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Low-grade intraventricular hemorrhage and neurodevelopment at 24 months of age

Hemorragia intraventricular de baixo grau e neurodesenvolvimento aos 24 meses de idade

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ABSTRACT

AIMS: To evaluate the impact of low-grade intraventricular hemorrhage on neurodevelopmental outcome in preterm infants at 24 months of age.

METHODS: We conducted a retrospective case-control study of infants with gestational age less than 34 weeks, admitted to a Neonatal Intensive Care Unit between January/2006 and December/2015. Cases were defined as those with low-grade intraventricular hemorrhage (grades I or II), diagnosed by cranial ultrasonography. For each case, a control with the same gestational age but without intraventricular hemorrhage was selected. Follow-up examinations of neurodevelopment were performed at 24 months of age in cases and controls using the Griffiths Mental Development Scale. Cerebral palsy, neurodevelopmental delay (developmental quotient <2 side deviations below the mean), hearing impairment and/or blindness were considered as severe neurodevelopmental impairment.

RESULTS: The study included 172 preterm infants: 86 cases and 86 controls. In the univariate analysis, a difference between the two groups was identified for the following clinical findings: antenatal corticosteroid complete cycle (57% in cases *vs*. 80% in controls; p=0.001; OR: 0.33, 95%CI 0.17-0.64); male gender (63% cases *vs.* 41% controls; p=0.004; OR: 2.45, 95%CI 1.3-4.5); outborn (26% cases vs. 9% controls; p=0.005; OR: 3.3 95%CI 1.4-8.0); Clinical Risk Index for Babies higher than 5 (24% in cases *vs.* 12% in controls; p=0.029; OR: 2.4 95%CI 1.1-5.6); intubation in the delivery room (47% cases *vs.* 27% controls; p=0.007; OR: 2.38 95%CI 1.3-4.5); and neonatal sepsis (34% in cases *vs*. 20% in controls; p=0.039; OR: 2.1 95%CI 1.03-4.1). After logistic regression, differences were only maintained for antenatal corticosteroid (p=0.005; OR 0.34, 95%CI 0.16-0.72) and male gender (p=0.002; OR 2.9, 95%CI 1.4-5.8). A severe neurodevelopmental deficit was present in three cases (3.5%) and one control (1.2%). No statistically significant differences in outcome were found between cases and controls.

CONCLUSIONS: In this sample, preterm infants with low-grade intraventricular hemorrhage diagnosed by cranial ultrasonography had no difference in early neurodevelopmental outcome when compared with controls.

KEYWORDS: cerebral intraventricular hemorrhage; preterm infant; neurodevelopmental disorders.

RESUMO

OBJETIVOS: Avaliar o impacto da hemorragia intraventricular de baixo grau no neurodesenvolvimento de lactentes prematuros aos 24 meses de idade.

MÉTODOS: Foi conduzido um estudo de caso-controle retrospectivo em lactentes com idade gestacional inferior a 34 semanas, internados em uma Unidade de Terapia Intensiva Neonatal entre janeiro de 2006 e dezembro de 2015. Os casos foram definidos como aqueles com hemorragia intraventricular de baixo grau (graus I ou II), diagnosticada por ultrassonografia craniana. Para cada caso, foi selecionado um controle com a mesma idade gestacional, mas sem hemorragia intraventricular. A avaliação do neurodesenvolvimento foi realizada aos 24 meses de idade, em casos e controles, com a *Escala de Desenvolvimento Mental de Griffiths*. Paralisia cerebral, atraso no neurodesenvolvimento (quociente de desenvolvimento <2 desvios padrões abaixo da média para a idade), deficiência auditiva e/ou cegueira foram considerados comprometimento grave do neurodesenvolvimento.

RESULTADOS: O estudo incluiu 172 prematuros: 86 casos e 86 controles. Na análise univariada, identificou-se diferença entre os dois grupos para os seguintes achados clínicos: ciclo completo de corticosteroide pré-natal (57% nos casos *vs.* 80% nos controles; p=0,001; OR: 0,33; IC95% 0,17-0,64); sexo masculino (63% casos *vs.* 41% controles; p=0,004; OR: 2,45, IC95% 1,3-4,5); nascidos em outro hospital (26% casos *vs.* 9% controles; p=0,005; OR: 3,3 IC95% 1,4-8,0); Índice de Risco Clínico para Bebês acima de 5 (24% nos casos *vs*. 12% nos controles; p=0,029; OR: 2,4 IC95% 1,1-5,6); intubação na sala de parto (47% casos *vs.* 27% controles; p=0,007; OR: 2,38; IC95%: 1,3-4,5); e sepse neonatal (34% nos casos *vs.* 20% nos controlos; p=0,039; OR: 2,1 95% CI 1,03-4,1). Após a regressão logística, as diferenças foram mantidas apenas para o corticosteróide antenatal (p=0,005; OR 0,34, IC 95% 0,16-0,72) e sexo masculino (p=0,002; OR 2,9, IC95% 1,4-5,8). Um déficit grave de neurodesenvolvimento esteve presente em três casos (3,5%) e um controle (1,2%). Não houve diferenças estatisticamente significativas no desfecho entre casos e controles.

CONCLUSÕES: Nesta amostra, os prematuros com hemorragia intraventricular de baixo grau diagnosticados pela ultrassonografia craniana não apresentaram diferença no desenvolvimento neurológico precoce quando comparados aos controles.

DESCRITORES: hemorragia cerebral intraventricular; recém-nascido prematuro; transtornos do neurodesenvolvimento.

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Abbreviations: CRIB, Clinical Risk Index for Babies; GMDS, Griffiths Mental Development Scales; GMFCS, Gross Motor Function Classification System; GDQ, Global Developmental Quotient; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; US, ultrasonography.

INTRODUCTION

Due to the advances in prenatal and neonatal medicine, survival rates of preterm infants are increasing within the last decades. Nevertheless, this group is at high risk for developing severe complications. Intraventricular hemorrhage (IVH) is an important cause of brain injury in premature infants. Although its incidence has decreased during the last decades, IVH remains a significant problem because of the greater number of survivors with this condition [1-3]. Risk for IVH increases with decreasing gestational age and birth weight, being inversely related to infant maturity [2]. Recent multicenter epidemiological studies reported an incidence rate of IVH of 25-30% for very low birth weight infants and even higher for extreme low birth weight infant [4, 5]. The described rate for low-grade IVH (grades I-II) is 11% and for severe IVH (grades III-IV) is 3-5% [4, 6, 7].

In preterm infants, cerebral bleeding originates generally in small blood vessels of the subependymal or germinal matrix (also termed the ganglionic eminence) which is located between the caudate nucleus and the thalamus at the level of the foramen of Monro, from where neurons and glial cells arise during fetal development. Cranial ultrasonography (US) is the most commonly used imaging technique to diagnose IVH, because of its high sensitivity for detecting acute bleeding, its portability, and the lack of ionizing radiation [7].

Several studies have shown the negative impact of severe IVH on mortality and neurodevelopmental outcome of affected patients [8, 9], but there is no agreement about the impact of low-grade IVH. Although data from large population studies suggest that preterm infants with IVH grades I and II are not at risk for long-term neurodevelopmental impairment [10, 11], other studies indicate that this population is vulnerable to poor outcome [12-14]. Vohr et al. [12] suggested that grade II IVH is a marker for increased risk of learning disabilities, including cognitive and executive function deficits in adolescence. Ann Wy et al. [10] found that low-grade IVH was not an independent risk factor for worse outcomes in intelligence, academic achievement and behavior, at ages three, eight and 18 years. O'Shea et al. [15] advocated that a relevant association between IVH and adverse developmental outcome occurs only in the presence of a white matter lesion.

In view of these controversies and taking into account the importance of this subject, the aim of this study was to determine the impact of low-grade IVH on the early neurodevelopmental outcome in preterm infants.

METHODS

We conducted a retrospective case-control study with preterm infants admitted to the neonatal intensive care unit (NICU) of the *Centro Hospitalar e Universitário de Coimbra, EPE*, in Coimbra, Portugal, between January 2006 and December 2015. The study protocol was approved by the institutional Ethics Committee and conducted in accordance with the principles of the Helsinki Declaration as revised in 2013. Patients' identity was preserved, confidentiality and data protection were maintained, and all ethical principles of research involving human beings were respected.

The case group was constituted by infants with gestational age less than 34 weeks, with IVH grades I or II, identified by US.

Cranial US examination was performed within 24-48h after admission, on days 3 and 7, and weekly until discharge. The IVH grade was defined according Papile et al. [16] (**Chart 1**). Each grade of IVH may be unilateral or bilateral, with either symmetric or asymmetric grades of IVH.

Chart 1. Grades of intraventricular hemorrhage according to Papile et al. [16]

Grade I	Bleeding is confined to the germinal matrix
Grade II	Intraventricular hemorrhage occupies 50% or less of the lateral ventricle volume
Grade III	Intraventricular hemorrhage occupies more than 50% of the lateral ventricle volume
Grade IV	Hemorrhagic infarction in periventricular white matter ipsilateral to large intraventricular hemorrhage (also called periventricular hemorrhagic infarction)

Exclusion criteria were congenital malformations, genetic syndromes, cystic periventricular leukomalacia, cerebellar hemorrhage, or focal infarction diagnosed by cranial US.

Cases were matched with controls without IVH on cranial US, based on year of birth and gestational

age. For each case, one control was selected. Maternal and perinatal data were retrieved from hospital databases.

In both groups, the presence of major morbidities was evaluated, namely the presence of broncho-pulmonary dysplasia, patent ductus arteriosus, neonatal sepsis, necrotizing enterocolitis, and retinopathy of prematurity. The diagnosis of bronchopulmonary dysplasia was established when supplementary oxygen was necessary at 36 weeks of postnatal age. Patent ductus arteriosus was only considered if treatment was required (indomethacin, ibuprofen or surgical).

Neonatal sepsis was defined with or without positive blood culture in the presence of clinical sepsis: symptoms and positive laboratory parameters (leukocyte count greater than 30000/mm^3 or less than 5000/mm^3 and C-reactive protein higher than 2 mg/dl). Clinical symptoms and signs included fever or hypothermia, newly developed or increased apnea or bradycardia, hypoglycemia or hyperglycemia.

Necrotizing enterocolitis was defined based on the modified Bell's staging criteria, of II A or greater [17]. Retinopathy of prematurity was classified according to the international classification [18]. In this study we only considered grade ≥3.

Chorioamniotitis was defined as an infection with resultant inflammation of any combination of the amniotic fluid, placenta, fetus, fetal membranes or decidua, with occurrence of rupture of membranes plus one or more of the following: maternal fever, mother's receipt of antibiotics antepartum, foul smelling amniotic fluid or uterine tenderness [19].

A small for gestational age infant was defined as having a birth weight below the 3rd percentile according the Fenton charts [20]. Clinical Risk Index for Babies (CRIB) score was based on severity of clinical conditions routinely available on the first 12 hours of the infant's life [21]. An "outborn" was defined if the infant was born in another hospital and then transferred to the Neonatal Unit under study.

At 24 months of age, the children underwent a follow-up assessment by certified examiners, consisting of neurologic evaluation and testing for hearing, vision and development. The neurological examination was based on the Amiel-Tison assessment, and included evaluation of tone, strength, reflexes, angles and posture. Cerebral palsy was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. The Gross Motor Function Classification System (GMFCS) was used to classify the severity of cerebral palsy [22]. Blindness was defined as corrected vision of less than 0.3. Deafness was defined as hearing loss needing amplification or cochlear implants.

An evaluation of psychomotor development with the Griffiths Mental Development Scales (GMDS) was performed and a global developmental quotient was calculated. Griffiths is composed of five subscales: Locomotor, Personal-Social, Hearing-Speech, Eye-Hand Co-ordination and Performance Scales. The raw scores from all the sub-scales are added to obtain a total raw score and then it was converted in General Developmental Quotient (GDQ) [23]. Presence of cerebral palsy, or deafness requiring a hearing aid, or blindness, or developmental quotient below 70, was considered as a severe neurodevelopmental delay.

Statistical analysis was performed using SPSS version 24.0 for Windows. For the univariate analysis, the chi-square test (or Fischer's exact test when indicated) was performed to examine the relation between all qualitative variables; the Student's t-test (symmetrical distribution) or Mann-Whitney U test (asymmetrical distribution) were used for quantitative variables. We evaluated the adjusted risk factors for gestational age and a logistic regression analysis was performed for all variables in which a statistical difference was observed with a probability of occurrence less than 0.05 in the univariate analysis.

RESULTS

Of 880 preterm infants with less than 34 weeks of gestational age admitted in the NICU, 112 infants had low-grade IVH, therefore the incidence of IVH was 12.7%, being 8.5% grade I and 4.2% grade II. Excluded patients included 26 infants who died, had congenital major malformations or additional cerebral injuries. Therefore, 86 preterm infants with low-grade IVH were included in the study and matched with 86 controls. The mean gestational age was 28.7±2.20 weeks in both groups. Mean birth weight was 1,167±311 g in the study group and 1,177±296 g in the control group.

In the univariate analysis, we found a positive association between low-grade IVH and antenatal corticosteroid complete cycle (p=0.001), male gender (p=0.004), outborn (p=0.005), CRIB>5 (p=0.029), intubation in the delivery room (p=0.007), and neonatal sepsis (p=0.039). After logistic regression, this difference was only maintained for antenatal corticosteroid (p=0.005; OR: 0.34 95%CI: 0.16-0.72) and male gender (p=0.002; OR: 2.9 95%CI: 1.4-5.8) (**Table 1**).

Table 1. Clinical characteristics of the 172 preterm infants with and without low grade intraventricular hemorrhage included as cases and controls.

Characteristic	Low-grade IVH (n = 86)	Control group (n = 86)	p	OR 95%CI	aOR 95%CI
Intraventricular hemorrhage (grade)					
Grade I	55 (64%)	–	–	–	–
Grade II	31 (36%)	–	–	–	–
Maternal characteristic					
Maternal age at delivery, years	30 (16-41)	29 (18-45)	0.408	–	–
Primiparous	47 (56%)	50 (58%)	0.773	–	–
Chorioamnionitis	3 (4%)	1 (1%)	0.312	–	–
Preeclampsia/high blood pressure	15 (17%)	17 (20%)	0.695	–	–
Diabetes	8 (9%)	9 (11%)	0.798	–	–
Educational level					
Basic education	24 (28%)	19 (22%)		–	–
High school	22 (26%)	40 (47%)		–	–
University education	32 (37%)	23 (27%)		–	–
Missing	8 (9%)	4 (5%)	–	–	–
Perinatal characteristic					
Delivery					
– vaginal delivery	37 (43%)	31 (36%)	0.349	–	–
– caesarean	49 (57%)	55 (64%)	0.349	–	–
Antenatal steroids, any	76 (88%)	80 (93%)	0.294	–	–
Antenatal steroids, complete cycle	49 (57%)	69 (80%)	**0.001**	**0.33 (0.17-0.64)**	**0.34 (0.16-0.72)**
Apgar score <7 at 5 min	7 (8%)	4 (5%)	0.339		
Intubated in the delivery room	40 (47%)	23 (27%)	**0.007**	**2.38 (1.3-4.5)**	–
Neonatal characteristic					
Male	54 (63%)	35 (41%)	**0.004**	**2.45 (1.3-4.5)**	**2.9 (1.4-5.8)**
Gestational age at birth, weeks - median (min-max)	29 (24-32)	29 (24-32)	1	–	–
Outborn	22 (26%)	8 (9%)	**0.005**	**3.34 (1.4-8.0)**	–
Birth weight, g - median (min-max)	1180 (440-1850)	1182.5 (560-1895)	0.847	–	–
Low for gestational age	9 (11%)	9 (11%)	1	–	–
Head circumference, cm	28 (20.1-35)	26.5 (22-31)	**<0.001**		–
Surfactant	34 (40%)	33 (38%)	0.876	–	–
Bronchopulmonary dysplasia	6 (7%)	7 (8%)	0.773	–	–
Patent ductus arteriosus treated	14 (16%)	11 (13%)	0.516	–	–
Hypotension	4 (5%)	5 (6%)	1		
Necrotizing enterocolitis ≥stage 2	3 (4%)	3 (4%)	1	–	–
Neonatal sepsis	29 (34%)	17(20%)	**0.039**	**2.1 (1.03-4.1)**	**–**
Retinopathy of prematurity ≥stage 3	5 (6%)	1 (1%)	0.096	–	–
CRIB >5	21 (24%)	10 (12%)	**0.029**	**2.4 (1.1-5.6)**	–
CRIB med - median (min-max)	1 (0-16)	1 (0-13)	**0.319**	–	–

Data are presented as medians (minimum and maximum) or n (%).
IVH, intraventricular hemorrhage; CRIB, Clinical Risk Index for Babies score; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Data on the neurodevelopmental outcome evaluation between 24-30 months of age were available for all children in the control group. Two children in the study group missed the GMDS test but they had a normal screening test.

GDQ was slightly lower in cases compared with controls (94.4±12.7 *vs.* 98.6±9.8, p=0.02), but when the GDQ <70 was analyzed we didn't found any statistical significance (2.3% vs 1.2; p=0.56 as shown in **Table 2**).

Table 2. Neurodevelopmental at 24 months of age, in infants with low grade intraventricular hemorrhage (case group) versus control group.

Neurodevelopmental characteristic	Case group (n = 86)	Control group (n = 86)	p
Global Developmental Quotient	94.4 ± 12.7	98.6 ± 9.8	0.02
Global Developmental Quotient <70	2 (2.3%)	1 (1.2%)	0.567
Cerebral palsy	1 (1.2%)	0	0.993
Visual impairment	0	0	
Hearing impairment	1 (1.2%)	1 (1.2%)	0.993
Severe adverse outcome	3 (3.5%)	1 (1.2%)	0.317

Case group: preterm infants with gestational age less than 34 weeks with intraventricular hemorrhage. Control group: preterm infants of matched for gestational age, without intraventricular hemorrhage.
Data presented as mean ± standard deviation or n (%).
A chi-square test of independence/Fischer's in qualitative variables and Student's t-test (symmetrical distribution) or Mann-Whitney U test (asymmetrical distribution) in quantitative variables.

Only one infant in the case group developed a unilateral spastic cerebral palsy classified by the Motor Function Classification System (GMFCS) in level I, (walk without restrictions but tend to be limited in some of the more advanced motor skills.

Three infants in the case group (3.5%) had a severe outcome, GDQ <70 in two cases (one of them with also hearing impairment) and cerebral palsy in other. One infant in the control group (1.2%) had GDQ <70 also with hearing impairment (**Table 2**).

There were no statistically significant differences between cases and controls in the rates of adverse outcome (i.e., cerebral palsy, neurodevelopmental delay, hearing impairment and/or blindness).

DISCUSSION

The incidence of low-grade IVH in this study group was 9.7%, but we cannot make a direct comparison with the literature data because gestational ages are different in the several studied samples.

IVH occurs most frequently in infants born before 32 weeks of gestation or with less than 1500 g birth weight. In our study, the median gestational age and birth weight were similar in the two groups, due to the opportunistic choice of controls. Risk factors other than birth weight and gestational age have been described in the literature: vaginal delivery, low Apgar score, severe respiratory distress syndrome, pneumothorax, hypoxia, hypercapnia, patent ductus arteriosus, thrombocytopenia, infection, hypotension requiring volume resuscitation and/or inotropic support, noxious stimuli, anemia, and neonatal resuscitation [24]. In this study we did not find statistically significant difference in the occurrence of these factors between cases and controls.

Regarding to sex, as described in other studies [25], males were the majority in the case group. This association possibly reflects improved neurovascular maturation and better regulatory mechanisms in the female fetus, with more strength to hormonal influences on the maturity of the female brain, compared with the male brain. In animal models, estrogen reduced brain injury in vivo and in vitro, and progesterone protected against ischemic or traumatic injury [26, 27].

Treatment of pregnant women with steroids before delivery is associated with a reduced risk of adverse outcomes [28]. The mechanisms by which corticosteroids decrease the risk of hemorrhage are unclear, but they appear to be independent of enhanced pulmonary maturation. The postulated effects include an anti-angiogenic effect with inhibition of micro vessel morphogenesis in the germinal matrix capillary network and stabilization of the microvasculature of the developing germinal matrix [29]. Our data support the association between antenatal steroids and decreased risk of IVH. Even after logistic regression, 80.2% of the infants in the control group had a complete cycle of antenatal corticosteroid, vs. only 57% in the case group, indicating a protection factor of 0.33.

Early neonatal systemic inflammation and hemodynamic disturbances seem to be linked with the pathophysiology of IVH. Increased serum levels of interleukin 6 were associated with severe IVH in extremely preterm infants. Regarding to infection, similar to what was described by other authors, in this study neonatal sepsis was associated with a larger number of IVH when compared to controls, but this association lacked statistical significance in the multivariate analysis [30-32].

Sauer et al. [33], in a retrospective cohort study including infants with less than 1500 g of birth

weight, found that increased intubation attempts in the delivery room were associated with increased incidence of severe IVH. In our study group, the need for resuscitation in the delivery room is evident as a risk factor for IVH, given that 46.5% of intubations in the delivery room occurred in the case group compared with only 26.7% in the control group. However, we did not assess the number of attempts for intubation. Also, the association was not maintained when adjusted for other risk factors. It is possible that the need for resuscitation was a proxy for worse birth conditions.

Published studies postulate that cerebral hyperperfusion following cerebral hypoperfusion and ischemia is fundamental to the hemodynamic basis of periventricular hemorrhage and IVH. The systemic blood pressure becomes the primary determinant of cerebral blood flow and pressure, which is a pressure-passive circulatory situation, in the absence of autoregulation. Rapid volume expansion with blood products or hypertonic solutions and excessive use of inotropes for the correction of hypotension results in a rapid increase of cerebral blood flow and can cause injury to the fragile germinal matrix capillaries [34, 35]. In this study, we could not find any association of the use of inotropes with low-grade IVH. The median CRIB score did not differ in the two study groups. CRIB is a valid index for evaluation of the initial neonatal risk, predicting neonatal morbidity and mortality. Sick premature infants in NICU undergo a high number of events (hypercapnia, hypoxia, apnea, bradycardia, non-closure of ductus arteriosus, requirement of high ventilator pressure, and others), which may result in fluctuation of blood pressure and alteration in cerebral hemodynamics, explaining why infants with high CRIB index had more IVH.

Concerns about detrimental effects of low-grade IVH have been raised by experimental studies, suggesting that germinal matrix injury may lead to impaired myelination and cortical development. This region provided glial precursors that migrate to cortical regions and become oligodendrocytes and astrocytes. Destruction or absence of these cells may affect the myelination or cortical developmental, especially when occurring in early gestational age [36].

Patra et al. [5], Bolisetty et al. [14], and Klebermass-Schrehof et al. [36] found a significantly higher rate of impairment in infants with low-grade IVH when compared to infants without IVH. In this study we had different results, possibly because the sample was composed by more mature preterm infants, so by the time of the insult, glial precursors had already migrated. Furthermore, we excluded infants with cystic periventricular leukomalacia in cranial US and with white matter lesion in those who performed magnetic resonance imaging (MRI).

In agreement with the present data, several studies did not find any differences in outcome between infants with and without low-grade IVH [10-11]. In this study, grade I and II IVH without white matter damage were not associated with severe neurobehavioral sequelae. We have only identified a slight reduction in GDQ in the case group. No other differences in neurodevelopmental outcome or any form of impairment were found between preterm infants with low-grade IVH and matched controls after logistic regression.

The overall incidence of impairment or developmental delay was low. This is difficult to compare with other studies because some authors evaluated only extreme birth weight infants, like Patra et al. [5], who concluded that low-grade IVH had poor outcome. We cannot exclude a relationship between IVH and social and communication dysfunction, attentional difficulties and learning disabilities, which are better identified in school age.

One strong point of this study is that we adjusted the results for gestational age and potential confounders described in the literature as factors that can interfere with the development. One limitation is that the developmental assessment was performed early, at 24 months, which does not exclude the possibility of later repercussions that may arise. Another limitation of this study is the low sensitivity of cranial US for the diagnosis of diffuse white matter abnormalities (non-cystic periventricular leukomalacia, diffuse white matter gliosis and neuronal-axonal injury of the white matter), mild-to-moderate gray matter abnormalities (neuronal loss and gliosis of the gray matter) and punctate white matter lesions. PWML are suggested to be seen by inhomogeneous echogenicity on cranial US, but can only be reliably detected by MRI. These neuropathological patterns, only detected through MRI, can have an impact on neurodevelopment, and should be considered in patients with a history of IVH. Two recent publications address the neuroimaging role, specifically conventional and high-performance MRI, in the motor and neurocognitive prognosis [37, 38].

In conclusion, low-grade IVH identified by cranial US had no impact in the early neuro-developmental outcome of this sample of preterm infants with less than 34 weeks of gestational age. We could not find it as an independent risk factor for severe

outcomes at 24 months of age. We should recognize that predicting cognitive and motor functions in growing and developing infants is difficult, especially among infants with a mild degree of impairment. Despite these limitations, these results are important to show that low-grade IVH, by itself, does not preclude preterm infants from having a good prognosis.

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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