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Clinical Features of 116 Near Term and Term Infants with Acute Bilirubin Encephalopathy in Eastern China

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Abstract ***Purpose:*** This study delineates the clinical features of near term and term infants with acute bilirubin encephalopathy (ABE) from east China and shares our experience in managing these patients. ***Methods***: This is a retrospective study conducted in a children's hospital in east China. Clinical charts of infants with ABE were reviewed. The data were collected by a detailed questionnaire and analysed. ***Results:*** From August 2004 to July 2011, 116 infants assessed to have developed ABE were recorded in this hospital. The infants had a mean birth weight of 3176±453 grams with gestational age of 38.1±1.6 weeks. Seventy infants (60.3%) were males. After admission, the highest bilirubin level was (486.0±169.4) μmol/L. The most common cause of ABE was ABO incompatibility (38, 32.8%), followed by sepsis and infection (14, 12.1%). Phototherapy was performed in 84.5% infants, and exchange transfusion was done in 45 infants (38.8%). Based on clinical bilirubin-induced neurologic dysfunction (BIND) scoring, 14 (12.1%), 83 (71.6%) and 19 (16.4%) infants were classified as subtle, moderate ABE and severe ABE respectively on admission. The severe ABE group had worse short-time outcomes than the subtle and the moderate ABE groups. ***Conclusions:*** Neonatal acute bilirubin encephalopathy in term and near-term infants is not a benign entity. It carries fairly high death rate and often leads to significantly poor short-term outcomes. BIND score should be evaluated after admission to evaluate short-time outcomes. Recognition of the whole clinical spectrum and progress of ABE is of paramount importance in the prevention and management of ABE.

Key words Acute bilirubin encephalopathy; Bilirubin-induced neurologic dysfunction; Infant; Newborn

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Introduction

Majority of healthy newborns develop clinical jaundice with increased concentration of total serum bilirubin (TSB). The outcomes for most infants are benign. However, infants with untreated, extremely high TSB levels can develop acute bilirubin encephalopathy (ABE). The incidence of ABE is unknown yet, but is reported to be rare in developed countries. A recent study from Canada reported an incidence of ~1 in 20 000 live births;[1] and a much lower incidence of 0.9/100 000 live births was reported from the United Kingdom.[2] But in developing countries, ABE is still a common complication of neonatal hyperbilirubinaemia. ABE occurs due to the toxic effects of free bilirubin on the neuronal cells in the basal ganglia, cerebellum and

brainstem nuclei in susceptible infants; and ABE may cause irreversible brain damage. Three phases of ABE have been described. An early acute phase is characterised by lethargy, hypotonia and poor suck; an intermediate phase by hypertonia (including opisthotonus and retrocollis), high-pitched cry, fever, moderate stupor or irritability; whereas in the advanced phase infants present with seizures, coma, apnea, pronounced retrocollis and opisthotonus, with death occurring in severe cases.[3,4] Prompt and effective treatment may be successful in preventing or reducing chronic kernicteric sequelae, therefore early diagnosis of ABE is vital to paediatricians. Shapiro indicated that the faster and the more aggressive the treatment, the more reversible and better the outcomes.[5]

The objective of this study was to describe the experience of ABE management from a tertiary children's hospital, China.

Methods

This observational study was conducted at the neonatal care unit in the Children's Hospital, Zhejiang University School of Medicine over a 7-year period (from August 2004 to July 2011). This hospital is a tertiary children's hospital providing general and specialist paediatric services including neonatal care to newborn babies referred from other government-owned hospitals and privately-owned health facilities in east China. The study was approved by the Research Ethics Committee of the Children's Hospital.

Eligibility

Inclusion criteria included infants with estimated gestational age ≥35 weeks and with ABE (early, intermediate or advanced). Infants with chromosomal disorders, cranio-facial malformations or family history of hearing loss since childhood were excluded. All patients were born at outside birthing facilities or at home. They were transferred to our unit due to hyperbilirubinaemia or ABE. History was obtained from the mothers or from the records of local hospitals using a questionnaire. Laboratory testing included total serum bilirubin, serum direct bilirubin, determination of blood group, Rh, glucose-6-phosphate dehydrogenase (G6PD) assay (qualitative method performed at the discretion of the attending staff), direct antibody test and admission blood culture when clinical signs of sepsis were suspected. Outcomes were ascertained by a review of post-discharge outpatient records.

Clinical Management

The patients were examined and followed by the resident doctor on call in the neonatal care unit. A neurologic evaluation was performed within 12 hours of admission using the bilirubin-induced neurologic dysfunction protocol (BIND score)[3,6] based on clinical signs characteristic of ABE.[7,8] The infants were managed according to the unit protocol based on the recommendations of the American Academy of Pediatrics (AAP) for the management of severe neonatal jaundice.[4] Two infants had been given herbs before admission. All babies were forbidden to be exposed to any heral tea during hospitalisation. Infants with bilirubin level exceeding the 95th percentile (high-risk zone) (Figure 1) received phenobarbitone orally for 3 days. The dosage was 5 mg. per kg. per day in two equally divided twelve-hourly doses. Our phototherapy units consisting of six blue fluorescent tubes were used and placed at a distance of 30 cm from the infants. Neonates were naked except for eye pads and a diaper for hygiene. Continuous phototherapy was implemented in 98 infants and only interrupted to allow for feeding. Infant position was changed every 2 hours to allow for maximal skin exposure to the light footprint. During phototherapy, bilirubin levels are determined at least one time every 8 hours and more frequently if deemed necessary by clinical judgment. The TSB level for discontinuing phototherapy depended on the age at which phototherapy was initiated and the cause of the hyperbilirubinaemia. In general, phototherapy may be discontinued when the TSB level falls below 239 μmol/L. Double volume exchange transfusion was performed according to the guideline in 2004 AAP guidelines (Figure 2). If isoimmune haemolytic disease was considered, especially for those with Rh and /or ABO incompatibility, intravenous immunoglobulin was applied after informed consent obtained from parents. If the infant had any clinical signs of ABE, he/she was subjected to magnetic resonance imaging (MRI) brain and brainstem auditory evoked potential (BAEP).

Definitions

(a) Acute bilirubin encephalopathy: ABE was defined in infants with TSB>342 μmol/L using abnormal muscle tone, mental status and cry pattern.[9-11]

(b) Kernicterus: kernicterus was the chronic and permanent clinical sequelae of bilirubin toxicity.[4]

(c) The bilirubin-induced neurologic dysfunction protocol: BIND score is used to evaluate changes in mental state, muscle tone, and cry; a score of 0 to 3 was assigned to

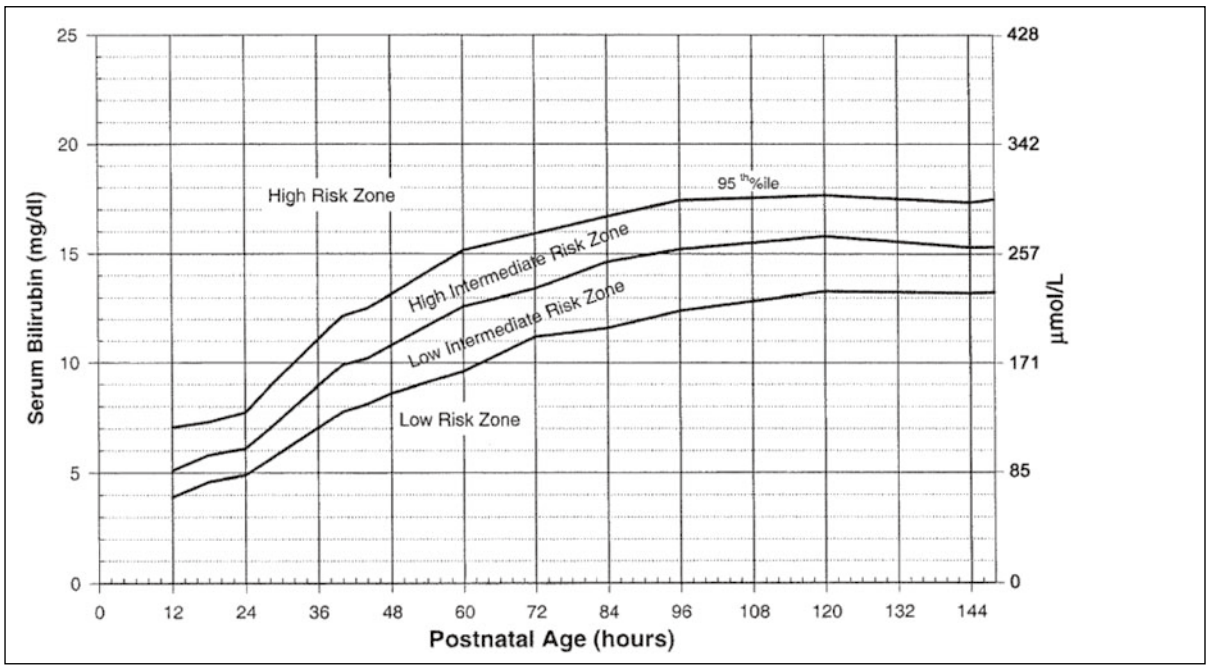

Figure 1 Nomogram for designation of risk in neonatal hyperbilirubinaemia.

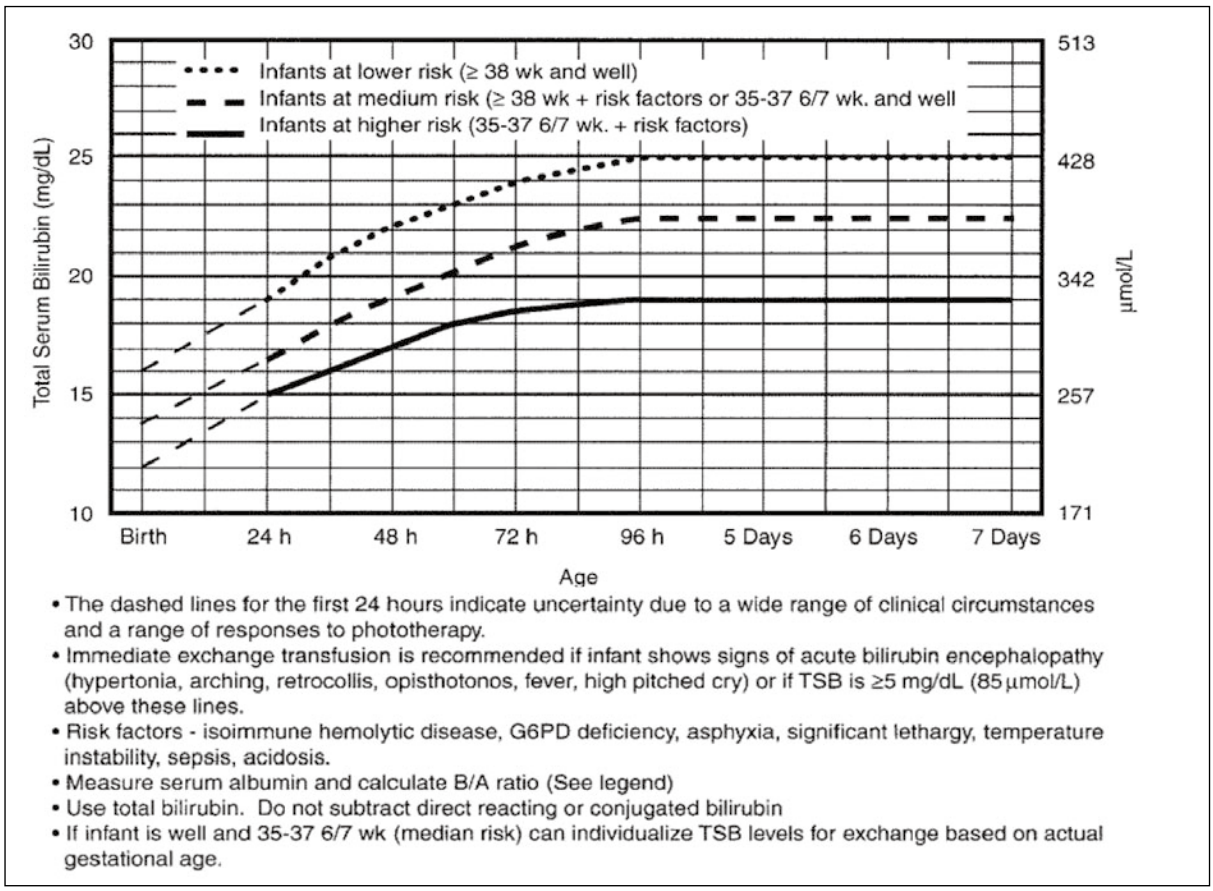

Figure 2 Guidelines for exchange transfusion in infants of 35 and more weeks' gestation.

each category, yielding a total score ranging from 0 to 9. A total BIND score of 1 to 3 suggests subtle, normally reversible, toxic effects of bilirubin. Scores of 4 to 6 are thought to reflect moderate but potentially reversible ABE, whereas scores of 7 to 9 indicate severe ABE.[7] But an abnormal BAEP or 'referred' automated BAEP is indicative of likely bilirubin neurotoxicity. So infant with non-specific signs (score 1-3) and a failed ABR hearing screen is suggested to have moderate ABE.[12]

(d) Glucose-6-phosphate dehydrogenase (G6PD) deficiency: The clinical and laboratory diagnosis of deficiency required a quantitative kinetic G6PD assay interpreted for age and gender and carried out in a reputable laboratory, done on the infant's pre-exchange transfusion blood. The diagnosis was confirmed, or sometimes first made by assay of blood collected after the age of 3 months.[12]

(e) Birth trauma: Excessive trauma was defined as presence of extensive bruising, subgaleal haemorrhage, presence and size of a cephalohaematoma or other concealed or contained haemorrhage, a fractured clavicle or other trauma related to shoulder dystocia.[12]

(f) Haemolytic disorders: Haemolysis was defined by presence of anaemia (haematocrit ≤40% within 2 weeks of age), higher than normal reticulocyte counts for postnatal age, a peripheral blood smear suggestive of haemolysis, such as spherocytes, schistocytes, RBC fragments, and other stigmata like positive direct antibody test (DAT, Coombs's).[12]

(g) Sepsis and infection: In our study infection means "local bacterial infection", such as umbilicus infection, pneumonia and so on. Sepsis was defined as culture-proven sepsis or presumed (culture negative) sepsis based on laboratory studies and clinical risk factors and treated with a full course of antibiotics.[12]

Statistical Analysis

Demographic, clinical, laboratory, intervention and outcome data were recorded in case report forms. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) 16.0 software package. For continuous variables, the data were expressed as mean±standard deviation (SD) and were compared by student's t-test. A Chi-square test was used for categorical variables. A value of $p<0.05$ was considered of statistical significance.

Results

During the 7-year study period, a total of 116 near term and term infants were admitted to the neonatal care unit for management of ABE. The demographic and clinical characteristics of the 116 infants are presented in Table 1. Seventy infants (60.3%) were males and 46 infants (39.7%) were females. One hundred (86.2%) cases were term infants, and 16 (13.8%) cases were near term infants. The mean birth weight of all infants was (3176±453) grams; mean gestational age was (38.1±1.6) weeks. Of all the 116 cases, the age on admission was (5.2±4.3) days. After admission, the bilirubin level on admission was 442.3±142.4 μmol/L, with the highest bilirubin level of 486.0±169.4 μmol/L and Bilirubin/Albumin Ratio was 13.3±4.9 (μmol/L)/(g/L).

The aetiologies of hyperbilirubinaemia, are listed in Table 2. More than one forth of all infants (n=33, 28.4%)

Table 1 Demographic and clinical characteristics of study subjects

Characteristics	n=116
Gender	
Male (n)	70 (60.3)
Female (n)	46 (39.7)
Nationality	
The han nationality (n)	114 (98.3)
Minority nationality (n)	2 (1.7)
GA≥35 to <37 weeks	16 (13.8)
Mode of delivery	
Vaginal delivery (n)	83 (71.5)
Cesarean delivery (n)	33 (28.4)
Positive history in siblings (n)	96 (82.8)
Breast-feeding (n)	60 (51.7)
Perinatal asphyxia (n)	8 (6.9)
Birth weight (g)	3176±453
Gestational age (weeks)	38.1±1.6
Age at admission (days)	5.2±4.3
Age at onset of jaundice (days)	2.9±2.0
Age at onset of ABE (days)	5.8±3.9
Peak bilirubin (μmol/L)	486.0±169.4
Bilirubin level on admission (μmol/L)	442.3±142.4
Bilirubin/Albumin ratio [(μmol/L)/(g/L)]	13.3±4.9

ABE: acute bilirubin encephalopathy

had no identifiable cause of jaundice. The most common cause of ABE was ABO incompatibility (n=38, 32.8%); 7 (6%) cases were due to Rh incompatibility and 14 (12.1%) were to sepsis and infection. Five infants had sepsis; three infants had umbilicus infection and sepsis at the same time; one infant had abdomen skin infection and induced sepsis because his parents acupunctured in his abdomen skin; five infants had umbilicus infection only.

Immediate intensive phototherapy was accomplished in about 84.5% infants according to the 2004 AAP guidelines.[4] Forty-five infants (38.8%) were treated with urgent exchange transfusion. And albumin and liver enzyme inducing drug (phenobarbital) (60.3% and 70% respectively) were administered. After informed consent obtained from parents, 44 infants (37.9%) were given intravenous immunoglobulin to block immunoglobulin constant fragment receptors and the resultant inhibition of haemolysis of antibody-coated erythrocytes. Most patients (n=101, 87.1%) were given prophylactic antibiotics, and antibiotics were changed according to the results of drug sensitivity test when the culture results were positive (Table 3).

After admission, 36 infants received MRI examination at the ages of 10±6 (2-33) days. Ti weighted MRI showed bilaterally symmetrical hyperintensity in the globus pallidi in 69% of patients (25 of 36 cases). A total of 76 patients received maximum length sequences BAEP on day 9±5 (3-28) before discharge. Fifty-three (70%) cases had abnormal BAEP results such as prolongation of the latencies, interpeak intervals with depression of amplitudes and so on.

Among the 116 inpatients enrolled in this study, 14 (12.1%), 83 (71.6%) and 19 (16.4%) infants were classified as subtle, moderate and severe ABE, respectively on admission according to the clinical BIND score. There were no significant differences in the main clinical characteristics of ABE between the three groups. There were also no significant differences among the children with sepsis and infection, Rh incompatibility and/or ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency and birth trauma. The moderate ABE group had a higher peak bilirubin level than the subtle ABE group while the severe ABE group had a higher peak bilirubin level than the moderate ABE group ($p<0.05$). In the subtle ABE group, no (0%) infant died and 1 (7.1%) infant discharged with hypertonia; the rest (92.9%) discharged without any evidence of bilirubin encephalopathy. In the moderate ABE group, 7 (8.4%) infants died, including 4 infants directly related to ABE and 3 to other complication; 4 (4.8%) infants died because their parents discontinued treatment; 31 (37.3%) infants had persistent evidence of bilirubin encephalopathy such as hypertonia and hypotonia at the time of discharge; the rest (49.4%) discharged without evidence of bilirubin encephalopathy. In the severe ABE group, 15 (78.9%) infants died of invalid rescue, including 9 directly related to the ABE and 6 to other complication; 1 (5.3%) infant died because their parents discontinued treatment, and 2 (10.5%) infants had persistent evidence of bilirubin encephalopathy at the time of discharge; only 1 (5.3%) infant discharged without any evidence of bilirubin encephalopathy. There were significant differences in the death rate of invalid rescue between the severe ABE group and the moderate/subtle ABE group (p=0.000, 0.000); and

Table 2 Causes of acute bilirubin encephalopathy

Causes	n	%
Haemolytic disorders		
Rh incompatibility	7	6.0
ABO incompatibility	38	32.8
Combined Rh and ABO incompatibility	1	0.9
Glucose-6-phosphate dehydrogenase deficiency	6	5.2
Birth trauma		
Subgaleal haemorrhage/cephalohaematoma	7	6.0
Visceral haemorrhage	4	3.4
Sepsis or infection	14	12.1
Polycythaemia		
Congenital heart disease	0	0
IUGR	2	1.7
Twin (IUGR)	0	0
Unidentified cause	1	0.9
Multiple causes	3	2.6
Unidentified cause	33	28.4

IUGR: indicates intrauterine growth restriction

Table 3 Therapies for study subjects (n=116)

Therapies	n	%
Intensive phototherapy	98	84.5
Exchange transfusion	45	38.8
Intravenous immunoglobulin	44	37.9
Albumin infusion	70	60.3
Blood transfusion	30	25.9
Liver enzyme inducing drug (phenobarbital)	87	75.0
Antibiotics	101	87.1

the moderate ABE group had more patients with discharge+bilirubin encephalopathy (BE) than the subtle ABE group (p=0.026) (Table 4). Therefore, the correlation between the severity of BE and short-time outcomes was high. A total of 50 (60.2%) babies with moderate ABE were followed up to 3 months of age. The rest of babies were lost to follow-up. On clinical testing, BAEP performed was abnormal in 33 of 50 (66.0%) cases at 3 months of age. Abnormal neurodevelopmental outcome (Epilepsy or hypertonia or developmental delay or abnormal BAEP) was found in 41 (82.0%) cases. All the babies with abnormal outcomes had TSB level ≥510 μmol/L after admission.

Discussion

Acute bilirubin encephalopathy is rarely encountered in the developed world due to effective preventive measures including pre-discharge risk assessment, stringent observance of the treatment guidelines and effective treatment modalities like intensive phototherapy. But in developing countries, such as in China mainland, it is still a not uncommon occurrence. In our study, 116 late preterm and term infants were admitted for management of ABE during the past 7 years. Lack of enough attention and appropriate medical care may be the major reasons behind the high prevalence of ABE in east China.

Johnson et al[12] reported that 67% reported cases of bilirubin encephalopathy were males; mean birth weight was 3281 g and mean gestational age was 38.0 week, which were similar to the results of our study. The onset of severe neonatal jaundice is closely associated with certain universally known risk factors such as Rh factor incompatibility, ABO incompatibility and G-6-PD deficiency. Johnson et al revealed G6PD deficiency (26/112), haemolysis (25/112) and birth trauma (18/112) were the three concurrent morbidities.[12] In our study, besides haemolysis and G6PD deficiency, sepsis and infection were also the main contributing causes of ABE, though they did not increase the clinical staging of ABE. Moreover 8 infants had umbilicus infection including 3 infants had induced sepsis at the same time. This situation was induced by some certain old Chinese traditions and poor living condition. If the infants were home-delivered, and their parents lacked enough health education, their umbilicus maybe covered with various unhygienic materials including enen ashes of incents. These practices often induce local infection which would track up to affect the liver.[13] Even minimum amount of inflammatory cytokines and endotoxin generated from such "minor infection" have been shown to enhance the bilirubin toxicity in a Hong Kong study.[14]

In China, healthy term and near-term neonates are discharged at or around 72 hours of life. Because the total serum bilirubin has not yet peaked by this time,

Table 4 Comparison of the main clinical characteristics, causes and outcomes in the three groups

	ABE			F value or χ^2 value	P value
	Subtle ABE (n=14)	Moderate ABE (n= 83)	Severe ABE (n= 19)		
Male (%)	9 (64.3)	47 (56.6)	14 (73.7)	1.983	0.371
Minority nationality (%)	0 (0)	1 (1.2)	1 (5.3)	1.782	0.410
Perinatal asphyxia (%)	3 (21.4)	4 (4.8)	1 (5.3)	5.241	0.073
Rh incompatibility and/or ABO incompatibility (%)	7 (50)	28 (33.7)	11 (57.9)	4.483	0.106
Glucose-6-phosphate dehydrogenase deficiency (%)	1 (7.1)	3 (3.6)	2 (10.5)	1.632	0.442
Sepsis and infection (%)	4 (28.6)	8 (9.6)	2 (10.5)	4.097	0.129
Birth trauma (%)	3 (21.4)	7 (8.4)	1 (5.3)	2.828	0.243
Peak bilirubin (μmol/L)	413.2±51.4[a]	467.1±124.4[ab]	612.5±103.4[b]	4.112	0.034
Death of invalid rescue (%)	0 (0)[c]	7 (8.4)[b]	15 (78.9)[b,c]	53.746	0.000
Discharge+BE (%)	1 (7.1)[a]	31 (37.3)[a,b]	2 (10.5)[b]	7.187	0.028

[a]p<0.05 between subtle ABE group and moderate ABE group; [b]p<0.05 between moderate ABE group and severe ABE group; [c]p<0.05 between subtle ABE group and severe ABE group.

ABE: acute bilirubin encephalopathy; BE: bilirubin encephalopathy

postdischarge hyperbilirubinaemia may occur.[15] In our study, the highest bilirubin level after admission was (486.0±169.4) μmol/L, mean gestational age of infants with ABE was (38.1±1.6) weeks and the age at admission was (5.2±4.3) days. The bilirubin level of our infants was much higher than that recommended by the 2004 AAP guidelines[4] for exchange transfusion. Actually, it is important to note that some of these peak levels were obtained more than 7 days after birth. So it is necessary to measure TSB level frequently, assess for the risk of developing severe hyperbilirubinaemia before discharge with the mothers and delay discharge until the period of greatest risk has passed. If discharge is unavoidable, enough information about hyperbilirubinaemia should be provided for the parents and earlier or more frequent follow-up should be provided too.

In our study, we classified different ABE groups according to the BIND score. There was high correlation between the severity of BE and the peak bilirubin level. And the correlation between the severity of BE and short-time outcomes was also high. Just like previous study reported,[16] a pretreatment BIND score was a very good predictor of outcomes. So BIND score should be performed after admission to evaluate short-time outcomes. The brain damage incurred by the toxicity of bilirubin is not always reversible. Nearly half of patients with moderate ABE and almost all those with severe ABE had persistent evidence of BE at the time of death or discharge, 82.0% of moderate ABE cases followed had abnormal neurodevelopmental outcomes at age of 3 months, and some may maintain the state for their whole life. It is too late to undergo intervention in infants presenting with intermediate or advanced stages of ABE. Only prompt and effective intervention during early phase can prevent chronic kernicteric sequelae.[17] So paediatricians should be very familiar the warning signs of bilirubin neurotoxicity and ensure to intervene timely and effectively.

Conclusion

Neonatal acute bilirubin encephalopathy in term and near-term babies is still not an uncommon occurrence in east China. It is not a benign entity, which can lead to significantly poor short-term outcomes. BIND score should be performed to evaluate short-time outcomes after admission. The physician' recognition of the whole clinical progress and feature of ABE is of paramount importance in the prevention and management of ABE.

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