational-age infants, convulsions, intracranial hemorrhage, hyperbilirubinemia, and the protein level of cerebrospinal fluid in ENBM group were higher than that in LNBM group ($P < .05$); the proportion of fever, elevated C-reaction protein and the abnormal of platelet counts in LNBM group was higher than that in ENBM group ($P < .05$). There was no difference in the incidence of complications and hospitalization time between 2 groups. The rate of effective treatment in LNBM group was significantly higher than that in ENBM group ($P < .05$).

Patients with conditions of amniotic fluid contamination, chorioamnionitis, small-for-gestational-age and PROM might be more prone to develop ENBM and ENBM had worse outcomes than LNBM.

Abbreviations: CSF = cerebrospinal fluid, ENBM = early onset neonatal bacterial meningitis, ICH = intracranial hemorrhage, LNBM = late onset neonatal meningitis, NBM = neonatal bacterial meningitis, NBNA = neonatal behavioral neurological assessment, PROM = premature rupture of membranes, SGA = small-for-gestational-age.

Keywords: bacterial meningitis, cerebrospinal fluid, clinical study, early neonates, group B Streptococcus (GBS), imaging, intrapartum antibiotic prophylaxis (IAP)

1. Introduction

For decades, despite of the application of novel treatments such as monoclonal antibodies or the use of steroids and antibiotics, Neonatal bacterial meningitis (NBM) remains a devastating infectious disease of central nervous system among newborn infants and the long term outcomes of this disease has not yet been improved.[1,2] To optimize the outcomes, rapid recognition and early initiation of antimicrobial therapy is crucial,[3] however, due to its subtle clinical signs, early awareness and intervention of this disease might be challenging. Early-onset neonatal bacterial meningitis (ENBM) refers to infants who develop bacterial meningitis within 1-week after birth. These newborns are in

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The datasets generated during and/or analyzed during the current study are publicly available.

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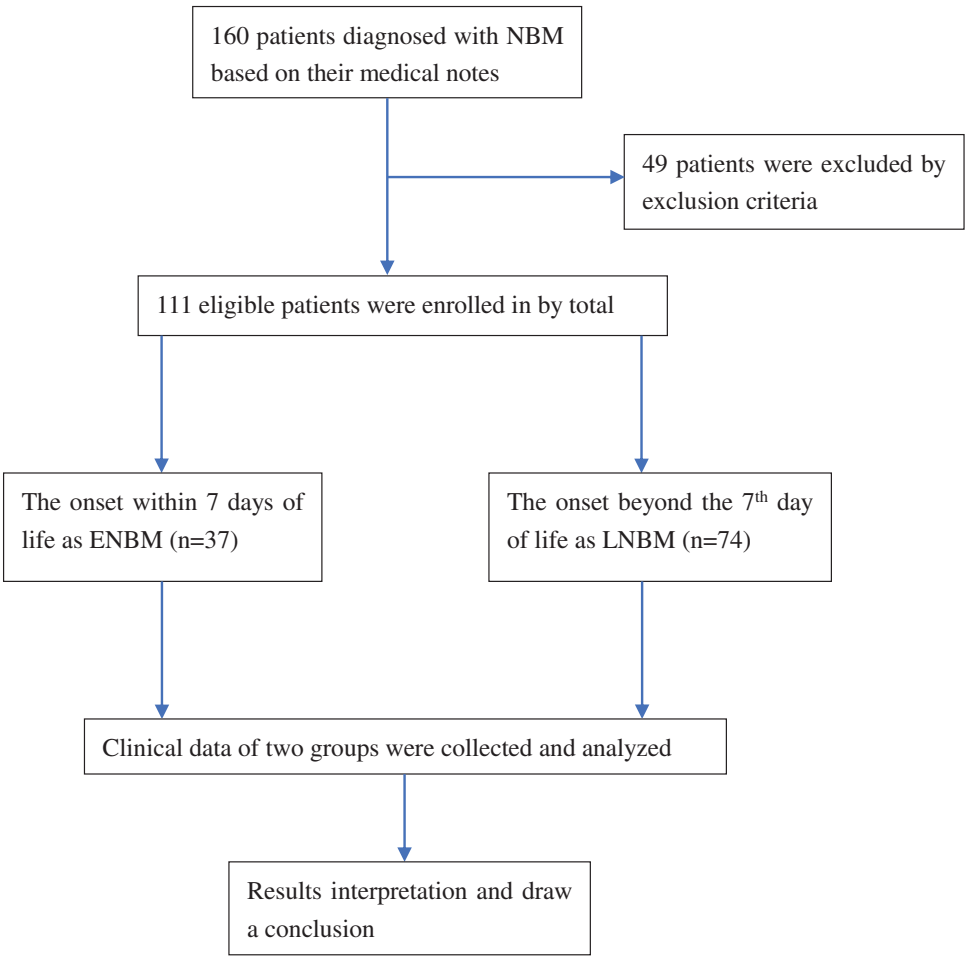

Figure 1. The flow chart of study design.

transition from the intrauterine to extrauterine environment, during which they have to face the highest risk of neonatal mortality. Among all the causes of neonatal death, a major one is bacterial meningitis. In terms of studies in China,[4] mortality of NBM in the recent 5 years is 9.1% and neurological complications occur at a rate of 5.9%. Nonetheless, to date, no domestic report on early NBM can be found. This study therefore provides a retrospective analysis of clinical characteristics of early NBM based on cases from the Department in the recent two and a half years, hopefully to render clinicians more informed of the disease.

2. Methods

2.1. Subjects

Data of neonatal infants who were diagnosed with NBM and hospitalized in the Neonatology Department of The Affiliated Xuzhou Children's Hospital of Xuzhou Medical University between January 1st, 2016 and June 1st, 2018, were collected in this study.

2.2. Study design

One hundred sixty patients' medical record were carefully reviewed and 49 were abandoned based on exclusion criteria, ultimately, 111 cases were registered in by eligibility requirements including 37 ENBM cases and 74 late onset neonatal meningitis (LNBM) cases. Clinical data of the 2 groups of patients were collected and analyzed. The flow chart of study design was presented in Fig. 1. Diagnostic criteria for neonatal bacterial meningitis in practice of the review "Bacterial meningitis in the neonate: Clinical features and diagnosis" published on Pediatrics 2017 was taken as reference[5] in this study and the clinical diagnosis was based on clinical manifestations, cerebrospinal fluid (CSF) test of the affected infants. Positive CSF culture or smear result provided identification of the disease. This study was approved by the Medical Ethics Committee of Xuzhou Children's Hospital of Xuzhou Medical University.

2.3. Eligibility requirements were as follows

(1) Term infants with gestational age more than or equal to 37 weeks;
(2) have no any severe congenital abnormalities or inborn errors;
(3) diagnosed with NBM admitted in by criteria mentioned before and
(4) with whole necessary laboratory and radiological examinations.

Table 1

General situations of patients, birth, and maternal age.

Group	N	Male (n,%)	gestational age (W)	Birth weight (kg)	SGA (n,%)	Asphyxia (n,%)	PROM and chorioamnionitis before labor (n, %)	Amniotic fluid contamination (n,%)	Cesarean section (n,%)	Maternal age (yrs)
ENBM Group	37	20(54.1)	39.15 ± 1.75	3.25 ± 0.57	8 (21.6)	8 (21.6)	10 (27.0)	13 (35.1)	13 (35.1)	27.43 ± 4.36
LNBMgroup	74	34 (45.9)	39.10 ± 1.62	3.37 ± 0.50	5 (6.8)	9 (12.2)	6 (8.1)	14 (18.9)	28 (37.8)	28.18 ± 4.94
χ^2/t		0.649	0.179	0.969	3.93	2.492	6.651	4.742	0.367	0.698
P		0.42	0.858	0.336	0.047	0.114	0.01	0.029	0.544	0.487

ENBM = early onset neonatal bacterial meningitis, LNBM = late onset neonatal bacterial meningitis, PROM = premature rupture of membranes, SGA = small for gestational age.

2.4. Exclusion criteria were as follows

(1) Incomplete clinical manifestations and related laboratory examinations and imaging which affected data collection;
(2) neonates with congenital hydrocephalus;
(3) other diseases complicated by bacterial meningitis during hospitalization.

2.5. Study allocation

The patients were allocated into 2 groups depending on age at onset (days): early-onset neonates group (ENBM group, onset within 1-week postnatal age) and late-onset neonates group (LNBM group, onset between 7- and 28-day postnatal age).

2.6. Treatment evaluation[4]

Healed: asymptomatic and CSF test turns into normal, no complication occurs.

Improved: asymptomatic but CSF test is not entirely normal, no complication occurs. Death: died during hospitalization or died in other medical institutions within 3 days after discharge against medical advice. Unhealed: clinical symptoms show no improvement and complications occur. Healed and improved are regarded as indicators of effective treatment. Follow-up was conducted on patients after discharge against medical advice or discontinuing therapy by phone call.

2.7. Data collection

Patients data: gender, gestational age, birth weight, small-for-gestational-age (SGA) and perinatal asphyxia. Maternal data: age, premature rupture of membranes (PROM), infectious diseases, chorioamnionitis, amniotic fluid contamination and delivery mode. Patients' clinical manifestations: fever, poor feeding, convulsion, hyperbilirubinemia, altered of muscle tone (hypertonic or hypotonic), and anterior fontanel bulging. Laboratory tests: C-reactive protein, platelet counts and blood culture; CSF cell counts, CSF biochemical panel, CSF smear and culture. Radiological findings: include intracranial hemorrhage (ICH) detected by B-mode ultrasonography, magnetic resonance imaging or computed tomography within 3 days after diagnosis, and subdural effusion and hydrocephalus after treatment. Hospitalization time and treatment outcomes.

2.8. Statistical analysis

Collected data were analyzed using SPSS (version 19.0) statistical software (SPSS, Chicago, IL). Variables complied with normal distribution were expressed as mean ± deviation (M ± SD) and nonnormatively distributional variables were expressed as M (P25, P75). The independent Student *t*-test was utilized to compare normal distributional variables while the Mann–Whitney *U* test was used to compare skewed distributional variables. Categorical variables were analysed by χ^2 tests or Fisher exact probabilities test. $P < .05$ was considered statistically significant.

3. Results

3.1. General situations of patients

One hundred eleven NBM cases matched the eligibility requirements, among which 37 cases were ENBM and 74 were LNBM. There was not any statistically significant difference in the gender, gestational age and birth weight between the 2 groups ($P > .05$), but the proportion of SGA in ENBM group was notably higher than that in LNBM group ($P < .05$). The results are presented in Table 1.

3.2. Perinatal factors

No significant difference in the proportion of perinatal asphyxia between the 2 groups ($P > .05$). The incidence of PROM and maternal upper respiratory tract infection in ENBM were significantly higher than that of LNBM, maternal diarrhea, chorioamnionitis before labor, and the proportion of amniotic fluid contamination in ENBM group were higher than that of LNBM group ($P < .05$). There was no significant difference in cesarean section rate and maternal age between the 2 groups ($P > .05$). The results are shown in Table 1.

3.3. Clinical manifestations and physical examination

There was no significant difference between the 2 groups in terms of poor feeding, altered muscle tone and bulging anterior fontanel ($P > .05$). The proportion of convulsion and hyperbilirubinemia in ENBM group was notably higher than that in LNBM group, while the proportion of fever was lower than that in LNBM group ($P < .05$). The results are shown in Table 2.

3.4. Laboratory and radiological findings

No notable difference in the CSF cell counts and glucose level between the two groups ($P > .05$). LNBM group showed higher C-reactive protein level, while ENBM group showed notably higher protein level in CSF. Abnormal platelet counts in ENBM group were lower than that in LNBM group and the proportion of ICH was significantly higher than LNBM group ($P < .05$). The results are presented in Table 2.

Table 2

Clinical manifestations, physical examination, and auxiliary tests.

Group	N	Fever (n, %)	Poor feeding (n, %)	Convulsions (n, %)	Hyperbilirubi-nemia (n, %)	Altered muscle tone (n, %)	Bulging anterior fontanel (n, %)	CSF cells ($\times 10^6$/L)*	CSF protein (g/L)*
ENBM Group	37	31 (83.8)	29 (78.4)	8 (21.6)	11 (29.7)	6 (16.2)	6 (16.2)	38,533	0.65,2.53
LNBM group	74	72 (97.3)	46 (62.2)	4 (5.4)	6 (8.1)	3 (4.1)	8 (10.8)	30,710	0.51,1.04
χ^2/t/Z		4.866	2.96	5.398	8.891	3.401	0.123	–0.46	–2.17
P		0.027	0.085	0.02	0.003	0.065	0.725	0.646	0.03

CSF glucose (mmol/L)	CRP (mg/dl)*	Abnormal PLT (n, %)	ICH (n, %)
2.5 ± 1.16	12.7, 22.3	16 (43.2)	16 (43.2)
2.4 ± 0.68	18.8, 57.4	52 (70.3)	2 (2.7)
0.662	3.52	7.592	29.03
0.51	0.015	0.006	<0.001

* Represents *Z* value.

CRP = C-reactive protein, CSF = cerebrospinal fluid, ENBM = early onset neonatal bacterial meningitis, ICH = intracranial hemorrhage, LNBM = late onset neonatal bacterial meningitis, PLT = platelet counts.

3.5. Bacteria culture of body fluids

Seven positive blood cultures were identified in ENBM group with 1 case of Micrococcus luteus, 2 Streptococcus agalactiae, 2 Staphylococcus hemolyticus, 1 Stenotrophomonas maltophilia and 1 Staphylococcus aureus but no positive CSF cultures were obtained. In LNBM group, 9 positive blood cultures were identified with 2 cases of Streptococcus agalactiae, 2 human staphylococcus, 3 Staphylococcus aureus and 1 Staphylococcus hemolyticus, among which 1 patient was diagnosed as having multidrug-resistant Acinetobacter baumannii with positive blood and CSF cultures.

3.6. Duration of hospital stay, complications and outcomes

There was not any notable difference in hospital stay between the 2 groups ($P > .05$) and no difference in the proportion of cases complicated with hydrocephalus and subdural effusion ($P > .05$). Treatment outcomes showed significant difference between the 2 groups ($P < .05$). The results are shown in Table 3.

4. Discussion

According to previous study,[6] 44% of under-5 deaths occur in the neonatal period, and bacterial meningitis plays a major role in neonatal mortality. It is reported[7–10] that the incidence of NBM worldwide is 0.8/1000 to 6.1/1000. A multi-center survey in Hebei Province, China, shows that[11] the incidence of NBM is 0.5/1000 among live-birth neonates. Study shows[12] that bacterial infections occur at a rate of 0.1% to 1% among newborns within 72 hours of life, accounting for about half of neonatal infections, and the mortality rate is projected to around 20%. Therefore, the early neonatal period is crucial for neonatal health care. The majority of neonatal infections are related to intrauterine infection,[13–17] and chorioamnionitis and maternal PROM are major factors which are consistent with our study.

The manifestations of NBM can be subtle and the medical staff is usually caught off by its rapid progress. In our study, there was no significant difference between the 2 groups including poor feeding, alteration of muscle tone and bulging anterior fontanel. Meanwhile, ENBM group showed a significantly lower rate of febrile than LNBM group. Therefore, symptoms of ENBM are more prone to be underestimated and misdiagnosed. In addition, the proportion of children with hyperbilirubinemia in ENBM group was notably higher than that in LNBM group and one probably reason for this is that ENBM group patients were going through the period vulnerable to physiological jaundice when excessive bilirubin was produced, and infection further affected the acid-base balance of body fluid leading to a disorder of metabolic enzyme activity for bilirubin and hence hyperbilirubinemia.

Clinical signs of NBM are nonspecific even asymptomatic, unless patients who are critically ill, could manifest with fever, convulsion, hyperbilirubinemia, poor feeding and so on. Frequently, findings associated with neonatal sepsis (eg, temperature instability, respiratory distress, jaundice, apnea) are manifest. Central nervous system signs (eg, lethargy, seizures [particularly focal], vomiting, irritability) more specifically suggest severe meningitis. Indeed, in our study, the incidence of febrile, seizure, jaundice as well as ICH did higher in EMBM group indicating more severe conditions and poorer prognosis, which consist with previous studies.[18,19]

Table 3

Hospitalization time and outcomes.

Group	No.	Hospitalization (d)	Complications		Treatment outcomes		
			Hydrocephalus (n, %)	Subdural effusion (n, %)	Healed and improved (n, %)	Unhealed (n, %)	Death (n, %)
ENBM group	37	25.54 ± 5.41	2 (5.4)	3 (8.1)	26 (70.3)	8 (21.6)	3 (8.1)
LNBM group	74	24.63 ± 6.43	2 (2.7)	4 (5.4)	65 (87.8)	7 (9.5)	2 (2.7)
χ^2/t		0.676	0.032	0.030	5.15	2.425	0.526
P		0.501	0.857	0.863	0.023	0.119	0.428

ENBM = early onset neonatal bacterial meningitis, LNBM = late onset neonatal bacterial meningitis.

Since clinical studies regarding ENBM are scarce, but the researches of neonatal early onset sepsis are numerous. It is known that most of the NBM cases are secondary to neonatal sepsis.[20] Moreover, early onset sepsis is firmly related to the development of neonatal meningitis.[21] Many previous studies bring home that the risk factors of early onset sepsis are: premature birth, SGA as well as maternal infections during perinatal period,[22–24] bring it together, the aforementioned risk factors may also attribute to the development of ENBM. In our study, the incidence of PROM, chorioamnionitis, amniotic fluid contamination and SGA in ENBM group was considerably higher than in LNBM group, which consists with previous studies mentioned before.

CSF test is essential to the diagnosis and prognosis of NBM. Typical findings of NBM include a remarkable elevated cell counts, predominance of multinucleated cells, increased protein level and decreased glucose. Other studies have demonstrated that the increase of CSF protein[25–28] is related to poor outcome. In our study, CSF protein level in ENBM group was significantly higher than that in LNBM group, which may suggest that ENBM group has dimmer outcome, but further follow-up is necessary. An observational trial performed by Tan et al revealed that a high level of CSF protein is a strong predictor for poor outcome in NBM patients,[28] in our study, the CSF protein level was much higher in ENBM group compared to LNBM group, which might also indicate that the ENBM patients have poorer outcome.

CSF smear or culture is the golden rule for pathogenic bacteria detection in bacterial meningitis diagnosis. Chinese domestic study shows that[11] the top 3 pathogenic bacteria are Escherichia coli, coagulase-negative staphylococcus and streptococcus while most of the developed countries are group B streptococci and listeria. Prenatal screening for GBS and intrapartum antibiotic prophylaxis (IAP) can reduce the incidence of NBM by over 90%.[5,29–32] In this study, positive blood culture rates in ENBM and LNBM group were 18.9% and 12.2% respectively, significantly lower than data in previous studies.[11] This is probably due to the fact that the majority (92/111) of the infants involved in this study were transferred from other hospitals where they might have received anti-infection treatment affecting the results of blood culture. Meanwhile, this study identified one case of multidrug-resistant Acinetobacter baumannii infection, and the patient was demised finally.

Currently, attributing to the "2-child policy" issued in China, the number of elderly parturient women is rising, which results in higher rate of preterm labor and higher VLBW infants population than before, and techniques such as mechanical ventilation, deep venous catheterization as well as broad-spectrum antibiotics are put in use, resulting in an increase incidence of drug-resistant bacteria infections that has subsequently caused great difficulties in clinical treatment, which requires considerable attention of clinicians. Within 3 days after diagnosis, 16 cases of intracranial hemorrhage (12 subarachnoid hemorrhage, 2 intraventricular hemorrhage and 2 cerebral parenchymal hemorrhage) were found in ENBM group by imaging. The number was significantly larger than that of LNBM group and the result consists with the study by Zhang et al.[33] Such phenomenon may related to the sensitivity of the cerebral vascular wall to basic products during early neonatal period, oxygen free radicals for instance, released due to ischemic changes during meningitis.[34]

There was no notable difference in hospitalization time and complication rate between the 2 groups, but treatment outcomes differed significantly. The rate of effective treatment in ENBM group was markedly lower than that in LNBM group, which may be in relation to the high rate of intrauterine infection in ENBM group, influencing immune system function and anti-infection treatment effect.

NBM is a critical disease among neonates due to its potential risks of causing short term death and sequelae such as epilepsy and cerebral palsy. Clinical severity of the disease is associated with abnormalities such as intrauterine infection, CSF protein concentration and the type of pathogenic bacteria, which requires great attention of clinicians. However, beyond this single-center retrospective study, there remains a need to conduct more data collection and prospective multi-center randomized controlled trials in order to facilitate further discussion of clinical and laboratory examination, treatment outcome and prognosis of early NBM.

4.1. Research limitations and strengths

Firstly, the sample size of this study was small, because the incidence of neonatal bacterial meningitis is low after all and this is just a single center study. Secondly, we did not adopt the electroencephalogram (EEG) and neonatal behavioral neurological assessment to further evaluate patients neurological outcomes which may be more important and appropriate for our study. We hope we could improve it in the future. Thirdly, the subjects in this study were restricted to term infants, whereas, the preterm infants are more vulnerable to meningitis, and the outcomes of which are poorer than term infants,[4,18,35] so we will conduct a similar study among premature neonates in the future. Fourthly, a confounding factor was not adjusted, which was the glycemic status of patients at the onset of meningitis, and the fluctuation of blood sugar may lead to significant neurological impairment in neonates that biases our results, this should be aware of at the beginning of study, we will revise it in the future. Other confounders like the record errors generated by medical staff, heterogeneity of CSF sampling technique caused by different health care providers should also have been noted, we will improve it by expanding sample size and standardizing procedures in the future.

To our knowledge, the study focusing on the early-onset neonatal bacterial meningitis is so rare, and this is the first time to compare the differences of clinical features, laboratory findings, perinatal conditions and short-term outcomes between ENBM and LNBM patients. Although this is a retrospective observational study done in a single center, the results yielded out also showed some valuable information regarding neonatal neurological infections offering some help to clinicians and pediatricians.

5. Conclusion

Patients with conditions of amniotic fluid contamination, chorioamnionitis, SGA and PROM might be more prone to develop ENBM and ENBM had worse outcomes than LNBM. Based on the results of the present study, perinatal infections played an essential role in the ENBM development, moreover, the therapeutic effect of ENBM patients was dimmer than that of LNBM patients. Therefore, preventing gravidas from being infected, such as intrapartum antibiotics for GBS prophylaxis (IAP) administration, caution perinatal hygiene and staying vigilant about the signs regarding maternal infections are critical.

Author contributions

Conceptualization: Xueping Zhu, Zhenguang Li.
Data curation: Zhenguang Li.
Formal analysis: Zhenguang Li.
Supervision: Xueping Zhu.
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Writing – review & editing: Shan He.

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