Survival and Neurodevelopmental Outcomes of Premature Infants with Severe Peri-Intraventricular Hemorrhage at 24 Months of Age

Hemorragia Peri-Intraventricular Grave em Prematuros: Impacto na Mortalidade e no Neurodesenvolvimento aos 24 Meses

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ABSTRACT

Introduction: Severe peri-intraventricular haemorrhage has been associated with higher mortality and neurodevelopmental impairment. The impact of peri-intraventricular haemorrhage alone (without white matter injury) remains controversial. The aim of this study was to evaluate the influence of severe peri-intraventricular haemorrhage, associated or not with cystic peri-ventricular leukomalacia, on mortality and neurodevelopment at 24 months.

Material and Methods: Retrospective cohort study, that included newborns with severe peri-intraventricular haemorrhage admitted to a maternity hospital with differentiated perinatal support between 2006 and 2015, and two controls with the same gestational age, without peri-intraventricular haemorrhage, who were admitted immediately after the case. Neurodevelopmental assessment, at 24 months, was performed in 99 children, using the Schedule of Growing Skills II scale in 52 and the Ruth Griffiths mental development scale in 47 children. Severe neurodevelopmental deficit was diagnosed in the following conditions: cerebral palsy, delayed psychomotor development, deafness requiring hearing aids and blindness.

Results: The study included 41 cases and 82 controls. Out of these, 23 died, 16 (39.0%) in the group of severe peri-intraventricular haemorrhage and seven (8.5%) in the control group (OR 7.6, 95% CI 2.6 - 20.4, $p < 0.001$). Severe neurodevelopmental deficit was diagnosed in seven (30.4%) in the severe peri-intraventricular haemorrhage group and one (1.3%) in the control group (OR 32; 95% CI 3.7 - 281, $p < 0.001$). Individualized analysis showed that mortality was higher in peri-intraventricular haemorrhage grade III with associated cystic peri-ventricular leukomalacia (OR 4.4 95% CI 1.3 - 14.2, $p = 0.015$) and in peri-intraventricular haemorrhage IV (OR 12; 95% CI 3.5 - 41.2, $p < 0.001$), when compared to controls. Differences were also noticed regarding severe neurodevelopmental deficit when compared with controls (1.3%) in grade III peri-intraventricular haemorrhage with associated cystic peri-ventricular leukomalacia, (75.0%, $p < 0.001$) and grade IV peri-intraventricular haemorrhage (50.0%, $p < 0.001$).

Conclusion: Preterm newborns with peri-intraventricular haemorrhage grade IV or grade III with cystic peri-ventricular leukomalacia, had a higher risk of mortality and severe neurodevelopmental impairment.

Keywords: Brain/diagnostic imaging; Cerebral Intraventricular Hemorrhage; Cranial Ultrasound; Developmental Disabilities/diagnostic imaging; Infant, Very Low Birth Weight

RESUMO

Introdução: A hemorragia peri-intraventricular grave tem sido associada a maior mortalidade e sequelas do neurodesenvolvimento. Mantém-se controverso o impacto da hemorragia peri-intraventricular isolada, sem lesão da substância branca. O objetivo deste trabalho foi avaliar a influência da hemorragia peri-intraventricular grave, associada ou não a leucomalácia peri-ventricular quística, na mortalidade e no neurodesenvolvimento aos 24 meses.

Material e Métodos: Estudo de coorte retrospetiva que incluiu os recém-nascidos com hemorragia peri-intraventricular grave, internados numa maternidade de apoio perinatal diferenciado, entre 2006 e 2015, e dois controlos com a mesma idade gestacional, internados logo a seguir ao caso, sem hemorragia peri-intraventricular. A avaliação do neurodesenvolvimento, aos 24 meses, foi realizada em 99 crianças, com recurso à escala *The Schedule of Growing Skills Scale II* em 52 e à escala de desenvolvimento mental de *Ruth Griffiths* em 47 crianças. Considerou-se défice grave do neurodesenvolvimento: paralisia cerebral, atraso do desenvolvimento psicomotor, surdez com necessidade de prótese auditiva ou cegueira.

Resultados: Foram incluídos 41 recém-nascidos com hemorragia peri-intraventricular grave e 82 controlos. Ocorreram 23 óbitos, 16 (39,0%) nas hemorragias peri-intraventricular graves e sete (8,5%) nos controlos (OR 7,6; IC 95% 2,6 - 20,4; $p < 0,001$). Verificou-se défice grave do neurodesenvolvimento em sete (30,4%) no grupo de hemorragia peri-intraventricular grave e um (1,3%) no grupo de controlos (OR 32; IC 95% 3,7 - 281; $p < 0,001$). Na análise individualizada, a mortalidade foi superior quer nas hemorragia peri-intraventricular grau III com leucomalácia peri-ventricular quística associada (OR 4,4 IC 95% 1,3 - 14,2; $p = 0,015$), quer na hemorragia peri-intraventricular grau IV (OR 12; IC 95% 3,5 - 41,2; $p < 0,001$), em relação aos controlos. Verificaram-se também diferenças no défice grave do neurodesenvolvimento em relação aos controlos (1,3%) na hemorragia peri-intraventricular grau III com leucomalácia peri-ventricular quística associada (75,0%, $p < 0,001$) e na hemorragia peri-intraventricular grau IV (50,0%, $p < 0,001$).

Conclusão: Os recém-nascidos com hemorragia peri-intraventricular de grau IV ou grau III com leucomalácia peri-ventricular quística associaram-se a maior mortalidade e sequelas graves do neurodesenvolvimento.

Palavras-chave: Cérebro/diagnóstico por imagem; Deficiências do Desenvolvimento/diagnóstico por imagem; Hemorragia Cerebral Intraventricular; Recém-Nascido de Muito Baixo Peso

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INTRODUCTION

Perinatal care has greatly improved over the past two decades, in association with the widespread use of antenatal corticosteroid therapy, the use of exogenous surfactant and in utero referral of patients to reference centres, with a subsequent increase in survival of preterm newborns, even at gestational ages within the threshold of viability.[1-4] However, despite an increased survival, neonatal morbidity remains relevant and there is an increased risk of clinical complications with an impact on neurodevelopment in the short and long term, including peri/intraventricular haemorrhage (PIVH).[3-10]

The onset of PIVH is usually found in the subependymal germinal matrix, where future neuronal and glial cells originate in immature brains.[10] The germinal matrix is characterised by high metabolic activity, with a very fragile and immature endothelial wall. These vulnerabilities are associated with immaturity of cerebral autoregulation, underlying a greater susceptibility to the development of haemorrhage.[7,10]

Transfrontanelle ultrasound is most frequently used for the diagnosis of PIVH due to its high sensitivity, the fact that it is radiation free and easily available in neonatal intensive care units.[11]

The Papile *et al.* classification has been classically used to assess the severity of haemorrhage.[12] Although recent studies have suggested the use of different and more accurate classification systems,[13] the Papile classification is still widely used in guidance, therapeutic decision and counselling.[14] Severe PIVH is associated with higher mortality and neurodevelopmental disorders, including cerebral palsy (CP), intellectual disability and neurosensory impairment.[5,7,9,10,15-17] Nevertheless, literature remains scarce, with very heterogeneous methodologies and small samples due to high mortality, in addition to the understanding on whether PIVH itself is responsible for the outcomes or these are due to white matter lesions, which remains controversial. Patients are selected according to birthweight (BW) in some studies, whilst others are based on patient's gestational age (GA) and few studies adjust for possible confounding factors.[8,14,16] Neonatologists are questioned by parents of preterm infants, during the acute phase of the disease, not only about survival but also about the possibility of severe outcomes, hence the relevance of an accurate definition of prognosis.

This study was aimed at the assessment of mortality and neurodevelopmental outcomes at 24 months of age in preterm newborns presenting with severe PIVH, with adjustment for cofactors with an influence on the results, in addition to an individual assessment of the impact of grade IV and grade III PIVH, with or without white matter involvement.

MATERIAL AND METHODS

This was a retrospective cohort study involving newborn patients with gestational age <34 weeks presenting with severe PIVH and admitted between January 2006 and December 2015 to the Neonatal Intensive Care Unit of the *Maternidade Bissaya Barreto - Centro Hospitalar e Universitário de Coimbra*. Two controls with similar GA, presenting with no PIVH, admitted upon each selected preterm patient were also selected, based on the registration department's database. Patient selection was based on the department's database, including the analysis of maternal, perinatal and neurodevelopmental clinical-demographic data, as well as on the consultation records available through the *SClínico Hospitalar* software (*SClínico*).

Patients with no available data on their neurodevelopmental assessment in the *SClínico* were excluded from the study. The presence of major congenital malformations was also considered as an exclusion factor.

Diagnosis was based on a sequential imaging assessment with brain ultrasound, according to the department practice, analysed by two experienced neonatologists with specific training, following the national consensus protocol.[18]

Severe PIVH was defined as the presence of grade III and IV PIVH, according to Papile's classification,[12] with grade III PIVH corresponding to haemorrhage occupying more than 50% of the lateral ventricle, usually leading to dilation, and grade IV showing PIVH associated with haemorrhagic infarction in the ipsilateral white matter.

Maternal and perinatal clinical-demographic data and neonatal morbidity were analysed in both groups.

Newborns with birthweight below the 3rd percentile for GA, according to Fenton curves, were considered as small for gestational age (SGA).[20]

Patent ductus arteriosus was systematically assessed by echocardiography according to protocol or clinical suspicion.[21] Sepsis was considered in patients presenting with a clinical status associated with positive laboratory parameters (leukocyte count >30,000/mm^3 or <5,000/mm^3 and C-reactive protein level >2 mg/dL), with or without positive blood culture.[22] Necrotizing enterocolitis was classified according to Bell's modified system.[23] Bronchopulmonary dysplasia was defined as the need for oxygen therapy at 36 weeks post-menstrual age.[24] Retinopathy of prematurity was based on the international classification.[25] The presence of cystic periventricular leukomalacia (PVL) was assessed according to the classification by De Vries *et al*.[26]

All patients born with GA < 32 weeks or with birthweight (BW) <1,500 grams were followed-up at outpatients and data were recorded in the *SClínico* software. The Schedule of Growing Skills Scale II (SGS-II) was used within the first six years of the study (52 patients) while the Ruth Griffiths Mental Development Scale (RG) was used within the last four years of the study (47 patients), for the evaluation of psychomotor neurodevelopment at 24 months, a current procedure in the department.[27,28] These scales were used by a technician with adequate training, who Is usually involved in the assessment of all children at neurological

risk and attending the outpatient clinic, with no knowledge on the presence or absence of VIH. SGS-II is a screening test for the assessment involving nine areas of skills and provides a developmental profile; the result is suggestive of significant developmental delay whenever two or more areas are mismatched in more than one age range on the profile sheet. The RG Mental Development Scale is used for the assessment of six skill areas and the results are presented as ratios (regarding each subscale and overall) and by mental age. Each subscale ratio may be converted into percentiles showing the child's performance when compared to the general population. In this study, we opted to use the global development quotient, corresponding to the result of the different subscales.

The presence of pervasive developmental disorders was considered with a global development quotient (QD) ≤ 70 obtained with the RG test or with SGS-II test profile suggesting the presence of a significant developmental delay.

The diagnosis of CP was established according to the international classification and the global motor function classification system.[29,30] Patients presenting with motor impairment were assessed and followed by a multidisciplinary team including a neuropaediatrician. The absence of CP was considered with no degree of motor impairment at 24 months.

Hearing and visual acuity were systematically assessed through speciality consultations.

Severe neurodevelopmental impairment was considered with at least one of the following: psychomotor developmental delay, CP, sensorineural hearing loss in need of hearing aid or blindness.

The initial neurodevelopmental impact of severe PIVH was assessed followed by the impact of grade IV and III PIVH with or without cystic PVL.

SPSS version 20 was used for statistical analysis. Univariate analysis was performed using Student's t-test for independent samples with quantitative variables and chi-square/Fisher's test for categorical variables; odds ratio (OR) and 95% confidence interval (95% CI) were obtained. An adjustment was made by logistic regression with the variables with statistical significance and with a contribution to neurodevelopmental impairment. A *p*-value < 0.05 was considered as showing statistically significant differences.

As this was a retrospective study and with anonymous data analysis, approval by the Ethics Committee was not considered. However, all procedures were performed in accordance with the regulations established by the Clinical Research and Ethics Committee and in accordance with the World Medical Association's Declaration of Helsinki.

RESULTS

A total of 1,004 newborn infants born with a GA <34 weeks were admitted to hospital during the study period [127 (13%) patients presenting with PIVH, 41 with severe PIVH (4%), including 24 with grade III (2.4%) and 17 with grade IV (1.7%) PIVH], including 538 very low birthweight newborns.

A 21% incidence rate (114/538) of PIVH (and a 7% rate of severe PIVH – 38/538) was found in these groups.

A total of 129 NB was assessed, six were excluded from the study due to unavailable record of neurodevelopmental assessment in *SClínico* and 123 NB were included in the study, 41 presenting with severe PIVH and 82 controls (Fig. 1).

The mean GA was 27 weeks in both groups and the mean birthweight was 1,077g in NB with severe PIVH and 991g in controls (Table 1).

When patients with severe PIVH were compared with controls as regards perinatal characteristics, it was found that more male patients presented with this pathology (73.2% *vs.* 45.1%, $p = 0.003$), a significantly lower use of antenatal corticosteroid therapy (70, 7% *vs.* 92.5%, $p = 0.003$) was found, more outborn deliveries were found (31.7% *vs*. 9.8%, $p = 0.002$) and showing a higher rate of resuscitation requiring positive pressure ventilation and subsequent endotracheal intubation and mechanical ventilation (75.6% *vs.* 48.8%, $p = 0.005$). The neonatal morbidity factors that showed significant differences included hypotension (36.6% *vs.* 12.2%, $p = 0.002$) and neonatal sepsis (53.7% *vs*. 28.0%, $p = 0.005$), respectively in NB with severe PIVH *vs.* controls. The following variables with a possible influence on neurodevelopment were included in the logistic regression model: antenatal corticosteroid therapy, gender, outborn delivery, sepsis and hypotension. Antenatal corticosteroid therapy showed a protective effect and only male gender, neonatal sepsis and hypotension remained as independent risk factors (Table 1).

Eleven patients with severe PIVH [26.8%: five patients (29.4%) with grade IV and six (25.0%) with grade III PIVH] (Table 1) presented with cystic PVL. Twenty-three deceased patients were found, 16 (39.0%) patients with severe PIVH and seven (8.5%) controls (OR 7.6; 95% CI 2.6 - 20.4; $p < 0.001$).

Eleven patients presented with hydrocephalus due to post-haemorrhagic dilation, seven from which underwent shunt surgery (four patients did not require any intervention). Four of the operated patients (ventricular reservoir or ventriculoperitoneal shunt) presented with severe neurodevelopment impairment, compared to the patients who did not require surgery, in whom no severe neurodevelopment impairment was found, even though these were not statistically significant differences (Table 2).

A 24-month follow-up was obtained in patients (99% of survivors).

Neurodevelopmental assessment is shown in Table 3. Severe PIVH was associated with more severe neurodevelopmental impairment than controls, 30.4% *vs.* 1.3%, ($p < 0.001$). A higher percentage of global neurodevelopmental delay compared to controls was found, respectively 12.5% *vs.* 1.3% ($p = 0.043$) and six patients (all within the PIVH group) presented with CP ($p < 0.001$). Global motor function ranged between grade I-II (four patients) and grade

III-IV (two patients). Only one patient (one control) presented with hearing loss in need for hearing aid and no patients presented with blindness.

A significantly higher mortality rate was found in patients presenting with grade III (OR 4.4; 95% CI 1.3 - 14.2; p = 0.015) and grade IV (OR 12; 95% CI 3.5 - 41.2; $p < 0.001$) PIVH, when compared to controls (Table 4).

The neurodevelopmental outcomes of patients presenting with grade IV and grade III PIVH, whether associated with white matter lesion, are shown in Table 4.

Mortality or severe neurodevelopmental impairment were significantly more frequent in infants presenting with grade IV or grade III PIVH with associated cystic PVL, when compared to controls, in contrast to no significant neurodevelopmental differences in patients presenting with grade III PIVH and without cystic PVL.

DISCUSSION

A 21% and 7% overall rate of PIVH and severe PIVH in very low-birthweight infants has been found, respectively, in line with literature.[1,3,17,31,32]

Other potential risk factors for PIVH adjusted for GA were found. Male gender, no antenatal corticosteroid therapy, neonatal sepsis and hypotension requiring the use of inotropes were identified as risk factors after logistic regression, in line with literature.[10,17]

A multifactorial action may be related to the protective effect underlying antenatal corticosteroid therapy of reducing the risk of PIVH, including (i) the acceleration of lung maturity, with subsequent decrease in respiratory disorders and promoting greater stability in cerebral blood flow, and (ii) the stimulation of germ matrix microvasculature maturation.[33]

In line with other studies, male gender was found as a risk factor for PIVH.[34] This association has been associated with better neurovascular maturation and brain regulation mechanisms in females. Oestrogens have been associated with reduced brain injury both in vivo and in vitro, and

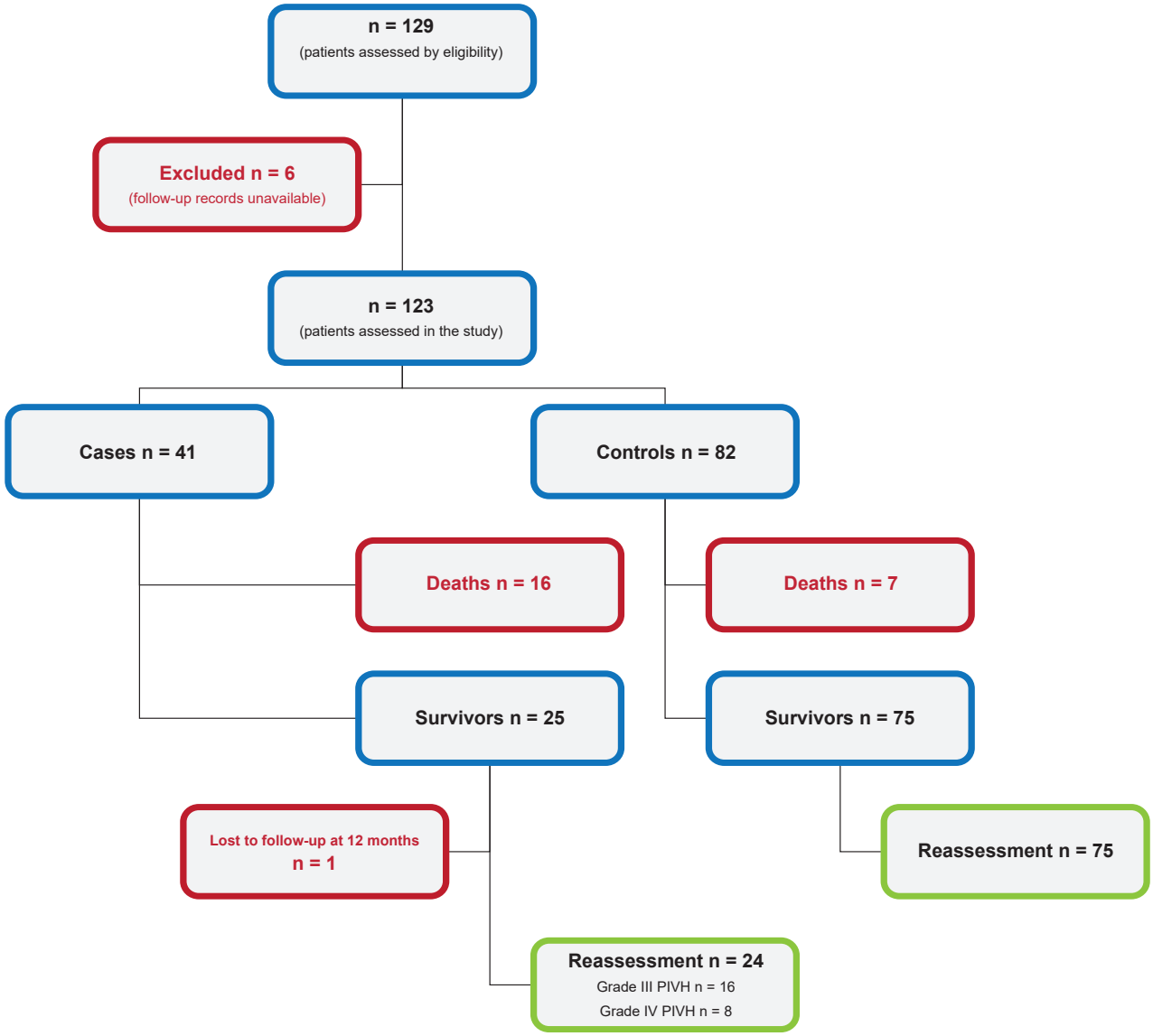

Figure 1 – Newborns included in the study

Table 1 – Clinical and demographic characteristics of patients presenting with severe peri/intraventicular haemorrhage and control patients

Total (n = 123)	Grade III-IV PIVH (n = 41)	Control group (n = 82)	*p*-value	OR (95% CI)	aOR (95% CI)
Maternal characteristics					
Maternal characteristics (years) [mean (sd)]	29.2 (4.9)	31.2 (5.5)	0.056*	-	-
Primiparous n (%)	22 (53.7)	48 (58.5)	0.61£	-	-
Chorioamnionitis n (%)	5 (12.2)	8 (9.80)	0.758†	-	-
Pre-eclampsia/High blood n (%)	7 (17.1)	17 (20.7)	0.63†	-	-
Education		0.3†			
Basic n (%)	8 (24.3)	15 (19.2)		-	-
Secundary n (%)	11 (33.3)	37 (47.4)		-	-
University n (%)	14 (42.4)	26 (33.3)		-	-
Perinatal characteristics					
Delivery – C-section n (%)	23 (56.1)	45 (54.95)	0.80£	-	-
Antenatal corticosteroid therapy n (%)	29 (70.7)	75 (91.5)	**0.003£**	0.22 (0.1 - 0.6)	**0.26 (0.1 - 0.9)**
5-minute Apgar score < 7 n (%)	9 (23.1)	8 (10.0)	0.056†	-	-
Advanced life support (ETT and mechanical ventilation) n (%)	31 (75.6)	40 (48.8)	**0.005£**	3.2 (1.4 - 7.6)	-
Newborn characteristics					
Male n (%)	30 (73.2)	37 (45.1)	**0.003£**	3.3 (1.4 - 7.5)	**4.7 (1.6 - 13.9)**
GA, weeks [mean (sd)]	27.3 (2.2)	27.4 (2.1)	> 0.99*	-	-
BW, g [mean (sd)]	1077 (315)	991(306)	0.257*	-	
Outborn delivery n (%)	13 (31.7)	8 (9.8)	**0.002†**	4.2 (1.6 - 11.4)	-
SGA n (%)	4 (9.8)	15 (18.3)	0.218†	-	-
Gemelarity n (%)	8 (20.0)	21 (25.6)	0.45†		
HDM n (%)	24 (58.5)	47 (57.5)	0.89£	-	-
Late-onset sepsis n (%)	16 (39.0)	16 (19.8)	**0.022£**	2.6 (1.1 - 5.9)	**2.8 (1.03 - 7.9)**
BPD n (%)	3 (7.3)	6 (7.9)	0.90†		
Treated PDA n (%)	11 (26.8)	13 (16.0)	0.15£	-	-
Hypotension n (%)	15 (36.6)	10 (12.2)	**0.002£**	4.1 (1.6 - 10.3)	**8.3 (1.8 - 37.6)**
NEC n (%)	6 (14.6)	8 (9.9)	0.54†	-	
ROP ≥ grade 3 n (%)	0	1 (1.3)	0.46†	-	-
CRIB > 5 n (%)	19 (46.3)	23 (28.0)	**0.044£**	2.2 (1.1 - 4.8)	-
Cystic PVL n (%)	11(26.8)	0	**< 0.0001†**		

aOR: adjusted odds ratio; BW: birthweight; BPD: bronchopulmonary dysplasia; CRIB: clinical risk index for babies; CI: confidence interval; Cystic PVL: cystic periventricular leukomalacia; ETT: endotracheal tube; GA: gestational age; HMD Hyaline membrane disease; NEC: necrotizing enterocolitis; NB: newborn; OR: odds ratio; PDA; patent ductus arteriosus; PIVH: peri/intraventricular haemorrhage; ROP: retinopathy of prematurity; SGA: small for gestational age; sd: standard deviation; £: chi-square; †: Fisher's test; * Student's t-test for independent samples, with a significance level < 0.05.

Table 2 – Neurodevelopment of newborns diagnosed with hydrocephalus

	NB with hydrocephalus treated with shunt, n = 7	NB with hydrocephalus with no shunt, n = 4	*p*-value
Moderate to severe PDD n (%)	2 (28.6)	0	0.49†
Cerebral palsy n (%)	4 (42.9)	0	0.23†
Neurosensorial impairment n (%)	0	0	
Severe impairment n (%)	5 (57.0)	0	0.19†

PDD: pervasive developmental disorders; NB: newborns; †: Fisher's test, with a significance level < 0.05

Table 3 – Neurodevelopment of newborns with severe peri/intraventricular haemorrhage at 24 months

	NB with III-IV PIVH n = 24	Control group n = 75	*p*-value	OR (95% CI)
Moderate to severe PDD n (%)	3 (12.5)	1 (1.3)	0.043†	10.5 (1.1 - 106)
Cerebral palsy n (%)	6 (25.0)	0	0.001†	
Neurosensorial impairment n (%)	0	1 (1.3)	0.56†	
Severe impairment n (%)	7 (30.4)	1 (1.3)	0.001†	32 (3.7 - 281)
Severe impairment/death (*) n (%)	23 (57.5)	8 (9.8)	< 0.001†	12.5 (4.7 - 32.7)

PDD: pervasive developmental disorders; CI: confidence interval; OR: odds ratio; NB: newborn (*) Rates related to the total N, including deceased patients; † Fisher's test with a significance level < 0.05

progesterone has shown a protective role against ischaemic or traumatic injury in animal models.[35-37]

Sepsis is a recognised risk factor for PIVH due to the release of cerebral vasoactive cytokines,[38,39] and was identified as an independent risk factor in this study. Cytokines may cause haemodynamic changes in the vascular endothelium of the germinal matrix,[10] while haemodynamic instability, metabolic acidosis and coagulation disturbances in a sepsis setting may lead to injury to the already immature and fragile vascular endothelium of the germinal matrix.

Hypotension, which is associated with decreased cerebral blood flow, may damage the germinal matrix capillaries by reperfusion, and this association has been described in other studies[39] as a risk factor for PIVH.

According to most authors, NB with post-haemorrhagic ventricular dilation are associated with worse prognosis.[7,40,41] The need for intervention due to ventricular dilation has more sequelae than NB whose dilation stabilised without the need for surgery.[7,42] Even though a higher rate of severe neurodevelopmental impairment has been found in the group of patients who required surgery, there was no statistically significant differences in this study, probably related to the small number of cases.

This study showed that NB with severe PIVH had a worse prognosis, higher mortality/severe neurodevelopmental impairment (57.5% *vs.* 9.8%, $p < 0.001$) when compared to controls. The high mortality found in patients presenting with grade IV PIVH (52.9%) was in line with other studies.[9,15,16,31]

Survivors with severe PIVH presented with more severe neurodevelopmental impairment, namely a higher rate of CP and psychomotor developmental delay. These results are in line with other authors,[14] even though the high mortality rate that was found in all studies makes neurodevelopmental studies more difficult.

Patients presenting with severe PIVH and sometimes even with associated parenchymal lesions are mainly assessed as a whole,[31] reducing the knowledge on the real impact of grade III and IV PIVH on short and long-term prognosis.

No significant differences were found in patients presenting with grade III PIVH and no cystic PVL, either regarding CP or psychomotor development, in line with the study by O'shea *et al.*,[8] who have found that white matter lesions could underly the impairment associated with PIVH.

Approximately 80% of patients presenting with grade IV PIVH died or presented with a severe impairment. Three of the eight survivors presented with CP (37.5%), in line with literature. Psychomotor developmental delay was found in 25% of the patients (2/8). The small number of survivors with grade IV PIVH is a limitation of our study, which is also described by most authors.[43]

A limitation of this study regarded the fact that it was a retrospective analysis. However, the accurate registration of patients in the department database and the systematic assessment in outpatients allows for a reduction in some

Table 4 – Neurodevelopment of children with grade III and IV peri/intraventricular haemorrhage

	Controls n = 75	Grade III PIVH and no cystic PVL n = 12	Grade III PIVH and no cystic PVL *vs* Controls (*p*)	Grade III PIVH with cystic PVL n = 4	Grade III PIVH with cystic PVL *vs* Controls (*p*)	Grade IV PIVH n = 8	Grade IV PIVH *vs* Controls (*p*)
Moderate to severe PDD n (%)	1 (1.3)	0	0.7†	1 (25.0)	0.09†	2 (25.0)	0.023†
Cerebral palsy n (%)	0	0	➢ 0.99†	3 (75.0)	< 0.001†	3 (37.5)	0.001†
Neurosensory impairment n (%)	1 (1.3)	0	0.7†	0	0.7†	0	0.7†
Severe impairment n (%)	1 (1.3)	0	0.8†	3 (75.0)	< 0.001†	4 (50.0)	< 0.001†
Severe impairment/death (*) n (%)	8 (9.5)	5 (29.4)	0.052†	5 (83.3)	< 0.001†	13 (76.5)	< 0.001†

PDD: pervasive developmental disorders; PIVH: peri/intraventricular haemorrhage; Cystic PVL: cystic periventricular leukomalacia; OR: odds ratio; (*) Rates are related to the total n, including deceased patients; †: Fisher's test with a significance level < 0.05

constraints usually related with this type of study, such as frequent information gaps. Another limitation regarded the assessment of neurodevelopment at an early age (24 months) and the use of the SGS-II screening test in a significant number of patients. However, the presence of no significant changes in this test at 24 months would make the presence of severe outcomes unlikely. In this study, few cases underwent magnetic resonance imaging (MRI), that could have detected lesions of the white matter and cerebellum that could not have been found on ultrasound imaging, which is another limitation to be considered.

A strength of this study was the selection of patients with severe PIVH and controls matched by GA. The effect of prematurity on the presence of neurodevelopmental disorders is well known and this type of adjustment will have allowed a better evaluation of the effect associated with haemorrhage. The isolated assessment of the effect of the different types of severe PIVH (grade III with and without cystic PVL and grade IV) on neurodevelopment is also a strength of this study, as a contribution to improve the information to be provided to parents, despite a possible underdiagnosis of diffuse parenchymal lesions, only detected by MRI.

In Neonatal Intensive Care Units, the definition of the outcomes of very preterm infants with severe PIVH is a challenging mission, which is a major concern for both health professionals and parents.[44,45] Knowing whether the patients will survive or will walk autonomously and have a normal life are the most immediate questions of all parents, which are difficult to answer, especially when several risk factors for neurodevelopmental impairment are associated. The results of this study represent the reality of a Neonatal Intensive Care Unit and may contribute to the knowledge of this issue in other similar units.

CONCLUSION

A higher mortality and severe neurodevelopmental outcomes in patients presenting with grade IV or grade III PIVH with cystic PVL when compared to controls have been found and this may contribute to improve the information provided by neonatologists and other professionals to parents of patients presenting with this pathology in the acute phase of the disease.

A multicentric, prospective and long-term follow-up study of these patients is crucial to assess the impact of severe PIVH, with and without parenchymal involvement.

AUTHOR CONTRIBUTION

JA, SP: Intellectual contribution, data analysis, writing of the manuscript.

DF: Intellectual contribution, manuscript revision.

CR, AT: Intellectual contribution, writing and revision of the manuscript.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical

Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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