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Association of Cystic Periventricular Leukomalacia and Postnatal Epilepsy in Very Preterm Infants

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Keywords
Cystic periventricular leukomalacia · Postnatal epilepsy · Preterm infants

Abstract
Introduction: Cystic periventricular leukomalacia (PVL) is the most common white matter injury and a common cause of cerebral palsy in preterm infants. Postnatal epilepsy may occur after cystic PVL, but their causal relationship remains uncertain. Our aim was to validate the contribution of cystic PVL to postnatal epilepsy in very preterm infants and demonstrate their seizure characteristics. ***Methods:*** This prospective cohort study enrolled 1,342 preterm infants (birth weight <1,500 g and gestational age <32 weeks) from 2003 to 2015. Cystic PVL was diagnosed by serial cerebral ultrasound, and other comorbidities were recorded during hospitalization. Neurological developments and consequences, including epilepsy, were serially accessed until the age of 5. ***Results:*** A total of 976 preterm infants completed a 5-year neurological follow-up; 47 (4.8%) had cystic PVL. Preterm infants with cystic PVL were commonly associated with other comorbidities, including necrotizing enterocolitis stage III, neonatal seizures, and intraventricular hemorrhage during hospitalization. At age 5, 14 of the 47 (29.8%) preterm infants with cystic PVL had postnatal epilepsy. After adjusting for gender, gestational age, and three common comorbidities, cystic PVL was an independent risk factor for postnatal epilepsy (adjust OR: 16.2; 95% CI: 6.8–38.4; $p < 0.001$). Postnatal epilepsy after cystic PVL was commonly the generalized type (13 of 14, 92.9%), not intractable and most occurred after 1 year of age. ***Discussion/Conclusion:*** Cystic PVL would independently lead to postnatal epilepsy. Preterm infants with cystic PVL are at risk of postnatal epilepsy after age 1 in addition to cerebral palsy.

Introduction

Advancements in neonatal intensive care over the last 2 decades have increased the likelihood of survival and improved the outcomes of preterm infants [1]. However, the intense stresses during the early postnatal period of preterm infants often leads to inflammatory or hypoxic events [2, 3]. These postnatal inflammation or hypoxic-ischemic events are the noxious stimuli for the maturation of the oligodendrocyte lineage in the subplate zone

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and often lead to myelination failure [4]. Thus, the white matter becomes a selectively vulnerable structure during the preterm period [4]. Periventricular leukomalacia (PVL) accounts for the greatest percentage of white matter injury among preterm infants and occurs in an overall 19.8–34.1% of preterm infants [1, 2]. Fortunately, only a small number of infants with PVL develop cysts in the white matter. Its incidence increases with decreasing gestation age, peaking at 24–32 gestational weeks, particularly in those with a birth weight less than 1,500 g.

The neuropathological hallmark of PVL in the acute phase is focal necrosis in the periventricular region and/or diffuse reactive gliosis in the surrounding white matter [5, 6]. These necrotic foci often appear as periventricular cysts, which may collapse to form a solid glial scar and reduce the white matter volume over time [6]. Thus, PVL would be diagnosed by detecting these periventricular cysts (cystic PVL) with the serial bedside cerebral ultrasound in the early life of preterm infants. Topographically, the cystic lesions of PVL show a parieto-occipital predominance with various degrees of extension in the frontal and lateral directions [7]. This may affect the corticospinal tract, thalamocortical fibers, optic radiation, superior occipital fasciculus, and the superior longitudinal fasciculus resulting in motor, visual, or higher cortical function deficits [8]. Thus, the most common neurological sequela of cystic PVL is cerebral palsy presented as spastic diplegia or quadriplegia, followed by cognitive or vision dysfunctions [4, 6]. However, some infants with cystic PVL developed postnatal epilepsy, even though epilepsy is often regarded as a manifestation of cortical damages instead of a consequence of white matter injuries. One may also argue that preterm infants often have other confounding comorbidities to cause epilepsy directly or indirectly in addition to cystic PVL. The aim of this prospective cohort study is to investigate the association between cystic PVL and postnatal epilepsy after adjusting other confounding comorbidities in preterm infants and the characteristics of postnatal epilepsy after cystic PVL.

Methods

Study Population

From Jun 2003 to Dec 2015, preterm infants (birth weight <1,500 g, gestational age [GA] < 32 weeks) admitted to neonatal intensive care units of the four tertiary medical centers/hospitals in Tainan City, Taiwan, were enrolled in this study. Data on demographic characteristics and clinical complications/comorbidities in the perinatal and postnatal periods were collected after obtaining parental informed consent. Brain ultrasounds were routinely performed by pediatric neurologists or trained neonatologists twice a week in the first week of age, weekly from week two until GA >32 weeks, and then monthly until discharge. After discharge, all infants were followed up prospectively at the corrected age of 12, 24 months and 5 years for neurodevelopmental assessments at a single medical center. Infants with congenital or chromosomal anomalies, who died before discharge, lost to follow-up, or were without a complete brain ultrasound survey, were excluded. This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (NCKUH-ER-98-135).

Definition of Clinical Co-Variables

Gestational diabetes and preeclampsia/eclampsia were diagnosed based on the guideline from the American College of Obstetricians and Gynecologists (ACOG) [9, 10]. Preterm premature rupture of membranes was a rupture of the fetal membranes for at least 18 h before labor began [11]. Respiratory distress syndrome, patent ductus arteriosus, retinopathy of prematurity, persistent pulmonary hypertension in the neonate, bronchopulmonary dysplasia, and necrotizing enterocolitis (NEC) were common comorbidities in very preterm infants and were diagnosed by their definition or diagnostic criteria [12, 13]. Bacteremia referred to detected bacteria in the blood culture. The neonatal seizure was diagnosed by neonatologists/pediatric neurologists based on clinical manifestations.

The brain ultrasound images were reviewed by board-certificated pediatric neurologists at National Cheng Kung University Hospital [14, 15]. Both intraventricular hemorrhage (IVH) and cystic PVL were diagnosed by brain ultrasound. Cystic PVL was defined as periventricular echolucent cystic lesions detected using ultrasound examination [16]. IVH was classified into three grades (I–III) based on the location and extent of hemorrhage and presence of ventricular dilatation [8]. Grade III IVH and any grade of IVH with periventricular hemorrhage were regarded as high-grade IVH [17].

Identification of Epilepsy and Its Associated Information

The parents underwent interviews and completed questionnaires containing seizure type, anti-seizure medication, and the severity of epilepsy at the follow-up visits. The seizure history reported by parents was further validated by reviewing medical charts from referral hospitals or pediatric practitioners after the last visit at the corrected age of 5. Epilepsy was defined when at least two unprovoked seizures occurred greater than 24 h apart, or one seizure was with a relevant abnormal electroencephalographic pattern, or a brain scan suggested a high probability of a second seizure [18]. The classification of seizure type and the diagnosis of epileptic syndrome, status epilepticus, and intractable epilepsy were based on the report by International League against Epilepsy [19, 20].

Neurodevelopmental Outcome Assessment

During the follow-up visits, pediatric neurologists performed neurological examinations, and child psychologists conducted standard neurocognitive assessments. At the age of 2, the neurodevelopment was assessed using the Bayley Scales of Infant Development-II (BSID-II, Harcourt Brace & Company, San Antonio, TX, USA) [21]. At the age of 5, the neurocognitive function was assessed using the Wechsler intelligence tests (the Wechsler Preschool and Primary Scale of Intelligence-Revised [WPPSI-R]) to estimate verbal intelligence quotient (IQ), performance IQ, and full-scale IQ scores [22]. Intellectual disability was defined when a full-scale IQ score was below 70. Cerebral palsy

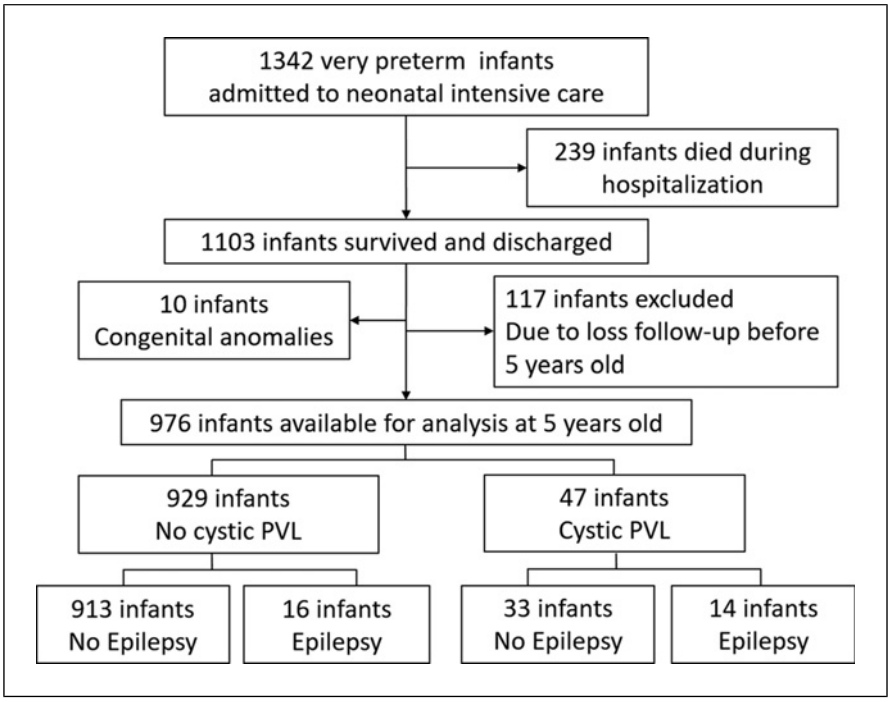

Fig. 1. Flowchart of study population. Flowchart of the recruitment of very preterm infants who were enrolled, survived till discharge, and were followed up prospectively for assessment to the age of 5 years.

was defined based on the abnormal muscle tonicity and the impairment of gross motor function above level II of Gross Motor Function Classification System [23].

Statistical Analysis

The statistical analyses were performed by using SPSS 20.0 software (IBM Corp., Armonk, NY, USA) or SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA). Continuous and discrete variables were analyzed using the independent *t* test and Fisher's exact test. Univariate logistic regression was used for risk factors to analyze the association between the morbidities and outcomes. The potential factors with $p < 0.05$ in the univariate analysis or with clinical significance were entered into a multivariate logistic regression model to calculate odds ratios and 95% confidence intervals. A statistical significance was considered when $p < 0.05$.

Results

In total, there were 1,342 very preterm infants enrolled in this study. Among them, 239 (17.8%) died before discharge, 10 had congenital anomalies, and 117 (10.7%) lost to follow-up at age 5 (Fig. 1). Thus, 976 preterm infants were included in the final analysis. Their mean GA was 28.9 ± 2.8 weeks, and their mean birth weight was 1,120 ± 252 grams. In this cohort, 47 (4.8%) preterm infants had cystic PVL.

Compared with the preterm infants without cystic PVL, the preterm infants with cystic PVL had a male predominance, younger GAs, lower birth weights, and smaller head circumferences at birth (Table 1). The prenatal factors such as eclampsia, maternal infections, or preterm premature rupture of membranes were not associated with preterm infants with cystic PVL. Among preterm-associated comorbidities during the neonatal period, preterm infants with cystic PVL were more common to have respiratory distress syndrome (which required the treatment of surfactants), patent ductus arteriosus, retinopathy of prematurity (more than stage III), and bronchopulmonary dysplasia than the preterm infants without cystic PVL ($p < 0.05$). They also more often had NEC (stage III) ($p = 0.005$) but not bacteremia ($p = 0.868$). Compared with the preterm infants without cystic PVL, the preterm infants with cystic PVL were also more likely to have other neurological comorbidities, such as neonatal seizures and IVH ($p < 0.001$). After adjusting for gender and GA, only NEC stage III and neurological comorbidities, including neonatal seizures and IVH, were independent comorbidities at risk for cystic PVL (Table 2).

The most common neurological consequence of cystic PVL was cerebral palsy (63.8%), followed by intellectual disability (40.4%) and postnatal epilepsy (29.8%) (Table 3). The prevalence of these neurological consequences was all higher in the preterm infants with cystic PVL than the preterm infants without cystic PVL ($p < 0.001$). As mentioned above, NEC stage III, neonatal seizures, and

Table 1. Demographics and neonatal comorbidities associated with cystic PVL

	No cystic PVL (n = 929), n (%)/mean±SD	Cystic PVL (n = 47), n (%)/mean±SD	p value
Basic information			
Gender (male)	462 (49.7)	34 (72.3)	0.003
GA (weeks)	29±3	27±3	0.001
Birth weight (g)	1,126±251	1,019±264	0.005
Head circumference (cm)	25.9±2.2	25.0±2.4	0.038
Prenatal associations			
Gestational diabetes	22 (2.4)	2 (4.3)	0.424
Preeclampsia/eclampsia	171 (18.4)	4 (8.5)	0.094
Maternal infections[a]	45 (4.8)	1 (2.1)	0.721
PPROM	293 (31.5)	16 (34.0)	0.749
Postnatal comorbidities			
Hypoxia associated			
RDS	872 (93.9)	45 (95.7)	0.617
RDS, surfactants	285 (30.7)	26 (55.3)	0.001
PDA	397 (42.7)	30 (63.8)	0.013
ROP	431 (46.4)	27 (57.4)	0.147
ROP ≥ stage III	78 (8.4)	9 (19.1)	0.021
PPHN	10 (1.1)	1 (2.1)	0.515
BPD	227 (24.4)	19 (40.4)	0.016
Inflammation associated			
NEC	158 (17.0)	9 (19.1)	0.712
NEC, stage III	3 (0.3)	2 (4.3)	0.005
Bacteremia	227 (24.4)	12 (25.5)	0.868
Neurology associated			
Neonatal seizure	9 (1.0)	6 (12.8)	<0.001
IVH	223 (24.0)	32 (68.1)	<0.001

BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of newborn; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity. [a]Maternal infections included bacteremia, genitourinary tract infection, or chorioamnionitis.

Table 2. Univariate and multivariate analysis of preterm comorbidities at risk for cystic PVL

	Crude OR (95% CI)	p value	Adjusted OR[a] (95% CI)	p value
RDS, surfactants	2.8 (1.5–5.0)	0.001	1.9 (0.9–3.6)	0.062
PDA	1.7 (1.1–2.5)	0.013	1.5 (0.9–2.4)	0.102
ROP ≥ stage III	2.5 (1.1–5.3)	0.021	1.5 (0.7–3.4)	0.333
BPD	2.1 (1.1–3.8)	0.016	1.1 (0.5–2.3)	0.850
NEC, stage III	13.8 (2.2–84.5)	0.005	10.2 (1.5–67.4)	0.016
Neonatal seizure	15.0 (5.1–44.0)	<0.001	11.1 (3.6–34.0)	<0.001
IVH	6.8 (3.6–12.7)	<0.001	5.6 (2.9–10.8)	<0.001

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity. [a]Adjust gender and GA.

Table 3. Neurological consequence of cystic PVL

	No cystic PVL (n = 929), n (%)	Cystic PVL (n = 47), n (%)	p value	Adjusted OR[a] (95% CI)	p value
Developmental outcomes at 24 months of age					
MDI <85	297 (32.0)	34 (72.3)	<0.001	6.9 (3.2–14.9)	<0.001
PDI <85	232 (25.0)	37 (78.7)	<0.001	15.5 (6.3–37.8)	<0.001
Neurological outcomes at 5 years of age					
Cerebral palsy	71 (7.6)	30 (63.8)	<0.001	22.8 (11.1–46.7)	<0.001
Intellectual disability (FIQ <70)	65 (7.0)	19 (40.4)	<0.001	9.4 (4.7–18.8)	<0.001
Postnatal epilepsy	16 (1.7)	14 (29.8)	<0.001	16.2 (6.8–38.4)	<0.001

MDI, Mental Developmental Index; PDI, psychomotor developmental index; FIQ, full-scale intelligence quotient; OR, odds ratio; CI, confidence interval. [a]Adjust gender, GA, neonatal seizure, IVH, NEC stage III.

IVH were the risk comorbidities for cystic PVL. After adjusting gender, GA, and the three risk comorbidities, cystic PVL was still an independent risk factor for postnatal epilepsy (adjusted odds ratio: 16.7; 95% confidence interval: 6.7–41.2; $p < 0.001$) in addition to cerebral palsy and intellectual disability.

The incidence of postnatal epilepsy in preterm infants with cystic PVL was 29.8% (14/47) in this prospective cohort. The overall incidence of postnatal epilepsy in preterm infants was 3.1% (30/976). In contrast, the incidence of postnatal epilepsy in preterm infants without cystic PVL was only 1.7% (16/929). The most common etiology of postnatal epilepsy in preterm infants without cystic PVL was IVH (43.8%, 7/16), particularly IVH grade III with or without periventricular hemorrhage (Table 4). Compared to preterm infants without cystic PVL, the onset age of postnatal epilepsy was older in preterm infants with cystic PVL ($p = 0.044$) and was usually after the age of 1-2 years (Fig. 2). The common seizure type of epilepsy in preterm infants with cystic PVL was generalized seizure, while it was focal seizure in preterm infants without cystic PVL. Three preterm infants (one with cystic PVL, two without cystic PVL) developed hypsarrythmia, and two of them evolved into Lennox-Gastaut syndrome (one in each group) later. In addition, postnatal epilepsy in preterm infants with cystic PVL was less often intractable ($p = 0.039$) and less often led to status epilepticus ($p = 0.026$) compared with postnatal epilepsy in preterm infants without cystic PVL.

Discussion

Cystic PVL is the leading cause of cerebral palsy and long-term neurological disability in children born preterm [3]. The current study showed that preterm infants with cystic PVL had a male predominance and younger GAs. Preterm infants with cystic PVL are commonly associated with many postnatal comorbidities. After adjusting for gender and GA, only NEC stage III, neonatal seizures, and IVH were independent risk comorbidities of cystic PVL. In this cohort, the most common neurological consequence of cystic PVL at the age of 5 was cerebral palsy, followed by intellectual disability and postnatal epilepsy. After adjusting the three risk comorbidities of cystic PVL, gender, and GA, postnatal epilepsy was also an independent neurological consequence of cystic PVL in addition to cerebral palsy and intellectual disability. Compared to preterm infants without cystic PVL, the seizure in preterm infants with cystic PVL was commonly generalized and less intractable and usually had older age of onset.

Gurses et al. [24] reported that 9 out of 19 (47%) children with PVL had epilepsy, and the majority of them had multiple seizure types. Ekici et al. [25] found that postnatal epilepsy developed in 35 out of 108 (32%) children with radiologically proven PVL. The most common seizure patterns were generalized tonic-clonic seizures (37%), followed by complex partial seizures (31%). Humphreys et al. [26] reported that 40 out of 154 (26%) children with radiologically confirmed PVL had postnatal epilepsy. These were all cross-sectional studies at a single medical center, and they obtained the data on epilepsy retrospectively. Neither did exclude the possible contribution of other neurological comorbidities to postnatal epilepsy. Compared with the studies mentioned above, our study identified the PVL patients in a prospective cohort of preterm infants from their neonatal period and longitudinally followed until age 5. The incidence of postnatal epilepsy after cystic PVL was 29.8%, which was close to the previous studies. In addition, the

Table 4. Very preterm infants with postnatal epilepsy subdivided by cystic PVL

	No cystic PVL (n = 16), n (%)/mean±SD	Cystic PVL (n = 14), n (%)/mean±SD	p value
Basic information			
Gender (male)	7 (43.8)	11 (78.6)	0.072
GA (weeks)	27.5±2.3	27.5±3.5	1.000
Birth weight (g)	999±276	1,028±304	0.784
Neonatal comorbidities			
NEC, stage III	1 (6.3)	1 (7.1)	1.000
Neonatal seizure	1 (6.3)	5 (35.7)	0.072
IVH	7 (43.8)	10 (71.4)	0.159
Epilepsy characteristics			
Seizure onset age (months)	16±12	26±15	0.044
Seizure type			
Generalized	8 (50.0)	13 (92.9)	0.017
Focal	11 (68.8)	4 (28.6)	0.066
Epileptic syndrome[a]	2 (12.5)	1 (7.1)	1.000
Intractable epilepsy	7 (43.8)	1 (7.1)	0.039
Status epilepticus	9 (59.8)	2 (14.2)	0.026

IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis. [a]Epileptic syndrome included infantile epileptic spasms syndrome and Lennox-Gastaut syndrome.

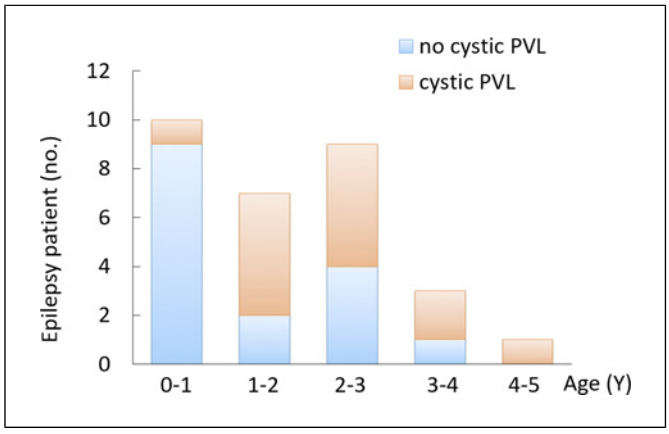

Fig. 2. Onset age of epilepsy in preterm infants with or without cystic PVL.

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results demonstrated that postnatal epilepsy was an independent neurological consequence of cystic PVL after adjusting the contribution of other risk comorbidities in preterm.

The neuropathological hallmark of PVL consists of focal necrosis with marked surrounding microgliosis and astrogliosis in the white matter. These damages usually result from the preterm-birth-associated inflammatory or hypoxic-ischemic insults during the GA range of 24–32 weeks [3–6]. During this critical period, the pre-oligodendrocytes are emerging in the white matter of the developing brain. Thus, the pre-oligodendrocytes might also be injured in these preterm infants with PVL. The damage or loss of pre-oligodendrocytes could lead to the disruption of axonal maturation and consequently impaired myelination in the white matter. It is known that gamma-aminobutyric acid (GABA)ergic neurons destined for the cerebral cortex migrate through the white matter during late gestation (gestation of 26–38weeks) [27]. The disruption of axonal maturation in the developing white matter of preterm infants with PVL would disturb the migration of the GABAergic neurons. This assumption could be supported by Robinson et al. [28]. They found a reduction of GABAergic neurons in the subplate from the postmortem cerebral samples in preterm infants with known white matter injury compared to controls with minimal white matter gliosis [28]. Thus, white matter injury resulting from PVL might disturb the migration of GABAergic neurons to the cerebral cortex and might subsequently reduce the development of cortical inhibitory circuits in preterm infants.

The epileptogenic process is quite unique in the immature brain because GABA is excitatory instead of inhibitory in the immature brain [29]. GABA becomes inhibitory later due to the delayed expression of chloride exporters, which leads to a negative shift in the reversal potential for chloride ions [30]. Based on the evidence from animal studies, the maturation of GABA-mediated

inhibition is gradually reached after the second postnatal week in rats, equivalent to around 1-2 years old in humans [31]. If the epileptogenesis of PVL is through the disturbance of GABAergic cortical circuit, epilepsy after PVL will be expected to occur after 1-2 years of age. This assumption was supported by our findings that postnatal epilepsy in preterm infants with cystic PVL almost occurred after 1-2 years of age (Fig. 2), and the onset age of epilepsy was older than it in preterm infants without cystic PVL. Nevertheless, future studies are needed to validate this assumption.

This study has its strengths and limitations. The strength is that it included a large cohort of very preterm infants with 5-year follow-up assessments. The limitations are a relatively small number of cystic PVL or epilepsy, a wide range of GA, and no genetic survey of epilepsy in our patients. The influence of the wide range of GA on neurological outcomes might be diminished by adjusting GA in the multivariate analysis used in our study. The individual etiology of epilepsy in our patients did not be comprehensively surveyed. For example, the influence of genetic problems could not be excluded. In addition, our study detected cystic PVL using ultrasound examination instead of magnetic resonance neuroimaging. Although magnetic resonance neuroimaging is believed to be more sensitive than ultrasound in detecting subtle white matter abnormalities, cystic PVL can be recognized with serial brain ultrasound.

Conclusion

Cystic PVL in very preterm infants is an independent risk factor for postnatal epilepsy. Preterm infants with cystic PVL are at increased risk of developing postnatal epilepsy after age 1 in addition to cerebral palsy.

Acknowledgments

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital (NCKUH-ER-98-135). Informed written consent was obtained from their parents.

Conflict of Interest Statement

All authors declare no conflict of interest and no financial relationships that could be broadly relevant to the work.

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Author Contributions

Dr. Po-Ming Wu collected data, carried out the initial analyses, drafted the initial manuscript, and revised the manuscript. Dr. Chen-Yu Wu collected data and carried out the initial analyses. Prof. Chung-I Li checked the results of statistical analysis and critically reviewed the manuscript for important intellectual content. Prof. Chao-Ching Huang designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Prof. Yi-Fang Tu conceptualized and designed the study, carried out the initial analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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