Original Article

Predictive Value of Cranial Ultrasound for Neurodevelopmental Outcomes of Very Preterm Infants with Brain Injury

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Abstract

Background: Compared with full-term infants, very preterm infants are more vulnerable to injury and long-term disability and are at high risk of death. The predictive value of ultrasound and imaging on the neurodevelopment is one of the hot topics. This study aimed to investigate the relationship between cranial ultrasound (cUS) variables and neurodevelopmental outcomes of very preterm infants.
Methods: Totally 129 very preterm infants (gestational age ≤28 weeks) in neonatal intensive care unit of Hunan Children's Hospital between January 2012 and November 2014 were included in this retrospective study. Serial cUS (weekly before discharge and monthly after discharge) was performed on the infants until 6 months or older. Magnetic resonance imaging (MRI) was performed on the infants at approximately the term-equivalent age. The mental developmental index (MDI) and psychomotor developmental index (PDI) were followed up until the infants were 24 months or older. The relationship between brain injury and MDI/PDI scores was analyzed.
Results: The consistency rate between cUS and MRI was 88%. At the first cUS, germinal matrix hemorrhage (GMH) Grades 3 and 4, hospitalization duration, and weight are significantly correlated with MDI/PDI and prognosis (MDI: odds ratio [*OR*] = 8.415, 0.982, and 0.042, *P* = 0.016, 0.000, and 0.004; PDI: *OR* = 7.149, 0.978, and 0.012, *P* = 0.025, 0.000, and 0.000, respectively). At the last cUS, gestational age, extensive cystic periventricular leukomalacia (c-PVL), and moderate and severe hydrocephaly are significantly correlated with MDI (*OR* = 0.292, 60.220, and 170.375, *P* = 0.004, 0.003, and 0.000, respectively). Extensive c-PVL and moderate and severe hydrocephaly are significantly correlated with PDI (*OR* = 76.861 and 116.746, *P* = 0.003 and 0.000, respectively).
Conclusions: Very premature infants with GMH Grades 3 and 4, short hospitalization duration, and low weight have low survival rates and poorly developed brain nerves. Cerebral palsy can result from severe cerebral hemorrhage, moderate and severe hydrocephaly, and extensive c-PVL. The sustained, inhomogeneous echogenicity of white matter may suggest subtle brain injury.

Key words: Brain Injury; Extremely Premature Infants; Magnetic Resonance Imaging; Neurodevelopment; Ultrasound

Introduction

A recent study reported that the incidence of premature births in China has increased from 5.0% to 8.1%, with a survival rate of 79.2–87.3%; extremely premature infants account for 18.5% of all cases of preterm births.[1] Compared with full-term infants, preterm infants are in a state of continuous and immature brain development, are more vulnerable to injury and long-term disability, and are at high risk of death. Studies have reported a 45–80% prevalence of cerebral palsy (CP) in survivors of intraparenchymal hemorrhage (IPH).[2-6] The extent of hemorrhage (defined as the number of lobes involved on the worst-affected side) and ventriculomegaly (VM) is significantly associated with the development of CP; however, the laterality (unilateral vs. bilateral) of the hemorrhage is not associated with neurodevelopmental outcomes.[7] Nonetheless, Maitre

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et al. found that infants with bilateral IPH have significantly worse motor and cognitive outcomes than infants with unilateral IPH.[4] The predictive validity of imaging findings for developmental outcomes has not been well established. Furthermore, premature infants may exhibit different brain injuries, and ultrasound (US) can be used to show the type of brain damage. In this study, we performed cranial ultrasound (cUS) to assess the brain injuries of very preterm infants.

Methods

Ethical approval

As a retrospective study and data analysis was performed anonymously, this study was exempt from the ethical approval and informed consent from patients.

Patients

Very preterm infants (gestational age [GA] ≤28 weeks) who were admitted to the neonatal intensive care unit of Hunan Children's Hospital between January 2012 and November 2014 were assessed for brain maturation and brain injury through cUS and magnetic resonance imaging (MRI). The exclusion criteria included congenital anomalies of the central nervous system, other severe congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

Cranial ultrasound

Image acquisition

Serial cUS scans were performed by a team of experienced examiners using a Mindray M5 scanner (Mindray Medical Systems, Shenzhen, China) with a special standardized preset in accordance with the standard protocol: scanning with a transducer frequency of 8 MHz within 48 h of birth and scanning weekly during admission until discharge or term-equivalent age (TEA) and again monthly until 6 months or older.

Assessment

Periventricular echodensities (PVEs) were defined and classified in reference to van Wezel-Meijler *et al*.[8,9] Cerebral hemorrhages were classified in accordance with the Papile's standard.[10] Hydrocephaly grades were classified into three degrees on the basis of ventricular index and in accordance with Levene *et al*.: mild hydrocephaly, <13 mm; moderate hydrocephaly, 13–15 mm; and severe hydrocephaly, >15 mm.[11] We obtained weekly and monthly ultrasonic reports of the infants for brain injury classification. Images of the first cUS, TEA-cUS, and last cUS were reviewed blindly by two doctors and classified into three degrees in accordance with PVE grade, hydrocephaly degree, and hemorrhage grade of the Papile's standard.

Magnetic resonance imaging

Image acquisition

MRI examinations were performed on living very preterm infants using Skyra 1.5-T Siemens MR system (Siemens Medical Systems, Avanto, Germany) in accordance with the standard protocol[12] for the imaging of newborn infant brains. The scans included at least T1-weighted (repetition time/echo time [TR/TE], 1860 ms/8.5 ms), T2-weighted (TR/TE, 4670 ms/99 ms), diffusion-weighted (TR/TE2, 3600 ms/102 ms), and susceptibility-weighted (TR/TE, 49 ms/40 ms) images on the transverse plane. MRI examinations were performed at approximately TEA, preferably between the 40- and 44-week postmenstrual ages (PMA, i.e., TEA-MRI).

Visual assessment

Special attention was given to the brain white matter (WM). Punctate WM lesions (PWMLs) were defined as small areas of high signal on T1-weighted images and of mostly low signal on T2-weighted images.[13,14] Diffuse excessive high signal intensity (DEHSI) was defined as areas of excessive high SI diffused within the periventricular and/or subcortical WM on T2-weighted images.[15,16]

Clinical follow-up

With the Bayley test, the mental developmental index (MDI) and psychomotor developmental index (PDI) of the infants were recorded at TEA and at 6 months, 1 year, 2 years, and after discharge. The results of the last follow-up were recorded, including intelligence (MDI), PDI, and clinical outcome. Exclusive of dead cases, the MDI and PDI were divided into three groups: normal (>85 points), mildly abnormal (70–85 points), and abnormal (<70 points).

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (International Business Machines, Armonk, NY, USA). A cross-table was used to assess the consistency between the results of TEA-cUS and TEA-MRI. The consistency ratio between TEA-cUS and TEA-MRI would be calculated as: consistency cases/(129 − died cases) × %. The correlation between the first cUS and last cUS was analyzed through Spearman's correlation in bivariate correlation analysis. The influence factors of MDI/PDI scores were analyzed through ordinal regression analysis. It was statistically significant with $P < 0.05$.

Results

Basic characteristics of patients

A total of 141 very preterm infants were eligible for the study and 129 infants (83 males and 46 females) were included; however, 6 infants lacked MRI results and 1 lacked MDI and PDI scores. Twelve infants were excluded from the study. The reasons for exclusion included death within a very short period after birth. The median GA and birth weight of the included infants were 27 weeks + 2 days (range: 22.5–28.0 weeks) and 1102 g (range: 500–1650 g), respectively. The clinical follow-up deadline was December 2016. The maximum and minimum age of the infants was 59 and 24 months, respectively, at the final follow-up. Among the 129 very premature babies, 38 died before TEA and 4 died after TEA. The mortality and survival rates of the infants were 32.8% and 67.3%, respectively. Among the

infants who survived, 72–73% were normal children, 20.9% had mild CP, and 5.8–6.9% had severe CP.

Brain injuries by the first cranial ultrasound

Brain injuries showed by the first cUS among the enrolled very preterm infants are summarized in Table 1.

Periventricular echodensities degree

Periventricular homogeneous echogenicity was more prevalent than adjacent choroid plexus (PVE-II) in 87.5% of extremely premature infants, and the 60% persistent period exceeded 2 weeks. However, 72% of PVE returned to normal at TEA and 86% normalized at the last cUS, indicating that the majority of early cerebral WM lesions can be improved through regular treatment. Only 12 (14%) infants with PVE continued to be classified as abnormal. Among the 12 infants, 9 and 10 had abnormal MDI and PDI, respectively.

Cerebral hemorrhage

Germinal matrix-intraventricular hemorrhage

In this study, the incidence of germinal matrix–intraventricular hemorrhage (GMH-IVH) is 20.9% (27/129) [GMH Grades 1–4, Table 1]. Two Infants with Grade 4 GMH-IVH died on the 24th and 69th day after birth, respectively. Of the 11 (9%) infants with Grade 3 GMH-IVH, seven died and four survived. The MDI and PDI scores of these infants were abnormal. The moderate hydrocephaly of one infant at TEA disappeared by the time of the last US. The MDI and PDI scores of this infant were normal, and the child is now studying in school. One infant had hemorrhagic echogenicity, which was absorbed at TEA, and mild hydrocephaly. The MDI and PDI scores of this infant were normal.

Twelve (9.4%) infants had Grade 2 GMH-IVH. Of these infants, three died before TEA and four lived. One infant exhibited mild ventricular expansion on the 7th day that turned to moderate expansion after 1 month. The MDI and PDI scores of this infant were abnormal. Two infants exhibited mild ventricular expansion after 1 month that turned to moderate hydrocephaly at TEA. The MDI and PDI scores of both infants were abnormal. One infant did not exhibit ventricular expansion but showed continuous parenchymal enhancement. The PDI score of this infant was mildly abnormal.

Three (2.3%) infants were classified as Grade 1 GMH. Of these infants, one died and two showed subependymal cysts and ventricular mild expansion at TEA. The PDI scores of the infants were mildly abnormal.

Choroid plexus hemorrhage

Choroid plexus hemorrhage (CPH) appears in US as an asymmetric echogenicity and swollen plexus. A total of 31 (24%) infants exhibited CPH at the first cUS that then completely disappeared at TEA. Nine infants had CPH accompanied by GMH-IVH.

Table 1: Brain injuries showed by the first and last cUS among the enrolled very preterm infants

Items	*n* (%)
The first cUS (*n* = 129)	
PVE-III	14 (10.9)
PVE-II	99 (76.7)
PVE-I	16 (12.4)
GMH Grade 3 + 4	13 (10.0)
GMH Grade 1 + 2	15 (11.6)
CPH	31 (24.0)
GMH + CPH	9 (7.0)
The last cUS (*n* = 86)	
Severe hydrocephalus	3 (2.3)
Moderate hydrocephalus	9 (10.4)
Mild hydrocephalus	22 (25.6)
Extensive c-PVL	3 (3.4)
Local c-PVL	4 (4.6)
Widened extracranial space	31 (36.0)
Subependymal cyst	7 (8.1)

cUS: Cranial ultrasound; PVE: Periventricular echodensities; GMH: Germinal matrix hemorrhage; CPH: Choroid plexus hemorrhage; c-PVL: Cystic periventricular leukomalacia.

Consistency of ultrasound and magnetic resonance imaging

The consistency ratio between TEA-cUS and TEA-MRI is 88%.

Brain injuries by the last cranial ultrasound

Brain injuries showed by the last cUS among the enrolled very preterm infants are summarized in Table 1.

Cystic periventricular leukomalacia

Five (2.3%) infants exhibited extensive multicystic lesions in WM that were classified as Grade 3 through cUS. Consistent with the MRI results, the lesions persisted in three infants until TEA. One infant showed diffuse cystic periventricular leukomalacia (c-PVL) that transformed from PVE-III after 2 weeks. The infant, however, died after several days. Two infants showed diffuse c-PVL at 2 and 6 weeks. The MDI/PDI scores of these infants were abnormal (<70). One infant showed extensive c-PVL at 2 weeks that turned to local c-PVL after 3 months but died of other unrelated serious diseases. One case showed PVE-III on the 1st day and diffuse c-PVL on the 7th day; these findings gradually narrowed after 2 months and disappeared by the 6th month. This infant had normal MDI and PDI scores. Meanwhile, one infant with moderately abnormal MDI/PDI scores was classified as Grade 2 through TEA-cUS (PVE-II + local cystic of WM) but was defined as Grade 3 with multicystic PVL through TEA-MRI. Four (3.1%) infants were found with local c-PVL through TEA-US. The US results of these infants were consistent with their MRI results, which showed homogeneous DEHSI or few PWML (≤6). The local cystic lesions of the three infants disappeared at the final cUS; of these infants, two had mildly abnormal PDIs.

Subtle white matter injury

In this group, six infants exhibited PWMLs. One case was diagnosed with multiple (>6) PWML and one case was diagnosed with small localized cystic lesions via MRI. The subtle white lesions were originally unrecognizable

but showed sustained, inhomogeneous periventricular WM echogenicity through cUS. One infant had abnormal MDI/PDI scores, three infants had mildly abnormal MDI/PDI scores, and four infants had normal MDI/PDI scores.

Hydrocephaly

Hydrocephaly is a common late manifestation secondary to GMH. In this study, the incidence of hydrocephaly was 38% (33/87). Three infants had severe hydrocephaly secondary to Grade 3 GMH. Of these infants, one died and two survived. The moderate hydrocephaly of the two surviving infants, however, gradually worsened. The hydrocephaly of one infant became severe after 40 days, whereas that of the other was moderately severe as observed at TEA-cUS and became severe at 1 year after birth. The MDIs/PDIs of both infants were abnormal.

Subependymal cyst and widening of extra-axial spaces

In this group, 36% (31/87) showed widening brain extra-axial spaces. Of these infants, 8% (7/87) showed subependymal cyst in last imaging.

Correlation between the first imaging and last cranial ultrasound imaging

The degrees of GMH and PVE at the first cUS were significantly correlated with hydrocephaly. Other variables were not significantly correlated with hydrocephaly [Table 2]. All variables at the first cUS were not significantly correlated with subependymal cyst [Table 2]. The PVE degree of the first cUS was significantly correlated with the widening of extracranial space. GMH, CPH, and GMH + CPH alone had no significant correlation with the widening of extracranial space [Table 2].

Correlation between cranial ultrasound and mental developmental index/psychomotor developmental index by ordinal regression

At first cUS, twins, or multiplets, GMH Grades 1–4, CPH, PVE-II, and PVE-III are harmful factors (odds ratio [*OR*] >1), whereas hospitalization duration, gestational age, and weight are protective factors for MDI/PDI and prognosis (*OR* <1). GMH Grades 3 and 4 GMH, hospitalization duration, and weight are significantly correlated with MDI/PDI and prognosis [$P < 0.05$, Tables 3 and 4]. At last cUS, twins or multiplets, widened extracranial space, subependymal cyst, c-PVL, and hydrocephaly are harmful factors (*OR* >1), whereas hospitalization duration, gestational age, and weight are protective factors for MDI and PDI (*OR* <1). Gestational age, extensive c-PVL, and moderate and severe hydrocephaly are significantly correlated with MDI [$P < 0.05$, Table 5]. Extensive c-PVL and moderate and severe hydrocephaly are significantly correlated with PDI [$P < 0.05$, Table 6].

Discussion

Hemodynamic alterations in premature infants could lead to various types of brain injury. In this group, early WM injury was defined on the basis of PVE. GMH-IVH and CPH were considered as primary injuries, and hydrocephaly, cystic periventricular leukomalacias, widened extracranial space, and subependymal cysts were considered as secondary injuries.

Consistent with a previous report,[17] in this group, Grade 2 GMH-IVH is the most common type of GMH-IVH observed at the first cUS. Among all infants with GMH-IVH, 54% later developed CP or mild CP. Moreover, 66% of infants with Grades 3 and 4 GMH-IVH died, and 50% of the surviving infants developed CP. These results are consistent with the results of previous studies. For example, Tsai *et al*.[7] reported that all infants who had experienced extensive hemorrhages involving three or more lobes developed CP. Previous studies have reported that the prevalence of CP among IPH survivors is 45–80%.[2-6] Recent studies have shown that 54% of infants who survived IPH developed CP.[18] The results of orderly regression analysis also suggested that GMH-IVH, especially Grades 3 and 4, is significantly correlated with CP and poor prognosis. Therefore, severe hemorrhage is a predictor of high mortality and high CP incidence. As previously reported,[19] the extent of hemorrhage (number of lobes involved on the worst-affected side) is significantly associated with the development of CP. Through treatment, however, the diagnoses of two infants with severe GMH were downgraded to mild CP, and one infant did not develop CP. In this study, the hemorrhage symptoms of 20 infants completely disappeared at TEA, and the infants did not develop CP. Pure CPH is not significantly correlated with CP. However, the intraventricular choroid plexus is the most common origin of IVH in premature neonates.[19] CPH may be caused or accompanied by IVH and hydrocephaly, which would influence nerve development. Thus, hospitalization duration and weight are significantly correlated with

Table 2: The correlation between the first and the last cUS imaging among very preterm infants

First cUS imaging	Last cUS imaging					
	Hydrocephalus		Widened extracranial space		Subependymal cyst	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
GMH-IVH	0.275	0.010	0.021	0.845	0.111	0.309
CPH	0.130	0.908	0.581	0.128	0.088	0.422
PVE degree	0.280	0.009	0.215	0.047	0.018	0.871
GMH + CPH	0.092	0.400	0.046	0.675	0.111	0.309

cUS: Cranial ultrasound; PVE: Periventricular echodensities; GMH: Germinal matrix hemorrhage; CPH: Choroid plexus hemorrhage; IVH: Intraventricular hemorrhage.

Table 3: Ordinal regression between the first cUS imaging, basic characteristics, and MDI among very preterm infants

Items		Estimate	SE	Wald χ^2	*OR*	*P*
Threshold value	[MDI = died]	9.527	6.206	2.356	1.000	0.125
	[MDI = abnormal]	9.837	6.210	2.509	1.000	0.113
	[MDI = mildly abnormal]	10.624	6.220	2.917	1.000	0.088
Basic characteristics	Twins or multiplets	0.121	0.399	0.092	1.129	0.761
	Hospitalization duration	−0.018	0.005	13.077	0.982	0.000
	Gestational age	−0.216	0.231	0.875	0.806	0.350
	Weight	−3.178	1.101	8.334	0.042	0.004
First cUS imaging	CPH	0.244	0.409	0.356	1.276	0.551
	GMH Grade 3, 4	2.134	0.882	5.857	8.415	0.016
	GMH Grade 1, 2	−0.856	0.567	2.280	2.354	0.131
	PVE III	1.213	0.868	1.955	3.364	0.162
	PVE II	0.157	0.590	0.071	1.170	0.790
	PVE I	0.000			1.000	

MDI: Mental developmental index; cUS: Cranial ultrasound; PVE: Periventricular echodensities; GMH: Germinal matrix hemorrhage; CPH: Choroid plexus hemorrhage; SE: Standard error; *OR*: Odds ratio.

Table 4: Ordinal regression between the first cUS imaging, basic characteristics, and PDI among very preterm infants

Items		Estimate	SE	Wald χ^2	*OR*	*P*
Threshold value	[PDI = died]	12.926	6.674	3.751	1.000	0.053
	[PDI = abnormal]	13.202	6.679	3.908	1.000	0.048
	[PDI = mildly abnormal]	14.063	6.693	4.415	1.000	0.036
Basic characteristics	Twins or multiplets	0.652	0.430	2.303	1.919	0.129
	Hospitalization duration	−0.022	0.005	15.919	0.978	0.000
	Gestational age	−0.336	0.247	1.857	0.715	0.173
	Weight	−4.448	1.262	12.429	0.012	0.000
First cUS imaging	CPH	0.015	0.425	0.001	1.015	0.971
	GMH Grade 3, 4	1.967	0.880	4.999	7.149	0.025
	GMH Grade 1, 2	0.734	0.576	1.628	2.083	0.202
	PVE III	0.932	0.856	1.184	2.540	0.277
	PVE II	0.191	0.610	0.098	1.210	0.754
	PVE I	0.000			1.000	

PDI: Psychomotor developmental index; cUS: Cranial ultrasound; PVE: Periventricular echodensities; GMH: Germinal matrix hemorrhage; CPH: Choroid plexus hemorrhage; SE: Standard error; *OR*: Odds ratio.

Table 5: Ordinal regression between the last cUS imaging, basic characteristics, and MDI among very preterm infants

Items		Estimate	SE	Wald χ^2	*OR*	*P*
Threshold value	[MDI = abnormal]	−37.513	11.937	9.876	1.000	0.002
	[MDI = mildly abnormal]	−34.775	11.792	8.697	1.000	0.003
Basic characteristics	Twins or multiplets	0.588	0.624	0.889	1.800	0.346
	Hospitalization duration	−0.002	0.008	0.054	0.998	0.816
	Gestational age	−1.232	0.427	8.320	0.292	0.004
	Weight	−0.069	1.467	0.002	0.933	0.963
Last cUS imaging	Widened extracranial space	0.551	0.634	0.754	1.735	0.385
	Subependymal cyst	0.241	1.075	0.050	1.273	0.823
	Moderate/severe hydrocephalus	5.138	1.111	21.366	170.375	0.000
	Mild hydrocephalus	0.170	0.690	0.061	1.185	0.805
	Extensive c-PVL	4.098	1.358	9.110	60.220	0.003
	Local PVL	0.407	1.250	0.106	1.502	0.745

MDI: Mental developmental index; cUS: Cranial ultrasound; SE: Standard error; *OR*: Odds ratio; PVL: Periventricular leukomalacia; c-PVL: Cystic-PVL.

MDI/PDI and prognosis ($P < 0.05$, $OR < 1$). This relationship indicated that the length of hospital stay and the weight of very premature neonates are crucial protective factors against mortality and CP incidence.

We found that hydrocephaly is significantly correlated with GMH. This finding is similar to the findings of previous studies. Hydrocephaly is a major complication of IVH. The incidence of hydrocephaly is inversely related with GA and

Table 6: Ordinal regression between the last cUS imaging, basic characteristics, and PDI among very preterm infants

Items		Estimate	SE	Wald χ^2	*OR*	*P*
Threshold value	[PDI = abnormal]	−23.174	10.912	4.510	1.000	0.034
	[PDI = mildly abnormal]	−19.859	10.739	3.419	1.000	0.064
Basic characteristics	Twins or multiplets	0.217	0.691	0.099	1.242	0.753
	Hospitalization duration	−0.012	0.010	1.608	0.988	0.205
	Gestational age	−0.682	0.392	3.028	0.506	0.082
	Weight	−1.980	1.713	1.335	0.138	0.248
Last cUS imaging	Widened extracranial space	0.095	0.639	0.022	1.100	0.882
	Subependymal cyst	1.087	1.431	0.577	2.965	0.447
	Moderate/severe hydrocephalus	4.760	1.147	17.223	116.746	0.000
	Mild hydrocephalus	0.276	0.757	0.133	1.318	0.716
	Extensive c-PVL	4.342	1.463	8.807	76.861	0.003
	Local PVL	1.082	1.749	0.383	2.951	0.536

PDI: Psychomotor developmental index; cUS: Cranial ultrasound; SE: Standard error; *OR*: Odds ratio; PVL: Periventricular leukomalacia; c-PVL: Cystic-PVL.

reaches up to 20–25% among infants with very low birth weight (VLBW).[20] The imaging variables in our study indicated that VM in either early or late imaging is strongly associated with CP. The results of ordinal regression analysis also showed that severe and moderate hydrocephaly is significantly correlated with CP development. Hemorrhage may progress to ventricular dilation and lead to CP. This finding has been consistently confirmed by multiple studies. Merhar *et al*.[21] found that among former VLBW infants, VM at TEA is a predictor of CP development and low intelligent quotient at 4.5 years of age. Roze *et al*.[22] found that among survivors of IVH, posthemorrhagic ventricular dilation is a risk factor for low intelligence and poor fine manipulative abilities at 4–12 years of age. Blood clots can cause cerebrospinal fluid blockage, which causes hydrocephaly in association with cerebral hemorrhage. Parenchymal hemorrhage or WM lesions can lead to WM loss and is another reason for hydrocephaly development. Although US imaging cannot be used to evaluate the degree of WM loss, it can be used to evaluate the degree of hydrocephaly, which, in turn, reflects the degree of WM loss. This relationship accounts for the association between serious hydrocephaly and high CP incidence. In this study, the degree of hydrocephaly changed with time: it progressed to severe hydrocephaly, improved to mild hydrocephaly, or eventually disappeared. TEA-cUS and later follow-up are necessary to observe or measure the degree of hydrocephaly. The serial HUS measurements of the lateral ventricular may play a key role in the early recognition and therapeutic evaluation of hydrocephaly and can be of prognostic value in neonates. In this study, GMH and PVE degree are significantly correlated with hydrocephaly. GMH, PVE degree, and CPH are not correlated with subependymal cysts because cysts secondary to GMH or WM injury may have been absorbed and some of the cysts which observed at last cUS may be caused by other factors, such as infection. Furthermore, the widening of extra-axial spaces is significantly correlated with PVE degree but not with cranial hemorrhage. This finding indicated that cranial hemorrhage is not the main cause of extra-axial widening.

In this group, PVE degree is significantly correlated with hydrocephaly and c-PVL. This diffuse and faint echogenicity appears within the 1st days of life and gradually normalizes. This echogenic region should be distinguished from the heterogeneous and highly echogenic regions that represent WM damage. In infants with GAs of 24 and 30 weeks, vascular watershed areas are located in the periventricular region, thereby rendering the periventricular VM vulnerable to hypoperfusion. WM damage can lead to WM loss, progress to local cysts, and ultimately lead to hydrocephaly and CP. In this group, 5 (2.3%) infants presented extensive multicystic lesions in their WM. Among the five infants, two died of accompanying serious diseases, two developed CP, and one had a normal outcome. Cysts are usually only visible for a few weeks: 4/6 of cysts appeared at approximately 2 weeks after birth and approximately 2/6 were resolved at TEA. The incidence of c-PVL is underreported because cysts are usually not detected when cUS is performed only during the 1st week after birth and once again at 36 weeks, as recommended by the CME guidelines for infants with ELGAN.[23] Hence, sequential cUS is required to detect the development of cysts in c-PVL. Continuous cerebral US is necessary to identify changes in cerebral WM damage and PVL. Permanent extensive c-PVL is a predictive factor of CP development. However, through treatment, cysts could decrease in size or even disappear, and the reduction in size or disappearance of a cyst is indicative of a good prognosis.

In this group, six infants exhibited PWMLs on MRI. PWMLs are subtle white lesions that are not easily recognizable but can be characterized by sustained, inhomogeneous periventricular WM echogenicity at TEA or at last cUS. The PVE of 12 (14%) infants persisted until the last cUS, and most infants developed CP (75% and 83%). Among the infants with PWMLs, 1 (16%) developed CP and 3 (50%) developed mild CP at follow-up. These results are consistent with those of several recent studies and suggested that the presence of PWML is associated with an increased risk of CP and abnormal MDI and PDI.[17,18] PWMLs can be hemorrhagic or ischemic in origin. Continuous,

inhomogeneous periventricular WM echogenicity in US is significantly correlated with PWMLs. Periventricular WM echogenicity that persists until TEA or beyond could indicate focal cerebral WM lesions, which may have local ischemic or hemorrhagic origins, and is a predictor of mild CP.

In this study, we analyzed the relationship between early cerebral hemorrhage or WM injury and advanced hydrocephaly or subependymal cysts. We also analyzed the relationship between brain injuries and CP. Although we obtained some important results, our retrospective study is limited by the lack of clinical treatment data. Thus, further studies with a large sample size should be established to identify correlations between different treatment strategies and the long-term neurological outcomes of very premature neonates.

In conclusion, GMH is significantly correlated with the development of hydrocephaly but not with subependymal cysts and the widening of extra-axial spaces. PVE degree is significantly correlated with the development of hydrocephaly and the widening of extra-axial spaces but not with subependymal cysts. Very premature infants with Grades 3 and 4 GMH, short hospitalization duration, and low weight have low survival rates and poorly developed brain nerves.

CP can result from severe cerebral hemorrhage, moderate and severe hydrocephaly, and extensive c-PVL. By contrast, the widening of the extra-axial space, choroid plexus, and mild hydrocephaly have limited effects. Sustained, inhomogeneous echogenicity WM may suggest the presence of subtle WM injury or local bleeding, which affects brain development.

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Conflicts of interest

There are no conflicts of interest.

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颅脑超声对极早产儿脑损伤脑神经发育预测价值的研究

摘要

背景：与足月儿相比，早产儿发生长期残疾或早死亡的危险性要高许多。超声及影像学对脑神经发育的预测价值是研究的热点之一，本研究拟总结极早产儿脑损伤的特点，分析不同早、晚期脑损伤与脑神经发育之间的相关性。
方法：129例孕龄 ≤28 w的，住院期间每周查超声一次，后每月查超声一次至出院，于等足月时对所有患儿进行核磁共振扫查，随访智力发育指数（mental developmental index -MDI）及精神运动发育指数（psychomotor developmental index -PDI）评分结果至2岁或更大，分析脑损伤与MDI、PDI的相关性。
结果：等足月超声与等足月核磁共振结果一致率为88%。首次超声：3、4级GMH、住院时间及体重与MDI、PDI及预后显著相关性（P＜0.05）。末次超声：出生孕周、中-重度脑积水及广泛的脑白质软化对MDI有显著影响（P＜0.05）。广泛脑白质软化及中-重度脑积水对对PDI有显著影响（P＜0.05）。
结论：3、4级GMH、短住院时间及极低体重是导致极早产儿生存率低、大脑神经发育不良的重要因素。重脑出血、中度及重度脑室扩张、大片脑白质软化是引起脑瘫的重要因素，超声下持续的、不均匀性的脑室旁白质回声增强可能提微小病灶的脑损伤，是影响脑神经发育不良危险信号。