Incidence of brain injuries in premature infants with gestational age ≤34 weeks in ten urban hospitals in China

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Background: **There is a large number (1.5 million per year) of premature births in China. It is necessary to obtain the authentic incidences of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), the common brain injuries, in Chinese premature infants. The present multicenter study aimed to investigate the incidence of brain injuries in premature infants in ten urban hospitals in China.**

Methods: **The research proposal was designed by the Subspecialty Group of Neonatology of Pediatric Society of the Chinese Medical Association. Ten large-scale urban hospitals voluntarily joined the multicenter investigation. All premature infants with a gestational age ≤34 weeks in the ten hospitals were subjected to routine cranial ultrasound within three days after birth, and then to repeated ultrasound every 3-7 days till their discharge from the hospital from January 2005 to August 2006. A uniform data collection sheet was designed to record cases of brain injuries.**

Results: **The incidences of overall IVH and severe IVH were 19.7% (305/1551) and 4.6% (72/1551), respectively with 18.4% (56/305) for grade 1, 58.0% (177/305) for grade 2, 17.7% (54/305) for grade 3 and 5.9% (18/305) for grade 4 in nine hospitals. The incidences of overall PVL and cystic PVL were 5.0% (89/1792) and 0.8% (14/1792) respectively, with 84.3% (75/89) for grade 1, 13.5% (12/89) for grade 2, and 2.2% (2/89) for grade 3 in the ten hospitals. The statistically significant risk factors that might aggravate the severity of IVH were vaginal delivery (OR=1.883, 95% CI: 1.099-3.228, *P*=0.020) and mechanical ventilation (OR=4.150, 95% CI: 2.384-7.223, *P*=0.000). The risk factors that might result in the development of cystic PVL was vaginal delivery (OR=21.094, 95% CI: 2.650-167.895, *P*=0.000).**

Conclusions: **The investigative report can basically reflect the incidence of brain injuries in premature infants in major big cities of China. Since more than 60% of the Chinese population live in the rural areas of China, it is expected to undertake a further multicenter investigation covering the rural areas in the future.**

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Introduction

Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), the common brain injuries in premature infants, are major causes for early death in the neonatal period and later motor and cognitive disabilities. Post-hemorrhagic

hydrocephalus and periventricular hemorrhagic infarction are major complications of IVH. PVL is an intractable brain injury in premature infants, pathologically characterized by focal necrosis and diffuse injury.[1] Ischemia and infection are believed to be the main pathogenic factors for PVL in premature infants. Especially, the peroxynitrite generated from lipopolysaccharide-activated microglia mediates the destruction of pre-oligodendrocytes (preOLs).[2] Either by periventricular hemorrhagic infarction following IVH or PVL induced by ischemia or infection, hypomyelination takes place finally because of a damage or loss of preOLs, leading to the sequelae of cerebral palsy and mental retardation.

In consideration of the higher absolute number (1.5 million per year) of premature births in China[3] and the severity of brain injuries in premature infants, a multicenter investigation for brain injuries in premature infants was conducted in China by the Subspecialty Group of the Neonatology of Pediatric Society, the Chinese Medical Association. This report describes the incidences of brain injuries (IVH and PVL) in premature infants with ≤34 weeks of gestational age in ten large-scale urban hospitals in China.

Methods

Participating hospitals

Ten large-scale urban hospitals that were the biggest hospitals at provincial level and all belonged to the Third Class and A Level (the highest level) in China participated in the multicenter investigation. Nine hospitals were involved in investigations of IVH and PVL incidences, and one hospital was only investigated for PVL incidence. Permission for the study was obtained from the human research committees of the participating hospitals, and informed consent was obtained from the relatives of the infants enrolled in this study.

Subjects and study course

Premature infants with the gestational age of ≤34 weeks were investigated from January 2005 to August 2006. Malformed premature infants were excluded.

Methods

Research proposal

The research proposal was drafted by the Subspecialty Group of Neonatology of the Pediatric Society, the Chinese Medical Association. The proposal was discussed and amended by famous neonatologists in the field of neonatal brain injuries in China. A uniform sheet for data collection was designed for recording cases of brain injuries.

Cranial ultrasound scan

An initial bedside real-time cranial sonography was performed by radiologists for all premature infants from the ten hospitals within 3-7 days of birth. Most infants had one or more follow-up examinations at intervals varying from every other day to weekly until discharge. IVH was graded 1 to 4 according to the system of Papile et al,[4] and grades 3 and 4 were considered "severe" IVH. Post-hemorrhagic hydrocephalus was diagnosed when there was progressive ventricular dilation on sonography. PVL was graded 1 to 4 according to the classification of de Vries et al,[5] and grade II and above was defined as cystic PVL, a more severe pathological type.

Statistical analysis

All data were taken from the records and entered into Foxpro software for analyses. Statistical analysis was made with Student's *t* test (unpaired), the chi-square test, and odds ratio with SPSS 11.5 software. Differences between the groups were considered statistically significant when $P<0.05$.

Results

General clinical data

Totally 1792 premature infants with ≤34 weeks of gestational age were enrolled for investigating the incidence of brain injuries. Of whom, 1551 were admitted to the nine hospitals that participated in the investigation of IVH incidence. IVH was found in 305 infants. Their average gestational age was 31.7±2.2 weeks (*n*=303, range: 27.0-34 weeks), and birth weight was 1751.1±462.7 g (*n*=305, range: 860-2500 g). The ratio of male to female of the premature infants was 1.63:1. Fourty-two infants were outborn. The Apgar score was 8.1±2.2 (*n*=285, range: 1-10) at one minute, including 18 infants with Apgar score ≤3; 9.0±1.7 (*n*=228, range: 1-10) at five minutes, including 5 infants with Apgar score ≤3. Vaginal delivery was taken in 149 infants, cesarean birth in 153, and forceps delivery in 3.

Altogether 1792 premature infants were admitted to the ten hospitals participating in the investigation of PVL incidence, and PVL was diagnosed in 89 infants. Their average gestational age was 32.0±1.9 weeks (*n*=87, range: 26.6-34 weeks), and birth weight was 1810.8±449.1 g (*n*=89, range: 960-2300 g). The ratio of male to female in the premature infants was 2.3:1. There were 15 outborn infants. The Apgar score was 7.8±2.4 (*n*=80, range: 1-10) at one minute, and 6 infants had an Apgar score ≤3. The Apgar score was 9.0±1.6

(n=60, range: 3-10) at five minutes, and one infant had an Apgar score ≤3. Vaginal delivery was taken in 45 infants, cesarean birth in 43, and forceps delivery in 3.

Incidence of brain injuries

The overall incidences of IVH and severe IVH (Table 1) were 19.7% (305/1551) and 4.6% (72/1551) in the nine hospitals, consisting of 18.4% (56/305) for grade 1, 58.0% (177/305) for grade 2, 17.7% (54/305) for grade 3 and 5.9% (18/305) for grade 4. Of the 305 infants 244 had bilateral IVH. The overall incidences of PVL and cystic PVL were 5.0% (89/1792) and 0.8% (14/1792) in the ten hospitals, which consist of 84.3% (75/89) for grade 1, 13.5% (12/89) for grade 2, and 2.2% (2/89) for grade 3. There were 58 infants with IVH complicated by PVL. Another 12 IVH infants were associated with infarction of central branches or cortical branches of the either left or right middle cerebral artery.

Gestational age in premature infants with IVH or PVL (Table 2) indicated the decreased incidence of brain injury in premature infants with increasing gestational age.

Possible perinatal risk factors for the occurrence of severe brain injuries in premature infants

There were no significant differences (P>0.05 for all) in the perinatal risk factors that might aggravate the severity of brain injuries, including fetal distress, abnormal fetal position, premature rupture of membranes, placental abruption, placenta previa, amniotic fluid contamination, cord around the neck, pregnancy-induced hypertension, gestational diabetes, uterus infection and perinatal asphyxia. The risk factors of statistical significance were mechanical ventilation (P=0.000) and vaginal delivery (P=0.020), which might aggravate the severity of IVH, and vaginal delivery (P=0.000) which might result in the development of cystic PVL (Table 3).

Outcome of infants with brain injuries

Among the 305 premature infants with IVH, 4 showed changes from grade 1 to grade 2 or above, 9 from grade 2 to grade 3 or above, and another 22 from grade 3 to grade 2. The rates for changes from mild to severe and from severe to mild were 5.6% (13/233)

Table 1. Incidence and severity of brain injuries in premature infants in ten urban hospitals of China (%)

Participating hospitals	Intraventricular hemorrhage (IVH)							Periventricular leukomalacia (PVL)					
	n	Overall IVH	Severe IVH	Grade 1	Grade 2	Grade 3	Grade 4	*n*	Overall PVL	Cystic PVL	Grade 1	Grade 2	Grade 3
Hunan Children's Hospital, Hunan Province	-	-	-	-	-	-	-	241	14	9 (3.7)	5 (35.7)	7 (50.0)	2 (14.3)
Jinan Women & Children Hospital, Shandong Province	115	27	3 (2.6)	1 (3.7)	23 (85.2)	3 (11.1)	0 (0.0)	115	16	0 (0.0)	16 (100)	0 (0.0)	0 (0.0)
Peking University First Hospital, Beijing	258	48	8 (3.1)	22 (45.8)	18 (37.5)	1 (2.1)	7 (14.6)	258	12	1 (0.4)	11 (91.7)	1 (8.3)	0 (0.0)
Shenyang Women Hospital, Liaoning Province	77	16	5 (6.5)	3 (18.8)	8 (50)	4 (25.0)	1 (6.3)	77	1	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)
Shenzhen Children's Hospital, Guangdong Province	369	84	15 (4.1)	1 (1.2)	68 (81.0)	14 (16.7)	1 (1.2)	369	15	2 (0.5)	13 (86.7)	2 (13.3)	0 (0.0)
Shenzhen City People's Hospital, the Second Affiliated Hospital of Jinan University Medical College, Guangdong Province	256	15	4 (1.6)	5 (33.3)	6 (40.0)	3 (20.0)	1 (6.7)	256	3	1 (0.4)	2 (66.7)	1 (33.3)	0 (0.0)
Shenzhen Maternity and Child Healthcare Hospital, Guangdong Province	227	40	11 (4.8)	19 (47.5)	10 (25.0)	7 (17.5)	4 (10.0)	227	2	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)
Ulumuqi Women & Children Hospital, Xinjiang Uyghur Autonomous Region	106	18	6 (5.7)	3 (16.7)	9 (50.0)	2 (11.1)	4 (22.2)	106	2	1 (0.9)	1 (50.0)	1 (50.0)	0 (0.0)
West China Second University Hospital, Sichuan University, Sichuan Province	35	15	12 (34.3)	0 (0.0)	3 (20.0)	12 (80.0)	0 (0.0)	35	12	0 (0.0)	12 (100)	0 (0.0)	0 (0.0)
Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai	108	42	8 (7.4)	2 (4.8)	32 (76.2)	8 (19.0)	0 (0.0)	108	12	0 (0.0)	12 (100)	0 (0.0)	0 (0.0)
Total	1551	305 (19.7)	72 (4.6)	56 (18.4)	177 (58.0)	54 (17.7)	18 (5.9)	1792	89 (5.0)	14 (0.8)	75 (84.3)	12 (13.5)	2 (2.2)

Table 2. Distribution of gestational age in premature infants with brain injuries in ten urban hospitals of China (%)

Gestational age (wk)	Intraventricular hemorrhage (IVH)			Periventricular leukomalacia (PVL)		
	n	Overall IVH	Severe IVH (%)	*n*	Overall PVL	Cystic PVL (%)
≤28	68	29 (42.6)	13 (19.1)	95	7 (7.4)	2 (2.1)
29-30	421	69 (16.4)	22 (5.2)	477	18 (3.8)	2 (0.4)
31-32	378	86 (22.8)	20 (5.3)	458	26 (5.7)	8 (1.7)
33-34	684	121 (17.7)	17 (2.5)	762	38 (5.0)	2 (0.3)
Total	1551	305 (19.7)	72 (4.6)	1792	89 (5.0)	14 (0.8)

Table 3. Possible perinatal risk factors for the occurrence of severe IVH or cystic PVL

Possible risk factors	Brain injury, *n* (%)	Odds ratio	95% CI	*P* value
For IVH				
Vaginal delivery	43/149 (28.9)	1.883	1.099-3.228	0.020
Mechanical ventilation	44/108 (40.7)	4.150	2.384-7.223	0.000
Fetal distress	2/14 (14.3)	0.526	0.115-2.408	0.604*
Abnormal fetal position†	3/20 (15.0)	0.552	0.157-1.942	0.506*
Premature rupture of membranes	20/100 (20.0)	0.736	0.411-1.317	0.300
Placental abruption	2/7 (28.6)	1.303	0.247-6.863	1.000*
Placenta previa	6/21 (28.6)	1.321	0.493-3.541	0.579
Amniotic fluid contamination	6/22 (27.3)	1.233	0.464-3.278	0.674
Cord around neck	5/21 (23.8)	1.012	0.357-2.866	0.982
Pregnancy-induced hypertension	11/54 (20.4)	0.797	0.387-1.641	0.537
Gestational diabetes	2/12 (16.7)	0.637	0.136-2.977	0.817*
Uterus infection	3/12 (25.0)	1.082	0.285-4.109	1.000
Mild asphyxia	19/68 (27.9)	1.346	0.730-2.481	0.340
Severe asphyxia	7/19 (36.8)	1.983	0.750-5.244	0.161
For PVL				
Vaginal delivery	14/45 (31.1)	21.094	2.650-167.895	0.000
Mechanical ventilation	7/30 (23.3)	2.261	0.711-7.190	0.160
Premature rupture of membranes	6/30 (20.0)	1.594	0.497-5.106	0.430
Cord around neck	3/6 (50.0)	6.545	1.170-36.608	0.071*
Uterus infection	2/6 (33.3)	2.958	0.487-17.973	0.518*
Diseases in pregnancy‡	3/11 (27.3)	2.284	0.524-9.955	0.496*
Mild asphyxia	3/20 (15.0)	0.930	0.233-3.722	1.000
Severe asphyxia	1/7 (14.3)	0.885	0.098-7.971	1.000

*: continuity correction χ^2 value; †: abnormal fetal position includes breech, transverse, etc; ‡: Diseases in pregnancy include thrombocytopenia, hepatic dysfunction, hyperthyroidism, nephropathy and cholestasis, etc. IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia.

and 30.6% (22/72), respectively. The mean duration of hospitalization in the 305 infants was 24.3±17.8 days (range: 1-98 days, median: 19 days). Twelve infants with severe IVH were complicated by hydrocephalus. Totally 256 infants with IVH were discharged with resolution or improvement. Forty-one infants left the hospital against medical advice, with a mean hospitalization duration of 12.1±11.2 days (range: 1-53 days, median: 7 days). Six IVH infants whose mean gestational age was 29.3±2.3 weeks (range: 27.1-33.1 weeks) died from pulmonary hemorrhage, respiratory failure, grade 4 IVH or growth failure. Their mean death age was 12.3±11.8 days after birth (range: 2-31 days, median: 8.5 days).

The mean duration of hospitalization in 89 PVL infants was 22.0±15.4 days (range: 4-90 days, median: 8 days). Seventy-three PVL infants were discharged with resolution or improvement. Twelve infants left the hospital against medical advice, with a mean hospital stay of 17.5±13.7 days (range: 4-53 days, median: 14 days). Three PVL infants whose mean gestational age was 31.7±3.2 weeks (range: 28-33.9 weeks) died from hyaline membrane disease, respiratory failure, multiple organ failure or growth failure, and their mean death age was 25.3±34.4 days after birth (range: 5-65 days, median: 6 days).

Discussion

In recent years, the incidence of IVH, which was up to 40%-70% 20 years ago,[6] has declined obviously. Data from multicenter surveys or from the neonatal network and databases showed that the incidence of IVH decreased to about 25%, even under 10% in some European countries.[7,8] In developing countries such as Syria, the incidence of IVH was 44.7% in 2006.[9] The

incidence of PVL reported in some countries was 19.8%-34.1% for overall PVL[10-13] and 2.5%-23% for cystic PVL.[14-16] The evidence of PVL in premature infants was found to be up to 75% in a pathological report.[17] Recent neuro-imaging research showed that the incidence of cystic PVL tended to decrease while non-cystic diffuse white matter injury became a main pathological type.[18,19]

The reported incidence of IVH in China was 40%-70% before 2004.[6] However, the data were from the episodic reports of some units and cannot objectively reflect the exact incidence of IVH in premature infants in this country. Moreover, the incidences of overall PVL and cystic PVL have not been reported in China except for some episodic reports on PVL cases. Thus this multicenter investigation for brain injuries in premature infants was conducted by the Subspecialty Group of the Neonatology of Pediatric Society, the Chinese Medical Association.

The investigation showed that the incidences of the overall IVH and severe IVH were 19.7% and 4.6% in nine hospitals; the incidences of the overall PVL and cystic PVL were 5.0% and 0.8% in ten large-scale hospitals, which were located in seven big cities in Beijing, Shanghai, Shenyang, Ulumuqi, Changsha, Jinan, Chengdu and Shenzhen. The clinical care patterns in all participating hospitals in this investigation were similar, and key management strategies were basically the same based on the guide issued by the Subspecialty Group of the Neonatology of Pediatric Society, the Chinese Medical Association. Therefore, the investigation can basically reflect the incidence of brain injuries in premature infants in major big cities in China.

Similar to the world's development tendency, the incidence of IVH decreases significantly in China. The incidence of PVL in the present investigation was lower than those reported elsewhere. The higher incidence of PVL was noticed to derive mainly from the single NICU or some developing countries,[14] and the lower incidence of PVL (<5%) was usually based on more than 500 cases.[15] The result of this investigation was obtained from 1792 premature infants at the gestational age of ≤34 weeks. Besides, there was a lower incidence of PVL in the infants at the gestational age of 33-34 weeks.

The overall incidence of IVH was close to 40% in some general hospitals. The incidence of severe IVH reached 35% in the West China Second University Hospital, a local biggest general hospital. Synnes et al[20] reported an incidence of severe IVH of 2%-20.5% in 17 neonatal units. Similarlly, an incidence of 2.9%-21.4% for severe IVH in 24 neonatal units was reported from New Zealand.[21] Sick neonatal infants are usually referred to general or children's hospitals, thus proper managerial practices and organizational processes in neonatal units may probably affect the incidence of brain injuries.

About 25%-50% of IVH and most of PVL premature infants are usually overlooked because of the absence of symptoms. Neuroimaging examination can enhance obviously the detection rate of neonatal brain injuries. Since the etiology of brain injuries in premature infants is complicated, the rapid change of systemic pressure may induce an unstable fluctuation of cerebral blood flow and the damage of blood flow anto-regulation, thereby resulting in the occurrence of brain injuries.[22] Thus CT scan or MRI examination is not recommended in premature infants early after birth. The bedside cranial ultrasound is a most suitable way to detect brain injury in premature infants because of a high sensitivity in detecting cerebral injuries in the central site of the brain and a facility for users. A bedside cranial ultrasound has been used as a routine approach for the diagnosis of brain injuries in premature infants in most countries.[23,24] A guide of "diagnostic suggestion for periventricular-intraventricular hemorrhage and periventricular leukomalacia in premature infants" was also issued by the Subspecialty Group of the Neonatology of Pediatric Society, the Chinese Medical Association in 2007,[10] in which a routine initial cranial ultrasound within 3 days of age and a follow-up examination each week are recommended for premature infants of ≤34 weeks of gestational age. It will be helpful to enhance the detection rate of neonatal brain injuries, to track clinical progress, and to adjust the treatment and intervention timely.

As a supplementary way, diffusion weighted imaging is highly sensitive to edema stage during early PVL. As a predictor of outcome for cerebral palsy, MRI at near-term in very low birth weight preterm neonates is superior to ultrasound for the improvement of brain assessment and the detection of anatomic abnormalities.[25] It is recommended that as a routine level care, all at-risk preterm infants with normal or abnormal early ultrasound findings should be given a brain MRI examination before their discharge from the hospital or at 40 weeks of postmenstrual age.

The possible risk factors resulting in brain injuries in premature infants included perinatal asphyxia, vaginal delivery, low birth weight, outborn, hypothermia, mechanical ventilation, respiratory distress syndrome, air leak, metabolic acidosis and hypercapnia. This investigation showed that the risk factors aggravating the severity of IVH were vaginal delivery and mechanical ventilation and that the risk factor that might result in cystic PVL was vaginal delivery. Other IVH risk factors reported recently are male sex, transport of premature infant, acute placental damage, eclampsia, no or incomplete antenatal steroid course, early sepsis, and use of vasopressors.[11,12,26-29] PVL risk factors include placental inflammation, chorioamnionitis,

premature rupture of membranes, hyperoxia, hypocarbia and vaginal delivery.[13,30-36] Utero methamphetamine exposure, late-onset circulatory dysfunction and neonatal cardiac surgery are also correlated with the development of PVL.[37-39] Avoidance of hypertension and abnormal gas change in the immediate neonatal period are important for reducing the incidence of brain injuries in premature infants.

Despite the development of sophisticated care techniques, the survival rate of critically ill infants or very low birth weight infants in the NICU continues to increase over the last decades. The incidence of neurodevelopmental disability among the survivors in NICU remains high. The extremely premature infants in particular appear to sustain a more severe course with appreciable mortality and morbidity. The long-term follow-up is important and necessary for premature infants with brain injuries. The follow-up result of the premature infants with brain injuries in this investigation was described in another report.[40] There were 58 IVH infants complicated by PVL, and the presence of IVH usually increased the risk of PVL.[41] Besides, the branch infarction of cerebral arteries and hypoxic-ischemia brain injuries which usually have characteristic appearances on ultrasound, CT or MRI[42] are also not uncommon in the premature infants.

The multicenter investigation reflects the incidence of brain injuries in premature infants in big cities of China. However, the number of the participating hospitals and the duration of the investigation are limited. It is expected to encourage more urban hospitals including those in medium or small cities to participate in the future investigation, and there may be a longer period of investigation. There are usually more sick infants in general hospitals than in maternity and infant hospitals. It is possible that the occurrence of brain injuries is more frequent in critical premature infants, which may be the major reason for the increased incidence of IVH in the 31-34 week group in the present investigation. The incidences of brain injuries in general hospitals and maternity and infant hospitals may be separately investigated in the future study. Since over 60% of the Chinese population live in the rural areas, there may be a higher incidence of brain injuries in premature infants because of limited medical sources in the rural areas. A more objective and perfect multicenter investigation for the incidence of brain injuries in premature infants is needed in this country covering the rural areas and medium and small cities.

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Contributors: Chen HJ contributed to the conception and design

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