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An Analysis of the Clinical Characteristics and Prognosis of Group B Streptococcal Infection in Neonates and Infants

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Abstract

Aim: To explore the clinical characteristics and challenges involved in treating group B streptococcal (GBS) infection in neonates and infants.

Methods: Clinical data of group B streptococcal infections in new-borns and infants (≤ 3 months old) admitted to The Children's Hospital, Zhejiang University School of Medicine, Department of Neonatology from May 2015 to January 2018 were retrospectively analysed. The clinical characteristics of group B streptococcal infection, difficulties involved in its treatment and its prognosis were analysed.

Results: A total of 52 patients were studied, among which, 29 were males and 23 were females. There were 39 neonates ageing from zero to 28 days and 13 infants ageing from 29 to 90 days. The age of onset was <7 days in 15 cases and >7 days in 37 cases. Premature infants were 12 in number and full-term infants, 40. The average duration from onset to hospitalization ranged from half a day to one day. The average hospitalization time was 12.45 ± 5.28 and 36.27 ± 17.68 days in the septicemia and meningitis groups respectively. The main clinical manifestations in the septicemia group were fever (77.27%), poor feeding, reduced crying and movement (59.09%) and finally respiratory distress (27.27%), while fever (96.15%), poor feeding, reduced crying and movement (92.31%), bulging of anterior fontanel or seizure (50%), were noted in the meningitis group. A decrease in white blood cells (WBC) was observed in 45.83% of cases, an increase in 22.92% of cases, and the remaining 31.25% were in the normal range, occurrence of thrombocytopenia was lower than 10.42% and C-reactive protein increased significantly in both groups. However, the recovery time of C-reactive protein in the septicemia group was significantly shorter compared to the meningitis group (7.33+3.31 days, 14.96+9.55 days, P<0.01). Cerebrospinal fluid manifestations: When cranial MRI of cerebrally injured and normal patients were compared, a significant difference was noted in their respective CSF cell count (3964+4279/ul, 1745+2396/uL, P<0.05), sugar level (0.94+0.9 mmol/L, 1.80+0.999 mmol/L, P<0.01), protein content (5366.0+1486.8 mg/L, 1591.6+860.2 mg/L, P<0.01) and positive bacterial smear (60%, 7%, P<0.01). Drug sensitivity: 52 cases of GBs were 100% sensitive to ampicillin, penicillin, vancomycin, linezolid and tigecycline. All patients were resistant to clindamycin, 84.61% to tetracycline and 23.08% to levofloxacin or ciprofloxacin.

Discussion: In the septicemia group, 68.2% (15/22) a combination of penicillin or ampicillin + cephalosporin was chosen, while in the meningitis group, 73.1% (19/26) of children were given a combination of either (a) penicillin or ampicillin + ceftriaxone or cefotaxime palate, or (b) vancomycin meropenem. Patients who had a slow CSF recovery or recurrent fever two weeks post initial antibiotic treatment were given vancomycin or linezolid or rifampicin in addition to their baseline treatment. Two patients in the local infection group did not use systemic antibiotics, and two patients chose a mono-antibiotic therapy. 8. Complications and prognosis: All patients in the septicemia group recovered and met discharge criteria, 4/22 had shock, 4/22 had respiratory distress syndrome, 1/22 had toxic enteroparalysis as complication (s). In the meningitis group, 92.3% (24/26) of the patients were discharged from hospital with normal or improved cerebrospinal fluid results (31.38 (+19.82 days), 1 child was discharged without recovery and 1 child unfortunately died; 10/26 of them had extensive brain injury, 6/26 had subdural effusion, 4/26 had shock, 3/26 had liver injury, and 2/26 had cerebral hernia.

Conclusion: Neonatal and infant GBS infections can cause sepsis, meningitis, respiratory distress syndrome, urinary tract infections, skin and umbilical infections, which progress rapidly and hence, need urgent medical intervention. Among all, the treatment of group B streptococcal suppurative meningitis is particularly challenging, thereby leading to a longer period of hospitalization and the risk of serious neurological complications is high. The authors believe that attention should be paid to the screening of group B *Streptococcus* (GBs) during pregnancy and also during nursing of the skin, umbilical cord and oral cavity of new-borns for early prevention of the infection.

Keywords: *Streptococcus agalactiae*; Neonates; Infants; GBS

Introduction

Group B *Streptococcus*, also known as *Streptococcus agalactiae* is a Gram-positive beta-hemolytic *Streptococcus*. Since the early 1970s, *Streptococcus agalactiae* has been one of the most common pathogens causing neonatal infections in European and American countries. During the past few years, neonatal *Streptococcus agalactiae* infections in China was considered to be relatively rare, however, in recent years, the incidence of sepsis and meningitis caused by GBS infection in China has been constantly on the rise, and is now one of the main pathogens causing severe infection in new-borns and infants [1]. The onset and progression of the disease is rapid, especially in GBS purulent meningitis, thereby leading to a longer period of hospitalization and the risk of serious neurological complications is high. The authors believe that paediatricians, especially neonatologists, should pay special attention to this infection in clinical practice. This study retrospectively analysed the clinical data of neonates and infants (≤ 3 months old) with *Streptococcus*

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agalactiae infection admitted to The Children's Hospital, Zhejiang University School of Medicine, Department of Neonatology from May 2015 to January 2018, and discusses the clinical characteristics and difficulties encountered during treatment of neonates and infants with *Streptococcus agalactiae* infection.

Subjects and Methods

Subjects

Neonates and infants (≤ 3 months old) with GBS positive blood culture and/or cerebrospinal fluid or umbilical cord secretion or urine culture who were treated in our hospital from May 2015 to January 2018 in our hospital were chosen and their data were analysed retrospectively.

Inclusion criteria and grouping

Blood, CSF and secretions were collected and cultured upon admission of patients, whereby drug sensitivity was tested upon positive results of GBS culture. The septicemia group consisted of patients who had a positive blood culture for GBS and a normal CSF with a negative GBS culture. The meningitis group consisted of patients who had a positive blood/CSF GBS culture and whose CSF biochemistry met the standard for the diagnosis of purulent meningitis. The local Infection Group consisted of children who had a positive culture of GBS from umbilical cord secretions or urine and a negative one for blood culture. Onset before <7 days of age was considered as early onset and beyond 7 days as late onset.

Diagnosis criteria

According to the diagnostic criteria from the 4th edition of Practical Neonatology, children who had the following symptoms of infection were considered: (1) abnormal body temperature, poor feeding, reduced crying and movement, respiratory distress, pathological jaundice, cold extremities, seizures and/or bulging of the fontanel; (2) increased WBC count (>20 × 10^2 g/L) or decreased WBC count (<5 × 10^2 g/L) and/or decreased platelet count (<100 × 10^2 g/L), increased C-reactive protein and procalcitonin; (3) Increase in CSF WBC, predominated polynuclear cell, a decrease in glucose level and increase in protein content; (4) A positive blood and/or CSF or umbilical cord secretion or urine culture of GBS.

Treatment and outcome

Patients with unclear diagnosis upon admission were given empirical antibiotic treatment either (a) Penicillin or Ampicillin+third generation cephalosporin or (b) Vancomycin × Meropenem. After a diagnosis of GBS was established, patients were given Penicillin or Ampicillin+third generation cephalosporin. Two weeks post initial treatment, vancomycin or linezolid or rifampicins were added to the baseline therapy for patients who had a non-satisfactory cerebrospinal fluid or recurrent fever. Re-examination of CSF and/or blood culture was carried out 3 to 7 days after posting initial treatment to evaluate recovery status. Simultaneously, blood test, C-reactive protein, procalcitonin, cytokines, ultrasonography and magnetic resonance imaging (MRI) were routinely carried out. For septicemia patients, discharge criteria were based on improvement of clinical symptoms, normalization of inflammatory biomarkers and negative blood culture. Meningitis children who had a normal CSF routine and biochemistry, two consecutives negative GBS culture and resolution of clinical symptoms were discharged.

Statistical methods

SPSS 17.0 statistical software was used. Qualitative data were expressed by percentage and chi-square test was used for analysis, while quantitative data were expressed in the form of mean (± standard deviation) and t-test was used for comparisons between groups. A p-value of $P<0.05$ was considered as being significant.

Results

General data

A total of 52 cases were included. There were 29 males and 23 females. The age of onset ranged from 0 to 7 days in 15 cases and 8 to 90 days in 37 cases. There were 12 preterm infants with gestational age <37 weeks and 40 full-term infants >37 weeks.

Clinical manifestations and laboratory examinations

Clinical manifestations and laboratory examinations are shown in Table 1.

The relationship between CSF lab values and prognosis

When cranial MRI of cerebrally injured and normal patients were

Variables	Septicemia Group%①	Meningitis Group%②	Local Infection Group %	p-value
Total Cases	22	26	4	--
Premature	7 (31.8%)	5 (19.2%)	0	--
Term	15 (68.2%)	21 (80.8%)	4	--
Early-Onset	8 (36.4%)	4 (15.4%)	3 (75%)	--
Late-Onset	14 (63.6%)	22 (84.6%)	1 (25%)	--
Fever	17 (77.3%)	25 (96.2%)	3 (75%)	--
Pathological Jaundice	5 (22.7%)	10 (38.5%)	3 (75%)	--
Poor feeding, reduced crying and movement	13 (59.1%)	24 (92.3%)	0	--
Respiratory Distress	6 (27.3%)	2 (7.7%)	0	--
Bulging Fontanel and Seizure	0	13 (50.0%)	0	--
Increased WBC	5 (22.7%)	6 (23.1%)	0	--
Leucopenia	9 (40.1%)	13 (50.0%)	0	--
Normal WBC	8 (36.4%)	7 (26.9%)	4	--
Thrombocytopenia	2 (9.1%)	3 (11.5%)	2	--
CRP Recovery Time (days)	7.33 ± 3.31	14.96 ± 9.55	0	<0.01 (①and②)
Hospitalization Time (days)	12.45 ± 5.28	36.27 ± 17.68	6.75 ± 1.85	<0.01 (①and②)

Table 1: Characteristics of the different groups.

compared, a significant difference was noted in their respective CSF cell count (3964+4279 /uL, 1745+2396/uL, P<0.05), sugar level (0.94+0.9 mmol/L, 1.80+0.999 mmol/L, P<0.01), protein content (5366.0+1486.8 mg/L, 1591.6+860.2 mg/L, P<0.01) and positive bacterial smear (60%, 7%, P<0.01).

Drug sensitivity

All the 52 cases of group B *Streptococcus* were sensitive to ampicillin, penicillin, vancomycin, linezolid, tegacycline. All patients were resistant to clindamycin, 84.61% to tetracycline, 23.08% to levofloxacin or ciprofloxacin.

Treatment and prognosis

In the septicemia group, 68.2% (15/22) a combination of penicillin or ampicillin+cephalosporin was chosen, while in the meningitis group, 73.1% (19/26) of children were given a combination of either (a) penicillin or ampicillin+ceftriaxone or cefotaxime palate, or (b) vancomycin × meropenem. Patients who had a slow CSF recovery or recurrent fever two weeks post initial antibiotic treatment were given vancomycin or linezolid or rifampicin in addition to their baseline treatment. Two patients in the local infection group did not use systemic antibiotics, and two patients chose a mono-antibiotic therapy. All patients in the septicemia group recovered and met discharge criteria, 4/22 had shock, 4/22 had respiratory distress syndrome, 1/22 had toxic enteroparalysis as complications. In the meningitis group, 92.3% (24/26) of the patients were discharged from hospital with normal or improved cerebrospinal fluid results (31.38 (+19.82 days), one child was discharged without recovery and one child unfortunately died; 10/26 of them had extensive brain injury, 6/26 had subdural effusion, 4/26 had shock, 3/26 had liver injury, and 2/26 had cerebral hernia.

Discussion

Streptococcus agalactiae is found in the normal flora of the human respiratory tract, rectum and vagina. While it has weak pathogenicity in adults, it can trigger sepsis, purulent meningitis, pneumonia and other diseases in children. Its cell wall polysaccharide consists of an antigen belonging to group B; therefore, it is called group B *Streptococcus*?GBS, group B *Streptococcus*. GBS is currently considered to be most common pathogen causing bacterial infections in new-borns in Western countries [2,3]. A retrospectively French study analysed the etiology of purulent meningitis in 444 neonates from different paediatric wards during a course of seven years and concluded that GBS infections accounted for 59% of all infections, followed by Escherichia coli, which was 28% [4]. Domestic reports indicate that purulent meningitis caused by GBS infection has been constantly increasing during the last few years. However, after a revision of the routine screening and treatment protocol of *Streptococcus lactis* in 1996 and 2002 by the CDC in the United States, a significant decrease in the incidence of the infection was observed from the year 2003 to 2005 (0.3/100) as compared to 1.8/100 in 1990s. Despite the fact that GBS infection is at a relatively stable stage presently, studies show that the incidence of late-onset *Streptococcus agalactiae* infection has not decrease, but rather, increased [5-7]. GBS infection is usually classified into early and late type, according to the age of onset. Early-onset infections are mainly transmitted directly from mother to infant, especially during vaginal delivery. The main clinical manifestations are sepsis and respiratory distress, and a minority of them are meningitis. Late-onset infections are usually nasopharyngeal colonization and postnatal transmission of GBS manifesting 7-10 days after birth.

During the last 3 years, most of the patients with GBS infection admitted to this hospital were mainly new-borns and infants under 3 months of age. Early-onset GBS infections were mainly sepsis (53.3%, 8/15), and late-onset GBS infections were mainly purulent meningitis (59.5%, 22/37). Premature infants predominantly had septicemia and respiratory distress (58.3%, 7/12), while full-term infants mostly had suppurative meningitis (52.5%, 21/40). GBS infection in the group studied started in an acute fashion with rapid progression. Onset to admission lasted from half a day to one day. The clinical manifestations were fever (86.5%), poor feeding, reduced crying and movements (71.2%), respiratory distress (15%) and pathological jaundice (34.5%). Meningitis patients with seizure and bulging fontanel accompanied by neurological symptoms accounted for 50%, consistent with recent literatures [2-9]. A significant decrease in peripheral WBC count was observed, suggesting severe infection, but the occurrence of thrombocytopenia was relatively low. An increase in both procalcitonin and C-reactive protein was noted. However, the recovery time of CRP in meningitis group was significantly longer than that of the sepsis group, thereby reflecting the severity of inflammation explaining the longer period of time needed for recovery. Current data show that GBS is generally sensitive to penicillin and remains the first-line drug of choice for the treatment of GBS infection in new-borns. The resistance of GBS to erythromycin and lincomycin is relatively high. The 52 cases of GBS in this study were sensitive to ampicillin, penicillin, vancomycin, linezolid, tigecycline and its resistance to clindamycin and tetracycline. Therefore, penicillin+cephalosporins can be used as empirical drugs for suspected GBS infections. Vancomycin or linezolid are recommended for patients allergic to penicillin and cephalosporins.

Prognosis of GBS infection

Many literatures [2-11] show that the duration of purulent meningitis caused by GBS is longer as compared to other pathogens, despite timely use of sensitive antibiotics. CSF improvement takes longer time. For patients with brain injury and nerve damage, recovery time of CSF takes an average of 31.38 +19.82 days and the incidence of severe brain injury is 38.5%. The occurrence of severe brain injury is closely related to the number of CSF cells, its protein content, glucose level, positive results of bacterial smear. It was noted that patients with glucose level <1 mmol/L and with positive CSF GBS smear had a higher probability of brain injury. 3.8% of patients accounted for voluntary discharge before clinical resolution and death. This study has shown that timely treatment of sepsis, respiratory distress; local infection leads to a better prognosis and considerably reduces the course of the disease/complications.

Conclusion

To conclude, group B streptococcal infection in new-borns and infants have increased in recent years, which causes sepsis, meningitis, respiratory distress syndrome, urinary tract infections, skin and umbilical infections, with rapid onset and progression. The treatment of group B streptococcal suppurative meningitis is relatively difficult, leading to a longer hospitalization period and risk of serious neurological complications is high. A diagnosis of GBS infection should be considered in new-borns and infants <3 months old presenting with fever, respiratory distress, poor feeding, reduced crying and movement, bulging anterior fontanel, leukopenia and especially when seizure is also a notable manifestation. Blood culture and CSF examinations should be performed before antibiotics are used so that the appropriate pathogens are identified in the early stage. At the same time, attention should be paid to the screening of GBS during pregnancy and nursing of neonatal skin, umbilical cord and oral cavity, so that early prevention and intervention can be carried out.

Conflicts of Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Ethics committee The Children's Hospital, Zhejiang University School of Medicine.

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