学位論文　博士（医学）甲

Factors associated with the development of epilepsy in very low birth weight infants

（極低出生体重児におけるてんかん発症関連因子の検討）

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Pediatrics and Neonatology xxx (xxxx) xxx

Available online at www.sciencedirect.com
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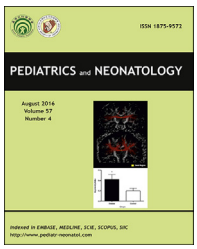

Original Article

Factors associated with the development of epilepsy in very low birth weight infants

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Received Apr 25, 2022; received in revised form Dec 10, 2022; accepted Dec 21, 2022
Available online ■ ■ ■

Key words
Cysticperiventricular leukomalacia;
Epilepsy;
Hypoxic ischemic encephalopathy;
Intraventricular hemorrhage;
Very low birth weight infants

Background: The survival rate of very low birth weight (VLBW) infants has recently improved. However, the occurrence of and factors associated with epilepsy in VLBW infants remain unknown. This study aimed to clarify the incidence, characteristics, and factors associated with epilepsy development in VLBW infants.
Methods: All VLBW infants admitted to our hospital between 2012 and 2017 were included in this study. VLBW infants with a follow-up period of <1 year were excluded. Chromosomal abnormalities, brain anomalies, severe intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), and hypoxic ischemic encephalopathy (HIE) were considered to be risk factors.
Results: Epilepsy occurred in 21/526 (4.0%) VLBW infants. Chromosomal abnormalities, brain anomalies, severe IVH, cystic PVL, HIE, neonatal seizures, advanced maternal age, maternal diabetes mellitus, no administration of antenatal corticosteroids, and low Apgar scores at 1 and 5 min were associated with a risk of epilepsy. The median time to epilepsy onset was 8 months (range: 0–59 months), and the onset occurred within 2 years in 15/21 patients (71.4%) and within 4 years in 18/21 patients (85.7%). VLBW infants with risk factors developed epilepsy earlier and at a significantly higher rate than those without risk factors. Among infants who had risk factors and who developed epilepsy, 86.7% did so within 2 years of age, compared to 33.3% of those who developed epilepsy but did not have risk factors.

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https://doi.org/10.1016/j.pedneo.2022.12.019

Please cite this article as: T. Fukao, F. Sano, A. Nemoto et al., Factors associated with the development of epilepsy in very low birth weight infants, Pediatrics and Neonatology, https://doi.org/10.1016/j.pedneo.2022.12.019

Conclusion: These findings regarding factors associated with a risk of development of epilepsy and temporal feature of epilepsy may contribute to the development of monitoring and treatment protocols for epilepsy in VLBW infants.

1. Introduction

Very low birth weight (VLBW) infants (<1500 g) account for approximately 1%–1.5% of all births but contribute to a considerable portion of neurodevelopmental impairments among survivors.[1] As a result of the advances in perinatal intensive care over the last decade, the survival rate and short-term outcomes of VLBW infants have improved significantly.[2] However, the long-term neurodevelopmental outcomes are still of great concern.[3,4] Previous studies have reported no decrease in the frequency of neurological sequelae, including cerebral palsy and other neurological disabilities.[5] A meta-analysis reported that the pooled prevalence of cerebral palsy, cognitive delays, and motor delays in VLBW survivors was 6.8%, 16.9%, and 20.6%, respectively.[6]

VLBW preterm infants have a high risk of adverse neurological outcomes compared to infants delivered at term. Several studies have analyzed long-term neurodevelopmental outcomes; however, few studies have been reported regarding the occurrence and risk factors of epilepsy, one of the major neurologic sequelae in VLBW infants. The reported incidence of epilepsy in VLBW infants is 1.7%–10.3%, which is greater than that in the general infant population.[7–10] While epilepsy can be considered a sequela of VLBW infants, the characteristics, age of onset, and factors associated with a risk of epilepsy in VLBW infants remain unclear.

The identification of features associated with epilepsy in VLBW infants will help healthcare providers identify newborns who require a proper follow-up due to an increased risk of developing epilepsy. Thus, this study aimed to clarify the incidence, characteristics, and factors associated with a risk of the development of epilepsy in VLBW infants.

2. Methods

2.1. Study design and participants

This retrospective, consecutive, observational cohort study included all VLBW infants admitted to the neonatal intensive care unit at our hospital from 2012 to 2017. The study conformed to the principles of the Declaration of Helsinki. Written informed consent for the research and publication of the results was obtained from the parents or guardians of all infants. The Neonatal Research Network of Japan (NRNJ) conducted a nationwide cohort study of VLBW infants in 2003.[11,12] The NRNJ database contains all perinatal records from birth to 3–6 years of age, and these data are recorded at each hospital. The data for this study were obtained from this database and from the medical records at each hospital. All VLBW infants (<1500 g) admitted to the neonatal intensive care unit at our hospital between January 1, 2012 and December 31, 2017 were included in this study. VLBW infants with a follow-up period of <1 year were excluded from the analysis.

2.2. Clinical data and variables

Clinical data regarding maternal complications and medications received during pregnancy and delivery were extracted. Antenatal corticosteroids (ACS) were administered when preterm delivery was inevitable. Chorioamnionitis was diagnosed based on clinical findings when histological specimens were unavailable.[13] Gestational age was calculated based on the monthly ultrasound examination and date of the last menstrual period. Small-for-gestational-age was defined as both birth weight and birth height below the 10th percentile of the Japanese birth size standards. Moderate-to-severe bronchopulmonary dysplasia was defined as a respiratory disturbance requiring supplemental oxygen or positive pressure at a gestational age of 36 weeks.[14] Patent ductus arteriosus was diagnosed using echocardiography, and it was treated with indomethacin or surgical ligation when symptomatic. Sepsis was defined as culture-proven septicemia or bacteremia during hospital admission. Severe intraventricular hemorrhage (IVH) was defined as grade 3 or 4 according to the scale reported by Papile et al.[15] Cystic periventricular leukomalacia (PVL) was defined as the formation of periventricular cysts. Necrotizing enterocolitis was diagnosed according to the signs of pneumoperitoneum on radiographic examinations.[16] Retinopathy of prematurity was diagnosed according to the international classification[17] and treated via laser/cryo-coagulation or the intravitreal injection of an angiogenesis inhibitor. Neonatal seizures were diagnosed in all patients based on both clinical symptoms and were confirmed with electroencephalography (EEG) findings, including amplitude-integrated EEG findings.

2.3. Definition of epilepsy

Epilepsy was diagnosed based on the diagnostic criteria of the 2014 International League Against Epilepsy (ILAE).[18] Epilepsy and seizure types were classified based on the 2017 ILAE classification.[19,20] VLBW infants with a history of neonatal seizures or febrile convulsions were not considered as having epilepsy. The incidence of epilepsy was determined using clinical records at the end of the follow-up period. The patients' age at seizure onset, epilepsy type, seizure type, paroxysmal EEG anomalies, and magnetic resonance imaging findings were evaluated.

2.4. Risk factors

In this study, chromosomal abnormalities, brain anomalies, severe IVH, cystic PVL, and hypoxic ischemic encephalopathy (HIE) were considered to be risk factors. If porencephaly was present at birth, it was classified as a brain anomaly. Patients were divided into groups based on the presence or absence of at least one risk factor to determine the association of risk factors and epilepsy.

2.5. Statistical analyses

All statistical analyses were performed using SPSS version 19 software (IBM, Chicago, IL, USA). Continuous data are presented as mean and standard deviation, and categorical data are presented as number and percentage. Continuous and binary variables were analyzed using Student's t-test and the chi-squared test, respectively. Thereafter, in consideration of potential interactions, a multiple logistic regression analysis was performed with all variables showing $P < 0.05$ in the bivariate analysis. Kaplan–Meier survival curves for composite and individual factors were analyzed using the log-rank test. Cumulative probability curves were analyzed using the Kolmogorov–Smirnov test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical characteristics

Among 594 VLBW infants who were enrolled in this study, 68 were excluded due to a follow-up period of <1 year as a result of death or loss to follow-up. In other words, this study included only infants who survived for >1 year in all cases, including those with chromosomal abnormalities. The final analyses included 526 patients (Fig. S1). The clinical and demographic characteristics are presented in Table 1.

Table 1 Patient characteristics.

	n = 526
Gestational age (weeks)	28.8 ± 3.4
Birth weight (g)	1052 ± 319
Maternal age (years)	31.4 ± 5.3
Sex (males:females)	239:287
Apgar score (1 min)	5.6 ± 2.2
Apgar score (5 min)	7.7 ± 1.7
Small-for-gestational-age	174/526 (33.1%)
Chromosomal abnormality	7/526 (1.3%)
Brain anomaly	7/526 (1.3%)
Intraventricular hemorrhage	
Grade I or II	35/504 (6.9%)
Grade III or IV	13/504 (2.6%)
Cystic periventricular leukomalacia	14/504 (2.8%)
Hypoxic ischemic encephalopathy	6/505 (1.2%)
Neonatal seizure	8/505 (1.6%)

Continuous data are presented as mean ± standard deviation. Categorical data are presented as numbers.

3.2. Incidence and factors associated with an occurrence of epilepsy

Epilepsy occurred in 21/526 VLBW infants (4.0%) during the follow-up period (mean follow-up: 5.3 years). The demographic data and characteristics of patients with epilepsy are summarized in Table S1. The incidence of epilepsy was significantly higher in patients with advanced maternal age ($P = 0.027$) and maternal diabetes mellitus (DM) ($P = 0.003$) and significantly lower in those who received ACS ($P = 0.025$) (Table 2). Low Apgar scores at 1 min ($P = 0.001$) and 5 min ($P = 0.001$), chromosomal abnormalities ($P < 0.001$), brain anomalies ($P < 0.001$), severe IVH ($P < 0.001$), cystic PVL ($P = 0.001$), HIE ($P < 0.001$), and neonatal seizures ($P < 0.001$) were also associated with an increased incidence of epilepsy in VLBW infants (Table 2). No patient had symptomatic hypoglycemia. In the logistic regression analysis, maternal DM ($P = 0.012$), Low Apgar scores at 5 min ($P = 0.049$), chromosomal abnormalities ($P = 0.003$), and cystic PVL ($P = 0.032$) were independently and significantly associated with the onset of epilepsy (Table 3). Among these variables, chromosomal abnormalities had the highest odds ratio of 50.7 (95% confidence interval: 5.92–434).

3.3. Incidence and factors associated with an occurrence of epilepsy among patients with or without risk factors

The clinical and demographic characteristics of patients with or without risk factors are shown in Table 4. Forty infants (7.6%) had risk factors, including 15 (37.5%) who developed epilepsy. Among the patients with risk factors, advanced maternal age ($P = 0.007$), low Apgar scores at 1 min ($P = 0.033$), SGA ($P = 0.013$), brain anomalies ($P < 0.001$), and neonatal seizures ($P < 0.001$) were associated with the incidence of epilepsy. The variables in the logistic regression analysis showed no significant difference (Table S2). Overall, 486 infants (92.4%) did not have risk factors, including six (1.2%) who developed epilepsy. Among patients without risk factors, the incidence of epilepsy was associated with maternal DM ($P = 0.008$), but no associations were observed between epilepsy and advanced maternal age ($P = 0.913$), Apgar scores at 1 min ($P = 0.912$), or neonatal seizures ($P = 0.871$). A logistic regression analysis was not performed for the patients without risk factors, as there was only one variable showing $P < 0.05$ in the bivariate analysis.

3.4. Temporal features of the onset of epilepsy

The median time to epilepsy onset was 8 months (range: 0–59 months) (Fig. 1A), including 12/21 patients (57.1%) who developed epilepsy within 1 year, 15/21 patients (71.4%) who developed epilepsy within 2 years, and 18/21 (85.7%) who developed epilepsy within 4 years (Fig. 1B).

VLBW infants with risk factors developed epilepsy at a significantly higher rate ($P < 0.001$) (Fig. 1C) and earlier ($P < 0.001$) (Fig. 1D) than those without risk factors. In the risk factors group, 13/15 patients (86.7%) developed epilepsy within 2 years, and 15 (100%) developed epilepsy

Table 2 Characteristics of VLBW infants with and without epilepsy.

	Epilepsy	Without epilepsy	*P*-value
	n = 21	n = 505	
Gestational age (weeks)	28.8 ± 4.2	28.8 ± 3.3	0.993
Birth weight (g)	982 ± 357	1055 ± 318	0.303
Maternal age (years)	34.0 ± 4.9	31.3 ± 5.3	0.027
Diabetes mellitus	5/21 (23.8%)	32/489 (6.5%)	0.003
Antenatal corticosteroid	9/21 (42.9%)	322/483 (66.7%)	0.025
Sex (males:females)	12:9	227:278	0.273
Apgar score (1 min)	3.9 ± 2.4	5.7 ± 2.1	0.001
Apgar score (5 min)	5.8 ± 2.6	7.8 ± 1.6	0.001
Small-for-gestational-age	10/21 (47.6%)	164/505 (32.5%)	0.148
Chromosomal abnormality	4/21 (19.0%)	3/505 (0.6%)	<0.001
Brain anomaly	7/21 (33.3%)	0/505 (0%)	<0.001
Severe intraventricular hemorrhage	4/21 (19.0%)	9/483 (1.9%)	<0.001
Cystic periventricular leukomalacia	3/21 (14.3%)	11/483 (2.3%)	0.001
Hypoxic ischemic encephalopathy	2/21 (9.5%)	4/484 (0.8%)	<0.001
Neonatal seizure	6/21 (28.6%)	2/484 (0.4%)	<0.001

Continuous data are presented as mean ± standard deviation. Categorical data are presented as numbers.

Table 3 Results of multiple logistic regression analysis.

	Odds ratio (95% confidence interval)	*P*-value
Maternal age (years)	1.07 (0.94—1.22)	0.277
Diabetes mellitus	7.70 (1.55—38.3)	0.012
Antenatal corticosteroid	0.61 (0.15—2.54)	0.493
Apgar score (1 min)	1.10 (0.68—1.79)	0.692
Apgar score (5 min)	0.57 (0.33—1.00)	0.049
Chromosomal abnormality	50.7 (5.92—434)	0.003
Brain anomaly	N.A.	N.A.
Intraventricular hemorrhage Grade III or IV	2.29 (0.20—25.8)	0.502
Cystic periventricular leukomalacia	17.4 (2.60—116)	0.032
Hypoxic ischemic encephalopathy	0.49 (0.01—27.4)	0.725
Neonatal seizure	26.9 (0.71—1028)	0.076

N.A.: not applicable.

within 4 years (Fig. 1D). Among the patients without risk factors, 2/6 (33.3%) developed epilepsy within 2 years, 3/6 (50%) developed epilepsy within 4 years, and 6/6 (100%) developed epilepsy within 5 years (Fig. 1D). The incidence of epilepsy was significantly higher in patients presenting any of the following risk factors (namely, chromosomal abnormalities [$P < 0.001$], brain anomalies [$P < 0.001$], severe IVH [$P < 0.001$], cystic PVL [$P < 0.001$], or HIE [$P < 0.001$]) than in those presenting no risk factors (Fig. 1E—H).

4. Discussion

Chromosomal abnormalities, brain anomalies, severe IVH, cystic PVL, HIE, neonatal seizures, advanced maternal age, maternal DM, no ACS received, and low Apgar scores at 1 and 5 min were identified as factors which were associated with a risk of the development of epilepsy in VLBW infants in this study. The results of the multivariate analysis suggested that chromosomal abnormalities, cystic PVL, maternal DM, and low Apgar scores at 5 min could be independently involved in the development of epilepsy in VLBW infants. Most (approximately 70%) of the VLBW infants developed epilepsy within the first 2 years of life, and epilepsy tended to occur earlier in patients with risk factors than in those without risk factors. These results regarding the qualitative and temporal risk factors for the development of epilepsy in VLBW infants are useful for the development of monitoring and treatment protocols for VLBW infants.

This study differs from a previous report[21] in that a geographically uniform patient population from two hospitals of the same region was included, allowing the evaluation of detailed outcomes, including epilepsy characteristics. Only a small number of patients were excluded.

In this study, 21/526 (4.0%) VLBW infants developed epilepsy. This rate is higher than the epilepsy rate reported in the general population, including that of Japan (0.3%—0.8%).[22—25] Although the direct comparison of the results of this study with those of previous studies is challenging due to differences in gestational age, birth weight, and follow-up period, previous studies have reported that VLBW or extremely low birth weight infants tend to have a higher incidence of epilepsy (1.7%—8.6%).[10,21,26] These results indicate that the complications of preterm birth in VLBW infants contribute to the development of epilepsy. In previous studies, the association between preterm delivery and epilepsy may be due to immaturity and brain insults, such as cerebral white matter gliosis or hippocampal sclerosis.[27—29]

Severe IVH, cystic PVL, and HIE have been identified as factors which are associated with a risk of the development of epilepsy in VLBW infants in this study. These brain insults

Table 4 Associations of risk factors and epilepsy.

	Patients with at least one risk factor			Patients with no risk factors		
	n = 40			n = 486		
	Epilepsy	Without epilepsy	*P*-value	Epilepsy	Without epilepsy	*P*-value
	n = 15	n = 25		n = 6	n = 480	
Gestational age (weeks)	29.1 ± 4.5	28.4 ± 2.8	0.547	28.2 ± 3.3	28.8 ± 3.4	0.632
Birth weight (g)	963 ± 380	1101 ± 298	0.209	1029 ± 319	1053 ± 319	0.857
Maternal age (years)	35.1 ± 4.4	30.2 ± 5.7	0.007	31.2 ± 5.3	31.4 ± 5.3	0.913
Diabetes mellitus	3/15 (20.0%)	3/25 (12.0%)	0.493	2/6 (33.3%)	29/464 (6.3%)	0.008
Apgar score (1 min)	3.1 ± 2.1	4.8 ± 2.3	0.033	5.7 ± 2.1	5.8 ± 2.1	0.912
Apgar score (5 min)	5.4 ± 3.0	6.9 ± 2.1	0.085	6.7 ± 1.6	7.8 ± 1.5	0.065
Small-for-gestational-age	8/15 (53.3%)	4/25 (16.0%)	0.013	2/6 (33.3%)	160/480 (33.3%)	0.999
Chromosomal abnormality	4/15 (26.7%)	3/25 (12.0%)	0.237	—	—	—
Brain anomaly	7/15 (46.7%)	0/25 (0%)	<0.001	—	—	—
Severe intraventricular hemorrhage	4/15 (26.7%)	9/25 (36.0%)	0.542	—	—	—
Cystic periventricular leukomalacia	3/15 (20.0%)	11/25 (44.0%)	0.123	—	—	—
Hypoxic ischemic encephalopathy	2/15 (13.3%)	4/25 (16.0%)	0.819	—	—	—
Neonatal seizure	6/15 (40.0%)	0/25 (0%)	<0.001	0/6 (0%)	2/459 (0.4%)	0.871

Continuous data are presented as mean ± standard deviation. Categorical data are presented as numbers.

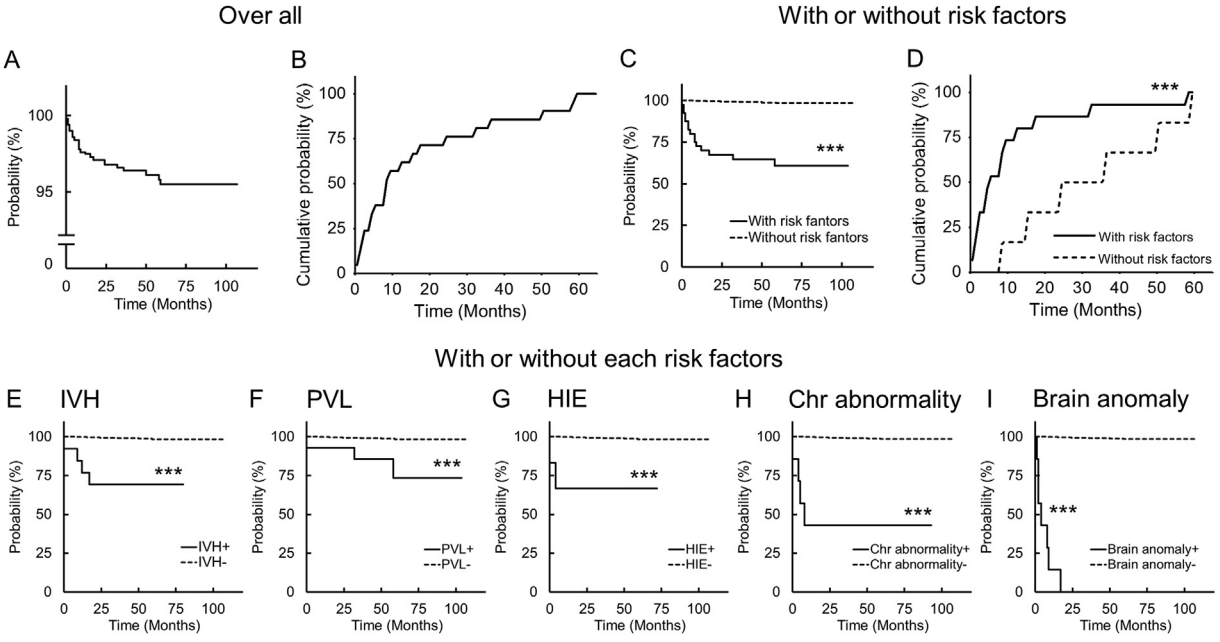

Fig. 1 Kaplan—Meier survival curves and cumulative probability curves for the development of epilepsy. A: Kaplan—Meier survival curves for the development of epilepsy in VLBW infants; B: Cumulative probability curve for the development of epilepsy in VLBW infants; C: Kaplan—Meier survival curves for the development of epilepsy in VLBW infants with and without risk factors (***$P < 0.001$); D: Cumulative probability curve for the development of epilepsy in VLBW infants with and without risk factors (***$P < 0.001$). The Kaplan—Meier survival curves for the development of epilepsy in VLBW infants with and without IVH (E), cystic PVL (F), hypoxic ischemic encephalopathy (G), Chr abnormalities (H), and brain anomalies (I) are also shown (***$P < 0.001$). Abbreviations: Chr: chromosomal; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; VLBW: very low birth weight.

can affect cortical and subcortical circuit formation, disturbing myelination process and dendritic connections.[9,10,21,29–31] In the present study, chromosomal abnormalities, brain anomalies, and neonatal seizures were identified as risk factors for the development of epilepsy. These results are similar to those of previous studies that included term infants.[32] Convulsions during the neonatal period have been reported as a risk factor for pediatric epilepsy.[23,33] Most seizures in neonates have symptomatic etiologies, including genetic or structural abnormalities that cause neurologic dysfunction. The etiology of seizures is one of the most important risk factors of the long-term outcome.[30] In particular, the results of our multivariate analysis suggested that cystic PVL and chromosomal

abnormalities could be independently involved in the development of epilepsy in VLBW infants. The results of the multivariate analysis also suggest that neonatal seizure, which was a significant risk factor for developing epilepsy in the univariate analysis, was a possible confounding factor. This suggests that neonatal seizure itself is not a risk factor for epilepsy, and underlying conditions that cause it, such as cystic PVL and chromosomal abnormalities, may be more important risk factors for epilepsy.

Advanced maternal age, maternal DM, the lack of ACS, and low Apgar scores were also factors to be associated with epilepsy in VLBW infants in this study. The results of the logistic analysis suggested that maternal DM and low Apgar scores at 5 min could be independently involved in the development of epilepsy in VLBW infants. A previous study reported that advanced maternal age may be associated with the development of epilepsy via an increase in congenital abnormalities (including chromosomal abnormalities and brain anomalies considered in this study).[34] Term and preterm infants with low Apgar scores have been reported to have increased risk of epilepsy,[35] which is consistent with the results of this study. Maternal DM has been reported to be associated with cognitive and behavioral disorders, including autism spectrum disorders (ASD),[36] although the association with epilepsy has not yet been reported. Previous studies have reported an association between obesity and its related conditions and ASD, indicating that adiposity-induced inflammation increases the risk of ASD.[37,38] Previous studies have reported that treatment of preterm infants with ACS has contributed to improved outcomes.[39] Although the effect of ACS treatment on the incidence of epilepsy in VLBW infants is unknown, it is suggested that ACS may also contribute to the prevention of epilepsy in these infants through the prevention of complications related to preterm birth, such as cystic PVL.

The incidence of epilepsy has been reported to be high in young children and to decline with age in both childhood and adulthood.[40] The age-adjusted incidence of epilepsy was 44 per 100,000 person-years, and it was the highest in the first year of life.[23] The age-adjusted incidence of epilepsy in VLBW infants remains unclear. In this study, 71.4% of patients with epilepsy were diagnosed within 2 years of age, and the incidence of epilepsy gradually decreased with age, similar to the epilepsy trends in the general pediatric population.[23,40] In addition, VLBW infants with risk factors developed epilepsy at a significantly younger age than those without risk factors. Our results suggest that VLBW infants with risk factors should be monitored closely within the first 2 years after birth, and those without risk factors should be monitored for approximately 5 years after birth.

This study has some limitations. Since it was performed in a specific area of Japan, the results may be biased, e.g., by race. Data regarding several potential risk factors for developing epilepsy, such as a family history of epilepsy, were unavailable. The data recording protocols of the administrative databases may have varied throughout the study period. Furthermore, unidentified confounding factors may affect the results. The follow-up time in this study may have been too short for some patients, especially those with idiopathic epilepsy. A receiver operating characteristic curve analysis could not be performed in this study. Finally, the results of the subgroup analyses for each risk factor, including the logistic regression analysis, may not be powerful due to the small sample size.

In conclusion, chromosomal abnormalities, brain anomalies, severe IVH, cystic PVL, HIE, neonatal seizures, maternal DM, no administration of ACS, and low Apgar scores at 1 and 5 min were identified as factors associated with risk of the development of epilepsy in VLBW infants. In addition, the incidence of epilepsy in VLBW infants is higher in early childhood and gradually decreases with age. These results can be used to help develop monitoring and treatment protocols for epilepsy in VLBW infants.

Funding/support

This work was supported by JSPS KAKENHI Grant Numbers JP16K19634, JP18K15701 and JP21K07793.

Ethics statement

The study was approved by the ethics committee of Yamanashi University and conformed to the principles of the Declaration of Helsinki. Written informed consent for the research and publication of the results was obtained from the parents or guardians of all infants.

Declaration of competing interest

None.

Acknowledgements

We thank the residents of the Yamanashi Prefectural Central Hospital and Nagano Children's Hospital for their assistance with the registration of patients, follow-up, and data collection. We also thank all of the members in the Department of Pediatrics at the University of Yamanashi for their contributions to the critical discussions regarding our study.

References

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;**10**(Suppl 1):S2.
2. Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among periviable infants. *N Engl J Med* 2017;**376**:617—28.
3. Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996—1997. *Pediatrics* 2005;**116**:1391—400.
4. Kono Y, Mishina J, Yonemoto N, Kusuda S, Fujimura M. Outcomes of very-low-birthweight infants at 3 years of age born in 2003—2004 in Japan. *Pediatr Int* 2011;**53**:1051—8.
5. Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *Lancet* 2007;**369**:43—50.
6. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and

very-low-birthweight infants born over the past decade: a meta-analytic review. *Dev Med Child Neurol* 2018;**60**:342–55.
7. Pisani F, Facini C, Bianchi E, Giussani G, Piccolo B, Beghi E. Incidence of neonatal seizures, perinatal risk factors for epilepsy and mortality after neonatal seizures in the province of Parma, Italy. *Epilepsia* 2018;**59**:1764–73.
8. Falsaperla R, Mauceri L, Motta M, Prezioso G, Ruggieri M, Pisani F. Beyond neonatal seizures - epileptic evolution in preterm newborns: a systematic review and meta-analysis. *Epileptic Disord* 2022;**24**:140–50.
9. Kohelet D, Shochat R, Lusky A, Reichman B, Israel Neonatal Network. Risk factors for seizures in very low birthweight infants with periventricular leukomalacia. *J Child Neurol* 2006;**21**:965–70.
10. Falchi M, Palmas G, Pisano T, Meloni M, Gaspa G, Puddu M, et al. Incidence of epilepsy in extremely low-birthweight infants (<1,000 g): a population study of central and southern Sardinia. *Epilepsia* 2009;**50**(Suppl 1):37–40.
11. Kusuda S, Fujimura M, Uchiyama A, Nakanishi H, Totsu S, for Neonatal Research Network, Japan. Identification of practices and morbidities affecting the mortality of very low birth weight infants using a multilevel logistic analysis: clinical trial or standardisation? *BMJ Open* 2013;**3**:e003317.
12. Maruyama H, Yonemoto N, Kono Y, Kusuda S, Fujimura M, Neonatal Research Network of Japan. Weight growth velocity and neurodevelopmental outcomes in extremely low birth weight infants. *PLoS One* 2015;**10**:e0139014.
13. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol* 2010;**37**:339–54.
14. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005;**116**:1353–60.
15. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;**92**:529–34.
16. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978;**187**:1–7.
17. International Committee for the Classification of Retinopathy of Prematurity. The international classification of Retinopathy of prematurity revisited. *Arch Ophthalmol* 2005;**123**:991–9.
18. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;**55**:475–82.
19. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French JA, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;**58**:512–21.
20. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 2017;**58**:531–42.
21. Matsushita Y, Sakai Y, Torio M, Inoue H, Ochiai M, Yasuoka K, et al. Association of perinatal factors of epilepsy in very low birth weight infants, using a nationwide database in Japan. *J Perinatol* 2019;**39**:1472–9.
22. Chiang KL, Cheng CY. Prevalence and neuro-psychiatric comorbidities of pediatric epilepsy in Taiwan: a national population-based study. *Epilepsy Res* 2014;**108**:1451–60.
23. Annegers JF, Dubinsky S, Coan SP, Newmark ME, Roht L. The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations. *Epilepsia* 1999;**40**:502–6.
24. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;**34**:453–68.
25. Oka E, Ohtsuka Y, Yoshinaga H, Murakami N, Kobayashi K, Ogino T. Prevalence of childhood epilepsy and distribution of epileptic syndromes: a population-based survey in Okayama, Japan. *Epilepsia* 2006;**47**:626–30.
26. Stoinska B, Gadzinowski J. Neurological and developmental disabilities in ELBW and VLBW: follow-up at 2 years of age. *J Perinatol* 2011;**31**:137–42.
27. Hüppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol* 1998;**43**:224–35.
28. Dieni S, Inder T, Yoder B, Briscoe T, Camm E, Egan G, et al. The pattern of cerebral injury in a primate model of preterm birth and neonatal intensive care. *J Neuropathol Exp Neurol* 2004;**63**:1297–309.
29. Evrard P, Gressens P, Volpe JJ. New concepts to understand the neurological consequences of subcortical lesions in the premature brain. *Biol Neonate* 1992;**61**:1–3.
30. Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. The incidence and risk factors of epilepsy in children born preterm: a nationwide register study. *Epilepsy Res* 2017;**138**:32–8.
31. Vesoulis ZA, Inder TE, Woodward LJ, Buse B, Vavasseur C, Mathur AM. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. *Pediatr Res* 2014;**75**:564–9.
32. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. *Semin Fetal Neonatal Med* 2013;**18**:224–32.
33. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics* 2006;**117**:1270–80.
34. Zhang XH, Qiu LQ, Ye YH, Xu J. Chromosomal abnormalities: subgroup analysis by maternal age and perinatal features in Zhejiang province of China, 2011–2015. *Ital J Pediatr* 2017;**43**:47.
35. Sun Y, Vestergaard M, Pedersen CB, Christensen J, Basso O, Olsen J. Gestational age, birth weight, intrauterine growth, and the risk of epilepsy. *Am J Epidemiol* 2008;**167**:262–70.
36. Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children. *JAMA* 2020;**323**:1924–33.
37. Li M, Fallin MD, Riley A, Landa R, Walker SO, Silverstein M, et al. The association of maternal obesity and diabetes with autism and other developmental disabilities. *Pediatrics* 2016;**137**:e20152206.
38. Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, et al. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. *Int J Epidemiol* 2015;**44**:870–83.
39. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2020;**12**:CD004454.
40. Sillanpää M, Lastunen S, Helenius H, Schmidt D. Regional differences and secular trends in the incidence of epilepsy in Finland: a nationwide 23-year registry study. *Epilepsia* 2011;**52**:1857–67.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.12.019.

Supplemental data

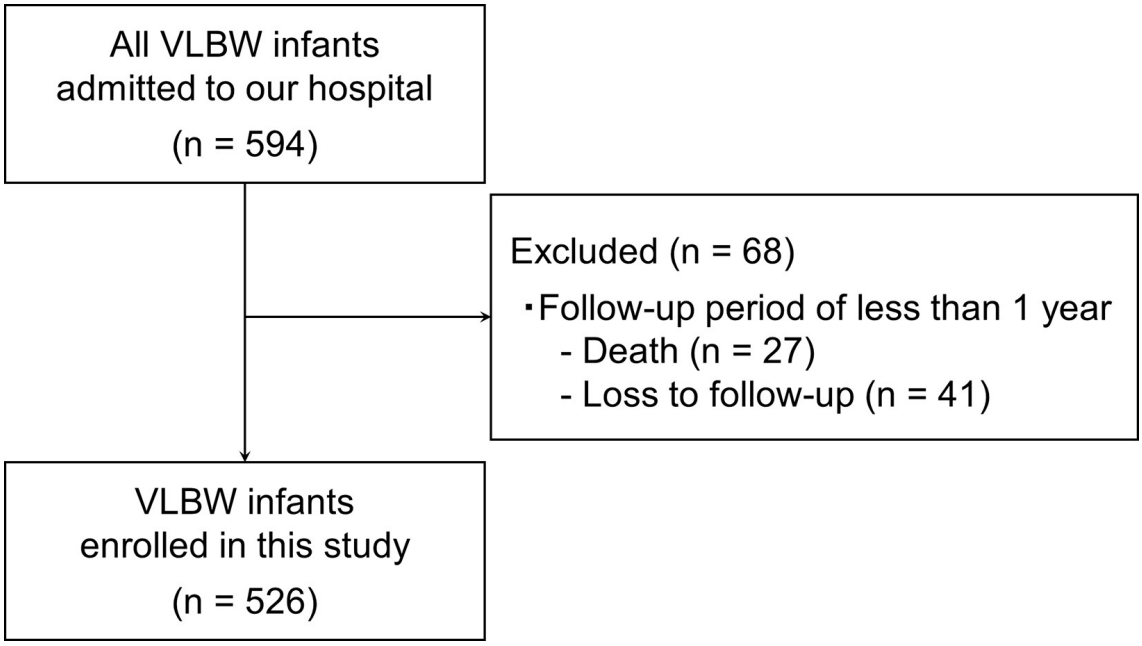

Figure S1. Study enrollment flowchart.
Abbreviations: VLBW: very low birth weight

Table S1. Characteristics of VLBW infants with epilepsy

	n = 21
Age at onset of epilepsy (months)	17.0 ± 19.1
Epilepsy syndrome	
Focal epilepsy	12 (57.1%)
Developmental and epileptic encephalopathy	9 (42.9%)
Etiology (overlapping)	
Structural	14 (66.7%)
Brain anomaly	
Holoprosencephaly	3 (14.3%)
Schizencephaly	2 (9.5%)
Porencephaly	1 (4.8%)
Polymicrogyria	1 (4.8%)
Intracranial complication	
Severe intraventricular hemorrhage	4 (19.0%)
Post-hemorrhagic hydrocephalus	4 (19.0%)
Cystic periventricular leukomalacia	2 (9.5%)
Hypoxic ischemic encephalopathy	2 (9.5%)
Genetic	9 (42.9%)
Chromosomal abnormality	
13 trisomy	2 (9.5%)
18 trisomy	1 (4.8%)
21 trisomy	1 (4.8%)
Type of seizure attack (overlapping)	
Focal onset	15 (71.4%)
Generalized onset	4 (19.0%)
Unknown onset	7 (33.3%)
Unclassified	1 (4.8%)
EEG abnormality	
Generalized discharge	8 (38.1%)
Focal discharge	10 (47.6%)
Within normal limits in interictal EEG	3 (14.3%)
Number of antiepileptic drugs	1.5 ± 0.9

Continuous data are presented as mean ± standard deviation. Categorical data are presented as numbers.

Abbreviations: EEG: electroencephalogram; VLBW: very low birth weight

Table S2. Multiple logistic regression analysis of infants without risk factors

	Odds ratio (95% confidence interval)	*P* value
Patients with at least one risk factor		
Maternal age (years)	2.39 (0.92–6.23)	0.074
Apgar score (1 min)	0.92 (0.38–2.27)	0.863
Small-for-gestational age	353 (0.47–2.63 × 10*6)	0.082
Brain anomaly	N.A.	N.A.
Neonatal seizure	N.A.	N.A.

N.A.: not applicable