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Original article

Neurodevelopmental outcomes of children with periventricular leukomalacia: the role of infection and ischemia

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Abstract

Introduction: Periventricular leukomalacia (PVL) is an important cause of preterm newborn's cerebral white matter disease. This study assessed neurodevelopmental outcomes of children with PVL and its etiologic subgroups.

Methods: Retrospective review of medical records of children with PVL diagnosis born at a tertiary center between 1996 and 2016. Subjects were divided into two groups according to the most likely etiology of PVL (ischemic versus infectious) using a classification system of risk factors. The neurologic and development outcomes were reviewed.

Results: A total of 34 newborns with a median gestational age of 29 weeks were selected. Sixteen newborns (51.6%) were included in the ischemic group, while 15 (48.4%) were included in the infectious group; a clear group classification was not possible in 3 cases. PVL was moderate to severe in 73.5% of cases. Cerebral palsy (CP) developed in 69.7% of the children, 29% had epilepsy and 15.6% were microcephalic. Children with moderate to severe PVL were significantly more impaired than children with mild PVL ($p < 0.05$). Moderate to severe PVL was observed in 93.3% of the children in the infectious group and 71.4% in the ischemic group ($p = 0.12$). Children in the infectious group were more prone to abnormal development and CP, while children in the ischemic group had more epilepsy and hearing impairment than the infectious group.

Discussion: Infection may be an important etiologic factor regarding severe forms of PVL. The infectious group presented a higher incidence of CP, which may be related to more severe white matter injuries. The ischemic group presented more epilepsy, suggesting the involvement of gray matter disease.

Keywords

Periventricular leukomalacia, etiology, cerebral palsy, neonatal brain white matter injury, cognitive outcome.

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Introduction

Significant advances in neonatal assistance have improved the survival of extreme preterm neonates. However, neurodevelopmental sequelae, such as cerebral palsy (CP), cognitive impairment and behavioral changes, remain a major concern [1].

In a developing organism, any insult to the central nervous system may have permanent consequences, depending not only on the nature of the insult but also on the timing in which it occurs. The brain, particularly the preterm's cerebral white matter, is extremely susceptible to ischemic and infectious insults. The two main brain lesions responsible for neurological sequelae in preterm newborns are periventricular leukomalacia (PVL) and periventricular hemorrhagic stroke [2].

PVL is the leading cause of non-hemorrhagic neuropathological abnormality in the cerebral white matter of a preterm infant [3].

From the anatomopathological point of view, PVL has two basic components: a deeper zone of focal necrosis and a more peripheral and extensive area where diffuse gliosis predominates. Histologically it is characterized by coagulation necrosis, microglial infiltration, astrocytic proliferation, and eventual cyst formation. The ultimate result is the loss of volume of cerebral white matter with secondary ventriculomegaly [4].

Previous data indicate that the pathogenesis of PVL is the consequence of the effect of hypoxia, ischemia and inflammation in the progenitor oligodendrocyte cells, which are particularly vulnerable to such insults, and are located in the periventricular area between the 23rd and 32nd weeks of gestation [5].

The main factors that explain PVL anatomic distribution and higher incidence in preterms are the distribution and development of brain vascularization, the lack of cerebral blood flow autoregulation and the intrinsic vulnerability of the cerebral white matter, rich in pre-oligodendrocytes. Any inflammatory or infectious process leads to systemic upregulation of pro-inflammatory cytokines and diffuse activation of microglia within the immature white matter, leading to injury [6].

The aim of this study was to analyze the neurodevelopmental outcomes of children with PVL. Additionally, we assessed the neurodevelopmental outcomes according to two major insults in PVL (ischemic and infectious), so as to help clarify the weight of each insult in the prognosis of PVL.

Methods

This study was conducted at a tertiary-care hospital. Medical records of preterm babies, born between 1996 and 2016, diagnosed with PVL, were retrospectively reviewed. The diagnosis was established by ultrasound, performed by expert neonatologists. Data concerning demographic and clinical characteristics were obtained from clinical records.

Based on brain ultrasound findings, PVL was classified in groups using a modified version of the classic classification: grade 1, transient periventricular echo densities persisting for > 7 days; grade 2, transient periventricular echo densities evolving into small, localized frontoparietal cysts; grade 3, periventricular echo densities evolving into extensive periventricular cystic lesions; grade 4, densities extending into the deep white matter evolving into extensive cystic lesions [7]. Grade 1 was classified as mild PVL and grade 2 to 4 as moderate/severe PVL.

All cases were classified by two independent researchers, according to the prenatal and neonatal history, in one of two groups: infectious group and ischemic group. The classification was carried out by scoring one point to the following risk factors: for presumed infectious origin – prolonged rupture of membranes (> 12 h), chorioamnionitis, maternal

fever, maternal leucocytosis, a high level of C-reactive protein (CRP), infectious pathological changes in the placenta and neonatal sepsis; for presumed ischemic origin – intrauterine growth restriction, preeclampsia, umbilical cord knot, placental abruption, ischemic pathological changes in the placenta, multiple pregnancies, hypoxemia and apneas with respiratory support, anaemia, hypotension and patent ductus arteriosus. The highest score in each cluster of risk factors defined the group.

Chorioamnionitis was established in the presence of fever of 37.8ºC or higher plus two or more minor signs (maternal tachycardia > 100 beats/min, fetal tachycardia > 160 beats/min, uterine tenderness, foul odour of the amniotic fluid and leucocytosis > 15,000/mm^3) [8]. Significant hypotension was considered in cases that needed resuscitation with fluids or drugs.

All children were regularly followed as out-patients upon hospital discharge and they all had at least two years of follow-up. The evaluation was performed using the Griffiths Developmental Scale. The results were presented according to the common metring system [9]. Audiology assessment through the auditory brainstem response was performed at least until 24 months of age. The children were also observed by an ophthalmologist during their stay at the Neonatal Intesive Care Unit (NICU) to identify signs of retinopathy and after discharge in the clinic.

CP diagnosis was performed by the neonatologist responsible for the follow-up of high-risk preterm babies. CP was classified as spastic, ataxic, and dyskinetic [10].

Data analysis was performed using the Statistical Package for the Social Sciences for Windows® (SPSS® version 25.0, IBM® SPSS Incorporated, Chicago, IL). Univariable analysis was performed through Chi-square tests (for categorical variables), t-tests (for categorical versus continuous variables with normal distribution) and U-Mann-Whitney tests (for categorical versus continuous variables without normal distribution). Multivariable analysis was not feasible due to the reduced number of patients included. A p-value of less than 0.05 was considered statistically significant.

According to the Institutional Review Board of our institution, all data was anonymised for record and subsequent analysis.

Results

A total of 34 newborns (55.9% male) with a median (P25-P75) gestational age of 29 (28-30) weeks were selected. From these, collected data allowed for group classification in 31 of the newborns: 16 (51.6%) mainly had ischemic risk factors thus classified in the ischemic group and 15 (48.4%) predominantly had infectious risk factors thus classified in the infectious group. Three newborns were excluded from the group classification because they had a mixture of ischemic and infectious risk factors, which did not enable a clear classification.

Demographic data, prenatal history and delivery details are described in **Tab. 1**.

Prolonged rupture of membranes occurred in 12 (37.5%) newborns, while chorioamnionitis occurred in 7 (21.9%). Assisted vaginal delivery or C-section occurred in 58.8% of the cases. There were 4 cases of placental abruption and 1 of knot of the umbilical cord.

Placental pathology report available for 18 newborns had ischemic findings in 5.6% of cases, infectious findings in 61.1% and a mixture of alterations in 5.6%. Placental pathology identified ischemia in 10.0% (1/10) of the newborns in the ischemic etiology group and inflammatory changes in 72.7% (8/11) of those in the infectious group.

The median length of total stay was 47 (33-63) days. PVL was classified as mild in 6 cases, moderate to severe in 25, while in 3 cases it was not possible to grade. Median days for PVL diagnosis were 6 (2.7-13.2), 53.8% being diagnosed during the first week of life. During hospitalization 87.5% of newborns needed respiratory support: invasive in 62.5% (n = 20) and only non-invasive in 43.8% (n = 14). Invasive ventilation needs were significantly more frequent in newborns with moderate to severe PVL when compared with mild PVL (n = 17, $p < 0.05$). Early neonatal sepsis occurred in 38.2%. Despite not statistically significant ($p = 0.057$), newborns with early-onset sepsis developed only moderate to severe PVL and not mild PVL. Intraventricular hemorrhage was identified in 25%. Retinopathy was present in 6 newborns (grade 1 in 5 cases).

All children were submitted to neurodevelopmental assessments for a minimum of 2 years. Nine children (26.5%) had a normal developmental outcome and the remainder (73.5%) had different grades of impairment in different areas (**Tab. 2**).

CP developed in 69.7% of the children, the majority of whom had spastic CP (63.6%). Microcephaly was present in 15.6% of the children and 29% had epilepsy. Every child who developed epilepsy belonged to the moderate to severe PVL group.

Table 1. Demographic data and hospitalization details.

Variables (n = 34 [a])		n (%)
Sex (male)		19 (55.9%)
Weight at birth (mean, min-max), g		1,305 (720-1,960)
Gestational age (median, P25-P75), weeks		29 (28-30)
Prenatal history		
Number of fetuses	1	21 (61.8%)
	2	12 (35.3%)
	3	1 (2.9%)
Intrauterine growth restriction		3 (8.8%)
Preeclampsia		2 (5.9%)
Prenatal steroids		25 (73.5%)
Delivery details		
Vaginal delivery		14 (41.2%)
Assisted vaginal delivery or C-section		20 (58.8%)
Placental abruption (n = 33)		4 (12.1%)
Chorioamnionitis (n = 32)		7 (21.9%)
Placental pathology (n = 18)	Ischemic findings	1 (5.6%)
	Infection findings	11 (61.1%)
	Overlapping findings	1 (5.6%)
	Feto-fetal transfusion syndrome	2 (11.1%)
	Non-specific	3 (16.7%)
Hospitalization details		
Length of stay (median, P25-P75), days		47 (33-63)
Need of respiratory support (n = 32)		28 (87.5%)
Non-invasive ventilation		14 (43.8%)
Invasive ventilation		20 (62.5%)
Anemia with need of transfusion (n = 32)		8 (25%)
Hypotension (n = 32)		9 (28.1%)
Arterial duct patency (n = 32)		10 (31.3%)
Neonatal sepsis (n = 32)		23 (71.9%)
Retinopathy (n = 33)		6 (18.2%)
Grade 1		5 (15.2%)
Grade 2		1 (3%)
Intraventricular hemorrhage (n = 32)		8 (25%)
PVL	Grade 1	6 (17.6%)
	Grade 2	10 (29.4%)
	Grade 3	14 (41.2%)
	Grade 4	1 (3%)
	Non-classified	3 (8.8%)

[a] Unless otherwise specified.
PVL: periventricular leukomalacia.

Table 2. Follow-up data of patients with periventricular leukomalacia (PVL).

Outcome variables (n = 34 [a])		n (%)
Normal development		9 (26.5%)
Normal hearing (n = 32)		29 (90.6%)
Ophtalmologic evaluation (n = 32)	Normal	15 (46.9%)
	Refractive errors	3 (9.4%)
	Strabismus	12 (37.5%)
	Visual impairment	2 (6.3%)
CP (n = 33)		23 (69.7%)
Spastic		21 (63.6%)
Dyskinetic		5 (15.2%)
Epilepsy (n = 31)		9 (29%)
Microcephaly (n = 32)		5 (15.6%)

[a] Unless otherwise specified.
CP: cerebral palsy.

During follow-up, 9.4% were found to have hearing loss and 53.1% altered ophthalmic evaluations (**Tab. 2**).

To assess quantitative development, Griffiths mental development scale was used in children who were approximately 3 years old. Only about a third (n = 10) of the patients were evaluated by Griffiths scale, either because of severe neurodevelopment limitations or lack of cooperation. Results were below average with greater expression in the locomotor development subscale (QA), especially in moderate to severe PVL. Children with moderate to severe PVL had significantly more neurodevelopmental complications than children with mild PVL during follow-up ($p < 0.05$). **Fig. 1** presents Griffiths subscales results according to PVL grade. **Fig. 2** plots the results of subscales regarding the two groups.

When we compared the ischemic and infectious groups (**Tab. 3**), moderate to severe PVL was seen in 93.3% of the children in the inflammatory group, and in 71.4% of the ischemic group ($p = 0.12$).

Children in the infectious group were more prone to abnormal development (80% vs. 62.5%, $p = 0.28$). CP also occurred more in the infectious group compared with the ischemic group (85.7% vs. 56.3%, $p = 0.11$). Children in the ischemic group had more epilepsy and hearing impairment than the infectious group.

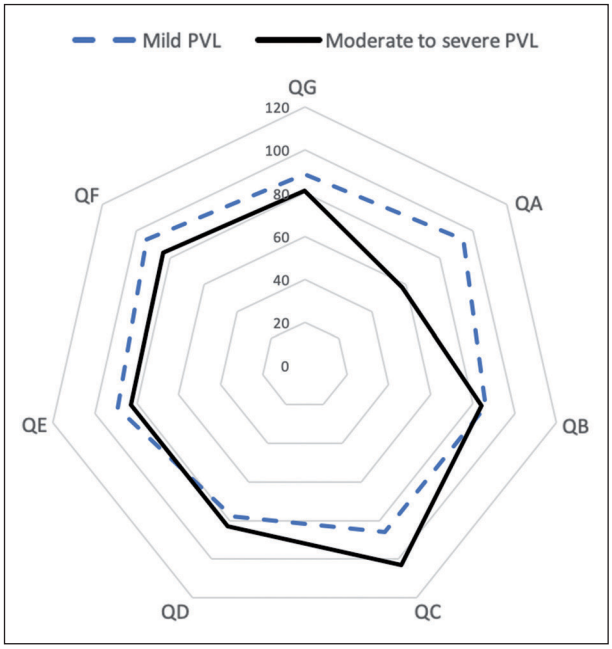

Figure 1. Relation between Griffiths Mental Development Subcales (median scores) and periventricular leukomalacia (PVL) groups.
QG: total scale; QA: locomotor development; QB: personal-social development; QC: hearing and speech; QD: hand and eye coordination; QE: performance tests; QF: practical reasoning.

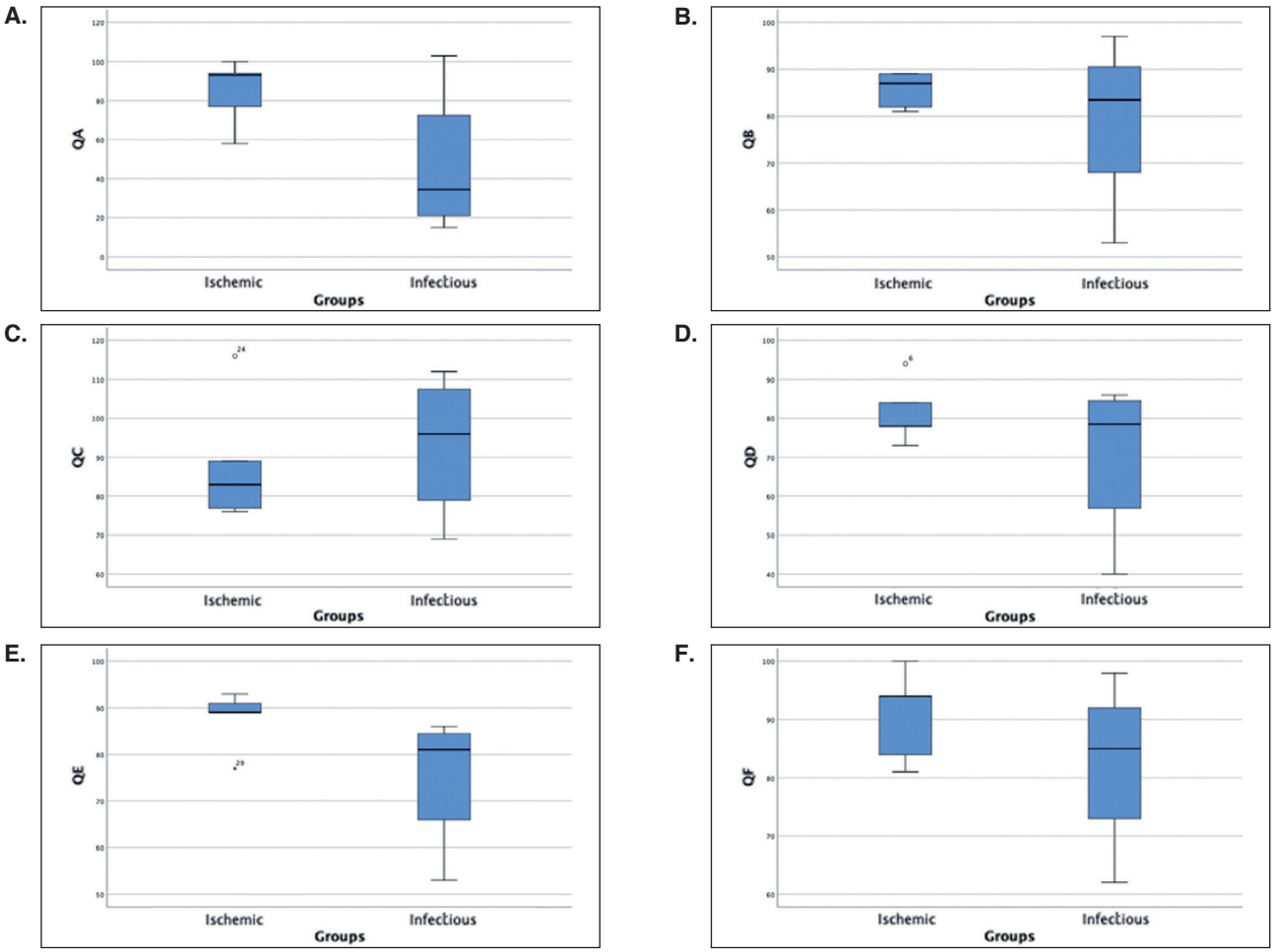

Figure 2. Relation between Griffiths Mental Development Scales (median scores) and etiologic groups.
QA: locomotor development; QB: personal-social development; QC: hearing and speech; QD: hand and eye coordination; QE: performance tests; QF: practical reasoning.

Table 3. Results of univariate analysis ischemic vs. infectious etiology group.

		Ischemic group (n = 16)	Infectious group (n = 15)	p
Sex (male)		8 (50%)	9 (60%)	0.72
Weight at birth (mean, SD), g		1,159 ± 206	1,421 ± 251	0.01
Gestational age (median), weeks		29 ± 1.8	30 ± 1.8	0.08
Chorioamnionitis		1/15 (6.7%)	6/13 (46.2%)	0.02
Placental pathology	**Infection findings**	3/10 (30%)	8/11 (72.7%)	0.31
	Ischemic findings	1/10 (10%)	0 (0%)	
	Overlap findings	1/10 (10%)	0 (0%)	
	Unspecific findings	3/10 (30%)	2/11 (18.2%)	
	Normal	2/10 (20%)	1/11 (9.1%)	
PVL	**Grade 1**	4/14 (28.6%)	1/15 (6.7%)	0.12
	Grade 2	6/14 (42.9%)	4/15 (26.7%)	
	Grade 3	4/14 (28.6%)	10/15 (66.7%)	
Intraventricular hemorrhage	**Grade 1**	1/16 (6.3%)	0/15 (0%)	0.13
	Grade 2	1/16 (6.3%)	1/15 (6.7%)	
	Grade 3	4/16 (25%)	0/15 (0%)	
Normal development		6/16 (37.5%)	3/15 (20%)	0.28
CP		9/16 (56.3%)	12/14 (85.7%)	0.11
Spastic unilateral		3/9 (33.3%)	0/12 (0%)	
Spastic bilateral		5/9 (55.6%)	11/12 (91.7%)	
Dyskinetic		1/9 (11.1%)	1/12 (8.3%)	
Epilepsy		5/16 (31.3%)	3/13 (23.1%)	0.28
Microcephaly		3/16 (18.7%)	1/14 (7.1%)	0.37
Retinopathy		4/16 (25%)	2/15 (13.3%)	0.54
Hearing impairment		3/16 (18.7%)	0/14 (0%)	0.22
Visual impairment		1/16 (6.3%)	1/14 (7.1%)	0.90

CP: cerebral palsy; PVL: periventricular leukomalacia.

Discussion

PVL has originally been attributed to ischemic insults; however, more recent studies suggest that infectious and inflammatory diseases are also important in the pathological, histologic, and structural changes that characterize PVL [11].

This study has assessed the outcome of patients with PVL who were admitted to our institution throughout a decade. Our overall findings were in accordance with previous series [12-14]. We only found 6 cases of mild PVL (grade 1). A possible explanation can be the failure to register mild cases in the hospital database. Another explanation can be the fact that cerebral ultrasound is less sensitive to minor and diffused white matter lesions, which can lead to underdiagnosis. However, cerebral ultrasonography is still the most widely used imaging technique in NICU, as it is a quick, non-invasive test that can be performed at the patient's bedside, making it the ideal screening tool for PVL. It is very important to perform sequential evaluations, especially in the first week of life, and continue this screening until the term age so as to diagnose the majority of cases of PVL [15]. Most newborns with PVL do not show clinical manifestations in early life; therefore, mild PVL may go by unnoticed. Magnetic resonance imaging (MRI) is a more accurate mean for PVL diagnosis; nonetheless, it is more expensive and less accessible, making its use limited in daily clinical practice [16, 17].

We found more cases of moderate to severe PVL in the infectious group as well as a higher prevalence of placental changes suggestive of infection. This suggests that infection may cause more prominent histologic and structural abnormalities in white matter than ischemia, which may also lead to a more serious form of PVL. It is established that the inflammatory pathway, mediated by cytokines, is highly involved in the nervous cell death by neuronal apoptosis [18]. The presence of infection may function as a coadjuvant, increasing vulnerability for minor ischemic insults, which alone would not be sufficient to cause injury. In a study with 172 newborns, Yoon and collaborators demonstrated that umbilical cord plasma IL-6 concentration was a significant predictor of PVL [19]. Leviton et al. published for the first time in 1976 that neonatal sepsis was related to PVL [20]. Moreover, there is strong evidence that very low birth weight infants with neonatal sepsis have a higher risk for white matter lesions and CP [21]. Accordingly, chorioamnionitis is a known risk factor for both CP and cystic PVL [22]. In our study, newborns with early-onset sepsis also had more severe PVL. These data support the role of infection in increasing the severity of PVL, which reinforces the importance of an adequate prenatal and postnatal infection management.

In our placental pathology reports, ischemic lesions were described in only 1 case against 11 cases with descriptions suggestive of infection. This could also reinforce the assumption that inflammation early in life (in the uterus) is probably an important contributor to white matter injury. Pathologic examination of the placenta should be routinely performed in all preterm deliveries to identify aetiologies that can predict different outcomes.

Concerning neurodevelopmental outcomes, as expected, impairments were more prevalent in the moderate to severe PVL group. The infectious group presented more abnormal development trajectories and a higher incidence of CP than the ischemic aetiology group, reflecting a more severe white matter injury.

In the neurodevelopmental assessment by Griffiths scale, children showed results below average, with greater expression in the QA. QA was considerably lower in the moderate to severe PVL group, a fact that has been described in the literature and correlates with the anatomic distribution of PVL [14]. QA was also lower in the infectious group compared to the ischemic group, which reflects the presence of more severe lesions in the former. Among the children submitted to the Griffiths scale (n = 10), 6 children (60%) had mild development delay and just 1 (10%) presented severe delay. This is related to the fact that the most severe cases were not evaluated through the Griffiths scale.

We found evidence of increased ophthalmologic complications in the moderate to severe PVL group, with strabismus being the most frequent finding, thus concordant with previous literature [23, 24].

Limitations

This study had some limitations: the limited number of patients in the mild PVL group, the difficulty to obtain complete data from newborns born between 1996 and 2016 (especially previous to computerized records) inherent to a retrospective study and also the small size of the sample, which did not allow for a wider validation through multivariate analysis. Additionally, neonatal brain MRI would have been useful for a better characterization of PVL disease and correlation with outcomes, especially in mild PVL.

Conclusions

Despite the limitations, to the best of our knowledge, this was the first study that has tried to identify a relationship between the type of insult (ischemic vs. infectious) based on risk factors and neurological outcomes of the preterm newborn. Infection seems to be a stronger trigger for PVL, so every effort should be made to prevent infection in preterm and this should be regarded as an additional neuroprotection measure to be aware of in the NICUs.

Preterm babies with PVL are at risk of several complications and neurodevelopment disorders. Further studies should be performed to identify patient subgroups with different outcomes that may benefit from specific types of interventions.

Our work pointed out that the infectious group presented a higher incidence of CP, which may be related to more severe white matter injury. In the ischemic group, epilepsy was more prevalent, suggesting the involvement of gray matter disease.

Declaration of interest

The Authors declare that there is no conflict of interest.

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