www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(1):e120114
doi: 10.7363/120114
Received: 2021 May 30; revised: 2021 Jul 09; accepted: 2021 Jul 11; published online: 2023 Jan 23

Original article

Neurodevelopmental outcomes of premature infants born at ≤ 32 weeks of gestational age with post-hemorrhagic hydrocephalus treated with ventriculoperitoneal shunt

Ana Rita Neves[1], Ana Vilan[2,3], Henrique Soares[2,3], Sara Almeida[4], Hercília Guimarães[2,5]

[1]Family Medicine, USF do Mar, ACeS Grande Porto IV – Póvoa de Varzim/Vila do Conde, Portugal
[2]Department of Gynecology-Obstetrics and Pediatrics, Faculty of Medicine of Porto University, Porto, Portugal
[3]Neonatal Intensive Care Unit, Department of Pediatrics, Centro Hospitalar Universitário de São João, Porto, Portugal
[4]Psychology Service, Neonatal Intensive Care Unit, Department of Pediatrics, Centro Hospitalar Universitário de São João, Porto, Portugal
[5]São João NIDCAP Training Center, Centro Hospitalar Universitário de São João, Porto, Portugal

Abstract

Introduction: In preterm newborns, post-hemorrhagic hydrocephalus (PHH) can lead to changes in development. There is no consensus on its treatment yet. The aim of this study is to evaluate the neurodevelopmental outcomes in preterm newborns with PHH treated with ventriculoperitoneal shunt (VPS).

Materials and methods: We evaluated all cases with ≤ 32 weeks gestational age who developed PHH and were treated with VPS between January 2007 and December 2017. An assessment of neurodevelopmental outcomes was made through their medical records at 3 years of age.

Results: Cerebral palsy (CP) was the most registered pathology (68.8%), followed by epilepsy (43.8%). No cases of bilateral deafness, use of hearing aids or total blindness were documented. Six (37.5%) of the children wore glasses. Regarding the Griffiths Mental Development Scales, 4 (50%) had General Quotient score corresponding to developmental delay. Delay was mostly observed in the Locomotor Scale (75%), followed by Eye and Hand Coordination Scale (62.5%) and Hearing and Speech Scale (50%). Practical Reasoning Scale (37.5%) and Personal-Social Scale (12.5%) had the lowest number of cases with delay.

Discussion: The results obtained were consistent with previous studies. The pathophysiology of brain injury in these children is multifactorial and the findings might be related to pressure effects of hydrocephalus and parenchymal injury.

Conclusion: CP, epilepsy and developmental delay may have a higher risk of developing in infants where VPS was used. No cases of hearing impairment were found, which may indicate that this pathology is not related to the use of VPS. Infants treated with VPS for PHH represent a high-risk group for the development of adverse neurodevelopment outcomes.

Keywords

Hydrocephalus, intraventricular hemorrhage, neurodevelopmental outcome, preterm infants, neonates, ventriculoperitoneal shunt.

Corresponding author

Ana Rita Neves, MD, Family Medicine Resident, USF do Mar, ACeS Grande Porto IV – Póvoa de Varzim/Vila do Conde, Portugal; email: anarita_neves97@hotmail.com.

How to cite

Neves AR, Vilan A, Soares H, Almeida S, Guimarães H. Neurodevelopmental outcomes of premature infants born at ≤ 32 weeks of gestational age with post-hemorrhagic hydrocephalus treated with ventriculoperitoneal shunt. J Pediatr Neonat Individual Med. 2023;12(1):e120114. doi: 10.7363/120114.

Introduction

The prevalence of premature birth is increasing, corresponding to 8% of live births in Portugal in 2018, according to the National Statistics Institute. Premature infants (newborns < 37 weeks) are affected by a variety of conditions that require close monitoring and multidisciplinary treatment decisions. Of these, intraventricular hemorrhage (IVH) is particularly relevant, since it is associated with several complications, particularly in newborns with very low birth weight [1]. Of these, preterm infants are at higher risk, as they have a fragile germinal matrix vasculature accompanied by altered brain self-regulatory mechanisms [1]. The presence of blood within the intraventricular space can alter the absorption and flow of cerebrospinal fluid (CSF), leading to progressive ventricular dilation (posthemorrhagic ventricular dilatation – PHVD), referred to as post-hemorrhagic hydrocephalus (PHH) [1].

PHH occurs in about one third of children with IVH [2]. The main risk factors for PHH are high-grade IVH (III and IV) and germinal matrix hemorrhage [3-5]. This pathology is detected in its early stages mainly by transfontanellar ultrasound. PHH can evolve, generally, in 3 ways, with around 40% requiring no intervention, 10% evolving rapidly and 50% showing a persistent slow progression, of which 20% do not progress after CSF drainage and 30% need shunt [3, 4].

Approximately 15-25% of children with IVH and PHH eventually need a ventriculoperitoneal shunt (VPS), due to the progressive increase in ventricular size [2]. The use of shunt as a way to treat this pathology is associated with several complications, and there are several factors that influence the outcome. Malfunction is the main source of complications of VPS and it is generally caused by infection or mechanical failure [6-8]. As such, several studies have been carried out, and it has been shown that survival using a shunt depends on the site where the shunt is revised, with distal revision being associated with a better outcome [9]. Concomitantly, weight > 1.5 kg and gestational age > 27 weeks are also related to better survival to VPS [9]. Taking into account the great morbidity associated with the VPS, it is preferable that the newborn has a weight of at least 2 kg and that proteinorrachia is less than 1.5 g/L in order to use this method [1, 10]. Magnetic resonance imaging demonstrated a decrease in the volume of deep gray matter and the cerebellum in patients with PHH [11]. A study revealed that the intervention time was more important for long-term development than the use or not of shunt [12]. Nonetheless, another study demonstrated that there was a higher risk of developing cerebral palsy (CP) when using shunt vs. non-shunt [2]. In preterm newborns, PHVD following severe IVH can lead to changes in development at 12 and 18-24 months [2]. Neuronal injury is caused by a combination of IVH and PHH, since hemorrhage results in neuronal injury to the parenchyma, either by mechanical factors or by factors that lead to inflammatory changes. This mechanism is further exacerbated by an increase in intracranial pressure, which will consequently decrease cerebral perfusion pressure [1].

Despite the many treatment options, there is still no consensus on the treatment of PHH and, to date, few studies have been carried out in children who have had PHH and required VPS for

treatment, regarding the assessment of changes in neurodevelopment outcomes. In 2017, Diwakar et al. showed changes in neurodevelopment in children who suffered PHH and in whom VPS was used with a population of premature newborns < 29 weeks of gestational age [2]. The aim of the present study is to evaluate the neurodevelopmental outcomes at 3 years of age in preterm newborns born at ≤ 32 weeks of gestational age in which VPS was used for the treatment of PHH in order to improve our practice in the management of this type of newborns.

Materials and methods

An observational retrospective study was conducted. The study population included preterm neonates ≤ 32 week of gestational age admitted to the Level III Neonatal Intensive Care Unit (NICU) of Centro Hospitalar Universitário São João (CHUSJ) do Porto (Porto, Portugal) between January 2007 and December 2017, with a diagnosis of PHH and who were treated with a VPS.

Data were obtained by consulting the newborn's medical record, discharge notes and reports. The patient's charts were reviewed for the clinical characteristics of age, sex, gestational age, weight at birth, administration of antenatal corticosteroid, chorioamnionitis, type of delivery, Apgar score, use of surfactant, non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), occurrence of bronchopulmonary dysplasia (BPD), early-onset and late-onset sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), IVH and age of diagnosis, hydrocephalus and age of diagnosis, cystic periventricular leukomalacia (cPVL), meningitis, PSV, age at of PSV placement and immediate complications, seizures, age at first ultrasound, length of stay in the NICU, neurological examination at discharge and early neurodevelopmental outcomes.

The diagnosis of BPD was based on the National Institute of Child Health and Human Development [13]. Early sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture at < 72 hours of life and late-onset sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture at ≥ 72 hours of life [14]. Meningitis was defined as CSF culture positive for a single organism during the hospital stay [15]. Diagnosis of NEC was established by the criteria of Bell [16]. cPVL was classified according to de Vries [17]. The diagnosis of ROP was based on the *International Classification of Retinopathy of Prematurity Revisited* [18]. NIMV was classified as the use of nasal continuous positive airway pressure (nCPAP) and IMV was classified as the use of high-frequency mechanical ventilation or conventional mechanical ventilation.

Cranial ultrasound examination

Cranial ultrasound was performed as soon as possible after admission, 3 to 4 times during the first week, at least once weekly until discharge. IVH was classified according to Volpe – in this study it was only considered grade 3 (transfontanellar ultrasound demonstrating intraventricular bleeding occupying > 50% of the ventricular area on parasagittal view) and periventricular venous hemorrhagic infarction (PVHI) [19]. PHH was diagnosed by serial cranial ultrasounds that demonstrate increasing PHVD. Using the Levene Index, the anterior horn width and the thalamus-occipital distance, it was possible to determine the need for intervention. The ventricular width was measured according to the criteria of Levene [20] and PHVD was defined as a measurement > p97.

Intervention

According to the protocol in force at CHUSJ at the date of the intervention, VPS was placed when there was progression of PHVD after performing lumbar puncture and diuretics. The first step in the progressive PHH approach consists of performing serial lumbar punctures, in which 10 mL of CSF per kg of weight must be removed and sent for cytological, biochemical and bacteriological examination. Concomitantly, diuretic treatment with isosorbide at a dose of 8 g/kg should be started, 6 times a day, orally, and this therapy should be continued for the first 6 months. If progression of PHVD occurred despite the mentioned procedures, VPS was considered. Immediate complications were defined as VPS obstruction, dehiscence or infection that occurred in < 8 days after VPS insertion.

Assessment of neurodevelopmental outcomes

The surviving infants were seen in the follow-up clinic at regular intervals. Assessment of developmental delay was based on Griffiths Mental Development Scales – Extended Revised (GMDS). The data were collected through a follow-up that occurred on average at 35 months of age. The GMDS are widely used to ascertain the level of mental

development from 0 until 8 years of age and provide a developmental General Quotient (GQ) in addition to 6 different subscales: Locomotor, Personal-Social, Hearing and Speech, Eye and Hand Coordination, Performance and Practical Reasoning Scales [21]. The Locomotor Scale measures movement with regard to graded coordination, economy of effort, and social control; the Personal-Social Scale covers growing self-awareness, independence, and social interaction; the Hearing and Speech Scale rates the child's ability to hear, listen, and comprehend, as well as to express themselves; the Eye and Hand Coordination Scale assesses visual competence with fine motor precision functionality; the Performance Scale pertains to determine visual perception awareness, including working speed and precision; the Practical Reasoning Scale corresponds to a 2- to 8-year-old child's ability to use past learning experiences to solve problems and their understanding of basic mathematical concepts and moral issues [22]. The mean of the GQ and each of the 6 subscale quotients is 100 points (SD = 15 points). The subscale quotients are calculated using the developmental age corresponding to each subscale divided by the actual chronological age and multiplying by 100 [23]. The GQ raw score is the sum of the subscales raw scores. When the quotient obtained is < 80 points, it is considered to be an indication of delay in development, while a quotient > 80 points indicates mild or no delay. CP refers to a non-progressive disability of movement and posture [24]. The severity of CP was graded according to the Gross Motor Function Classification System (GMFCS) [25]. Deafness was defined as a bilateral sensorineural loss requiring amplification or cochlear implants. Blindness was defined as bilateral visual acuity < 3/60. Epilepsy was defined as the occurrence of at least 1 epileptic seizure [26]. The assessment of the previously mentioned outcomes occurred through the analysis and consultation of medical records up to 3 years of age. The study was approved by the Health Ethics Committee of CHUSJ, which dispensed the need for informed consent for this study.

Analysis

Data was recorded in a digital database (Microsoft® Excel® 16.34 version) and descriptive statistics were calculated. Given the size of the sample, it was only possible to conduct a descriptive analysis.

Results

A preliminary survey allowed the identification of 73 newborns ≤ 32 weeks of gestational age diagnosed with PHH born between January 2007 and December 2017. An analysis of the electronic medical records and discharge notes was carried out and 55 of the previously identified cases were excluded, since VPS was not used in the treatment of these patients. Eighteen infants with PHH that needed VPS were identified. Then 2 infants died during the hospital stay. The final sample of the study consisted of 16 infants. A flow diagram of the study population is shown in **Fig. 1**.

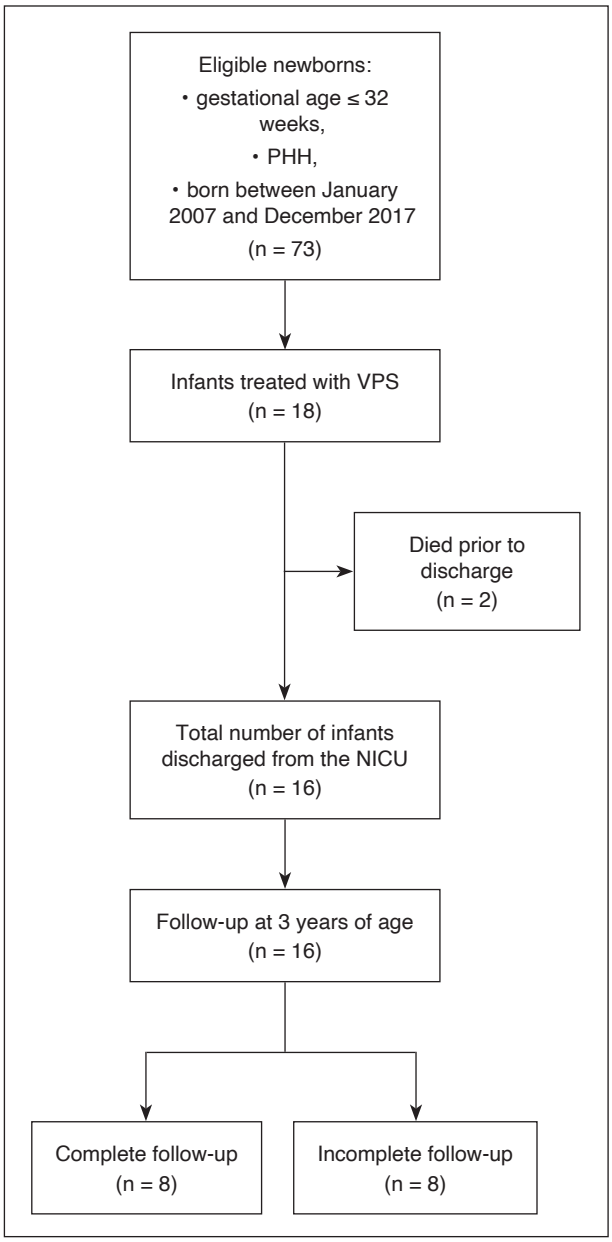

Figure 1. Flow diagram of the study population.
NICU: Neonatal Intensive Care Unit; PHH: post-hemorrhagic hydrocephalus; VPS: ventriculoperitoneal shunt.

Tab. 1 summarizes data regarding maternal and neonatal characteristics. All neonates required either NIMV or IMV. Sepsis occurred in 13 infants, 2 of which corresponded to early-onset sepsis and the remaining to late-onset sepsis. ROP was identified in 11 (68.8%) infants. Three (18.8%) infants were diagnosed with cPVL and 2 (12.5%) with meningitis. The median at the realization of the first cranial ultrasound was 2 days. There were 10 (62.5%) cases of IVH grade III, 6 (37.5) of PVHI and the median age at diagnosis was 5 days (2-26 days). The median age

Table 1. Maternal and neonatal characteristics (n = 16).

Characteristics			n (%) or mean (SD) or median (IQR)
Maternal characteristics			
Clinical choriamnionitis, n (%)			1 (6.3)
Antenatal corticosteroids, n (%)			14 (87.5)
Eutocic delivery, n (%)			7 (43.8)
C-section, n (%)			9 (56.3)
Presence of labor, n (%)			12 (75)
Neonatal characteristics			
Birth weight, g, mean (SD)			1,040.9 (227.7)
Gestational age, weeks, mean (SD)			27.3 (1.8)
Male, n (%)			5 (31.3)
Apgar score at 10 minutes, median (IQR)			8 (1.5)
Surfactant, n (%)			13 (81.3)
Number of surfactant doses, mean (SD)			1.8 (0.6)
nCPAP, n (%)			14 (87.5)
Days in CPAP, median (IQR)			32 (18.3)
Conventional IMV, n (%)			15 (93.8)
Days in conventional IMV, median (IQR)			13 (20.3)
High frequency IMV, n (%)			2 (12.5)
Days in high frequency IMV, mean (SD)			12.5 (2.1)
BPD, n (%)			3 (18.8)
Early-onset sepsis, n (%)			2 (12.5)
Late-onset sepsis, n (%)			11 (68.8)
NEC, n (%)			2 (12.5)
ROP	ROP (all stages), n (%)		11 (68.8)
	ROP stage I, n (%)		6/11 (54.5)
	ROP stage II, n (%)		4/11 (36.4)
	ROP stage III, n (%)		1/11 (9.1)
IVH	Grade III, n (%)		10 (62.5)
	PVHI, n (%)		6 (37.5)
	Age at diagnosis, days, median (IQR)		5 (10)
Hydrocephalus	Age at diagnosis, days, median (IQR)		15 (20.8)
VPS	Age at insertion, days, median (IQR)		46.5 (53.8)
	Immediate complications	Obstruction, n (%)	1 (6.3)
		Dehiscence, n (%)	1 (6.3)
		Infection, n (%)	0 (0)
cPVL, n (%)			3 (18.8)
Meningitis, n (%)			2 (12.5)
Seizures, n (%)			4 (25)
Age at first cranial ultrasound, days, median (IQR)			2 (2.8)
Length of hospital stay, days, median (IQR)			75 (18.8)

BPD: broncopulmonary dysplasia; cPVL: cystic periventricular leukomalacia; IMV: invasive mechanical ventilation; IQR: interquartile range; IVH: Intraventricular hemorrhage; nCPAP: nasal continuous positive airway pressure; NEC: necrotising enterocolitis; PVHI: periventricular venous hemorrhagic infarction; ROP: retinopathy of prematurity; SD: standard deviation; VPS: ventriculoperitoneal shunt.

at diagnosis of hydrocephalus was 15 days (2-31 days) and at VPS insertion was 46.5 days (23-115 days). Regarding the VPS complications, there was 1 dehiscence, 1 obstruction and no registered infections. Seizures occurred in 4 (25%) neonates. The length of hospital stay had a median of 75 days, having the largest stay occurred for 124 days and the shortest for 14 days.

The neurodevelopmental outcomes at 3 years of age are shown in **Tab. 2**. CP was an outcome seen in 11 (68.8%) children, 1 (9.1%) with level II CP, 4 (36.4%) with level III, 2 (18.2%) with level IV and 4 (36.4%) with level V. No cases of bilateral deafness or use of hearing aids were seen. Regarding the vision evaluation, there were no cases of total blindness and 6 (37.5%) children wore glasses at 3 years of age. Epilepsy was diagnosed in 7 (43.8%) children.

The results of GMDS assessment are presented in **Tab. 3**. The median of the GQ of the 8 children whose data were possible to obtain was 82 and the values obtained ranged from a score of 42 to a score of 104. The Locomotor Scale had the lowest median of the subscales, with a median of 67.5, with the lowest value being 40 and the highest 80. The median of the Personal-Social Scale was 95 (48-105), the Hearing and Speech Scale was 84 (40-110), the Eye and Hand Coordination Scale was 77 (40-112) and finally the Practical Reasoning Scale was 80 (40-118). One child had development delay (< 80 points) in all the scores obtained in the GMDS. Additionally, 4 (50%) children had GQ corresponding to delay. The Locomotor Scale was the one where delay was mostly observed, with 6 (75%) children obtaining a score lower than 80, followed by the Eye and Hand Coordination Scale with 5 (62.5%) children and Hearing and Speech Scale with 4 (50%). The subscales with the least number of cases were the Practical Reasoning Scale and Personal-Social Scale, with a number of infants obtaining a score < 80, of 3 (37.5%) and 1 (12.5%), respectively. Data regarding the Performance Scale was not available in the clinical records and as such it was not analyzed.

In **Tab. 4**, specific information concerning patient's individual characteristics and pre-natal diagnosis with their respective neuro-developmental outcomes during follow-up is shown. In 3 of the studied cases, no alterations in neurodevelopment were observed. Thirteen infants had a normal neurological exam at discharge. Two of the 3 children who had an altered neurological examination at discharge were then diagnosed with CP. Analyzing the cases that had CP, we verified that 2 were diagnosed with meningitis and 2 had seizures. Regarding the cases identified as needing to wear glasses, 2 had meningitis and 3 had seizures during hospitalization. In cases where a GQ with a score lower than 80 was determined, 1 had meningitis and 1 had seizures. The reported case that had a dehiscence of the VPS developed CP level II, epilepsy, had necessity to use glasses at 3 years of age and scored lower than 80 in the GQ. Of the children diagnosed with epilepsy, 1 case had meningitis and 2 had seizures during the hospital stay. In the reported case with VPS obstruction, there were no subsequent changes in any of the parameters evaluated at neurodevelopment level.

Table 2. Neurodevelopmental outcomes at 3 years of age (n = 16).

Variables		n (%)
CP	CP (all levels)	11 (68.8)
	CP level II	1/11 (9.1)
	CP level III	4/11 (36.4)
	CP level IV	2/11 (18.2)
	CP level V	4/11 (36.4)
Epilepsy		7 (43.8)
Hearing	Bilateral deafness	0 (0)
	Hearing aids	0 (0)
Vision	Total blindness	0 (0)
	Glasses	6 (37.5)

CP: cerebral palsy.

Table 3. GMDS outcomes at 3 years of age (n = 8) [a].

GMDS	Median (IQR)	Delay, n (%) [b]
GQ	82 (18.5)	4 (50)
Locomotor Scale	67.5 (19)	6 (75)
Personal-Social Scale	95 (21)	1 (12.5)
Hearing and Speech Scale	84 (38)	4 (50)
Eye and Hand Coordination Scale	77 (21.25)	5 (62.5)
Practical Reasoning Scale	80 (33.75)	3 (37.5)

GMDS: Griffiths Mental Development Scales – Extended Revised; GQ: General Quotient; IQR: interquartile range.
[a] Only 8/16 cases were considered, due to missing data for 8 cases.
[b] GQ or a subscale < 80.

Table 4. Individual clinical data and outcomes.

		Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Neonatal characteristics		Gestational age, weeks	27	28	27	29	31	26	24	25	29	28	26	28	26	29	26	28
		Weight at birth, g	995	1,136	1,140	1,320	1,410	725	875	820	1,260	933	940	985	820	1,490	855	950
		Cortico-therapy	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		Clinical chorioamnionitis	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No
		Apgar score at 10 minutes	9	7	8	4	10	7	8	7	8	10	8	6	9	6	8	8
		IVH classification	III	III	III	III	PVHI	III	PVHI	III	III	III	PVHI	III	PVHI	PVHI	III	PVHI
		Age at IVH diagnosis, days	5	10	23	4	14	2	5	10	3	2	26	4	3	10	2	18
		Age at hydrocephalus diagnosis, days	5	10	31	4	29	2	5	10	4	18	26	25	23	12	30	18
		Age at VPS insertion, days	55	43	115	25	42	64	28	57	23	34	29	26	98	50	91	88
		cPVL	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes
		Meningitis	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
		VPS obstruction	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
		VPS dehiscence	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No
		Seizures	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes
		Neurological evaluation at discharge	Normal	Normal	Normal	Hypotonia	Normal	Normal	Normal	Hyperreflexia /increased tonus	Normal	Normal	Axial hypotonia	Normal	Normal	Normal	Normal	Normal
		Age at first cranial ultra-sound, days	5	1	2	3	1	2	10	2	3	2	26	4	0	1	0.17	3
		Length of hospital stay, days	63	69	124	28	56	93	14	112	74	34	76	83	100	48	94	92
Neurodevelopmental outcomes	CP	CP	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
		CP grade	III	V	-	IV	III	IV	-	V	V	-	-	-	III	II	III	V
	GMDS	GQ	-	-	-	-	-	69	-	-	85	-	104	89	79	72	86	42
		Locomotor Scale	-	-	-	-	-	62	-	-	72	-	100	82	60	70	65	40
		Personal-Social Scale	-	-	-	-	-	82	-	-	100	-	102	98	92	80	105	48
		Hearing and Speech Scale	-	-	-	-	-	62	-	-	104	-	110	96	78	70	90	40
		Eye and Hand Coordination Scale	-	-	-	-	-	72	-	-	78	-	112	90	82	76	65	40
		Practical Reasoning Scale	-	-	-	-	-	68	-	-	99	-	118	80	80	72	104	40
		Epilepsy	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Yes	No	Yes
		Hearing aids or bilateral deafness	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
		Glasses	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes
		Total blindness	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

CP: cerebral palsy; cPVL: cystic periventricular leukomalacia; GMDS: Griffiths Mental Development Scales – Extended Revised; GQ: General Quotient; IVH: intraventricular hemorrhage; PVHI: periventricular venous hemorrhagic infarction; VPS: ventriculoperitoneal shunt.

Discussion

The present study revealed findings consistent with previous studies regarding the neurodevelopment outcomes of children who were treated with PVS after PHH. The preterm infants studied had adverse neurodevelopmental outcomes and were mainly reflected in the existence of CP, with the majority number of cases, followed by epilepsy.

The results obtained regarding the CP diagnosis, with 68.8% of cases developing this pathology, were coherent with the ones achieved by other studies. Diwakar et al. demonstrated that children who needed VPS had a higher risk of developing CP at 3 years of age, reporting 76% of moderate-severe CP in the shunt group [2]. Boynton et al. also reported consistent data, with severe motor handicap observed in almost half of the children and CP in 70% of the cases [27].

On the other hand, Brouwer et al. did not show any significant changes in the neurodevelopment in children who were treated with VPS after PHH [28].

The pathophysiology of brain injury in children with severe IVH and PHH is multifactorial. Neuronal injury is caused by a combination of various factors, namely the enlargement in ventricles leads to changes in the cerebral tracts, to poor inter-hemispheric connection and the hemorrhage leads to neuronal injury of the parenchyma. Furthermore, many mediators of highly importance for the central nervous system (CNS) development might be affected by inflammatory alterations that occur in these pathologies [1, 2, 29]. As such, the use of a VPS can cause neurological damage, leading to subsequent changes in neurodevelopment. It is very important to consider that CP might in part occur duo to a consequence of pressure effects of hydrocephalus and parenchymal hemorrhagic injury, which by themselves are already risk factors to adverse neurodevelopment outcomes [27]. In addition, our results reveled that both children who had meningitis during their stay at the NICU then were reported to have CP. These findings might indicate a contribution of meningitis to the overall prognosis of this infants. These data are consistent with other studies, since neurodevelopmental disorders have been previously described in premature children who had meningitis even after controlling for other risk factors such as IVH [30]. Data available reported a higher occurrence of CP in the children that developed VPS infection, an important factor that might be an addition potential risk for the development of this adverse outcome [2, 28]. In our study we did not observe cases of shunt infection, however the case in which a dehiscence was detected was diagnosed with CP grade II, while in the case with obstruction of the VPS, no adverse changes in neurodevelopment were recorded. The absence of cases of shunt infection may be related to a timely and adequate approach in placing VPS in these patients and their subsequent management in the hospital where the present study took place.

Thus, we realized that there is a need to better understand and relate the risk between meningitis and VPS complications and adverse changes in neurodevelopment in children in whom VPS was used for the treatment of PHH.

Developmental delay with a GQ < 80 was observed in 4 of the 8 children whose data we were able to obtain, with the Locomotor Scale having 6 (75%) of the children with a score lower than 80. Due to the small number of infants from whom we were able to obtain information regarding the GMDS, it is not possible to draw conclusions, however our data suggests that there might be a relation between the use of VPS and adverse development changes. The developmental delay is compatible with the physiological changes caused by the pathology in question, namely the impact that the ventricular enlargement imposes on the spinal tracts and its connection with the white matter, which can lead to alterations on the cognitive level [2].

Adams-Chapman et al. reported outcomes of children at 18-22 months. Their data showed that children with severe IVH associated with PHH in the VPS group were at significant risk for both cognitive and motor impairment (Psychomotor Development Index < 70 and/or a Mental Development Index < 70). They also stated that VPS insertion represents and additional factor, to the risk of neurodevelopmental changes already attributed to the existence of IVH [29]. In contrast, available literature [2, 28] also reported no changes in developmental delay in their studies. The disparity in results may occur due to the fact that outcomes may change over the course of the child's growth, namely decrease, increase or remain unchanged, requiring a long-term follow-up to understand whether there are indeed long-term changes at the cognitive level [2]. The fact that we were unable to observe Performance Scale data is probably related to the fact that up to 3 years old this subscale is not used in the GMDS and our average GMDS follow-up is 2 years and 11 months and as such it was not used for cognitive assessment in these children.

Sato et al. showed that VPS is highly related to the occurrence of epilepsy. They also demonstrated that shunt complications such as malfunction and infection implicated a higher risk of epilepsy [31]. As such, our findings of 43.8% diagnosed children with epilepsy by the age of 3 are consistent with the previous reports. A case of VPS dehiscence occurred among the children diagnosed with epilepsy, which corroborates in part the occurrence of complications in the shunt and increased risk of developing epilepsy.

No cases of hearing impairment or total blindness were observed in our study and 37.5% of the children wore glasses at the time of assessment, which is consistent with the finding of previous studies. Adams-Chapman et al. found that a higher proportion of children who required shunt insertion had vision impairment (24-33%), which is similar to the results found, since in their study the definition of vision impairment encompassed both the need to use corrective lenses or blindness [29]. Through a review of the literature [2, 28], we realized that there are no data that link the occurrence of blindness and the use of VPS, which again corroborates what was found in this study. Changes regarding hearing impairment were also not found in other studies [2, 29]. It is important in the future to study in more detail the changes that occur at the vision level and its relation to the use of VPS in the pathology addressed.

Three (75%) of the cases with developmental delay and 3 (42.9%) of the children diagnosed with epilepsy were reported to have had PVHI. Seizures were reported in a total of 4 children, with 3 having an adverse outcome. This information seems to fall in line with the evidence reported by other studies [27], having grade IV hemorrhage and seizures been described to be predictors of poor neurodevelopment outcomes; as such, they may be considered as additional factors to adverse outcomes in these children.

Of the 10 newborns who were diagnosed with grade III IVH, 7 (70%) were diagnosed with CP, 1 (10%) with developmental delay, 4 (40%) with epilepsy, and 4 (40%) needed to wear glasses. Six newborns were diagnosed with PVHI, of whom 4 (66.7%) children had CP, 3 (50%) had developmental delay, 3 (50%) had epilepsy and 2 (33.3%) wore glasses. As noted, the proportion of complications is similar between the 2 groups, except for developmental delay, which seems to be more associated with children who have been diagnosed with PVHI, which is in line with the greater severity of the clinical course of this grade of IVH. Regarding the children with grade III IVH, 2 were diagnosed with meningitis and 2 with cPVL, which may be related to the absence of differences in outcomes between grade III IVH and PVHI, since these are both factors that independently contribute to adverse changes in the neurodevelopment [30, 32].

In our study, 3 children (cases 6, 14 and 16) simultaneously presented CP, developmental delay, epilepsy and the need to wear glasses. Case number 6 had the lowest birth weight and during hospitalization meningitis was diagnosed. In case 14, maternal infection occurred, and it presented a dehiscence of the VPS. Finally, case 16 presented seizures during hospitalization.

As we have described, these 3 cases present a potential additional risk factor to VPS, namely the occurrence of meningitis, dehiscence and seizures, which may partly be related with the level of severity of the neurodevelopment conditions, but which, however, may not explain the totality of the observed changes. These cases did not show changes in the neurological examination at the time of discharge, so the factors previously mentioned do not explain completely the changes observed at various levels of development. The VPS was the constant factor that remained at the time of discharge and as such it might be the cause that explains the observed changes.

One of the strengths of our study was that it was conducted in a tertiary hospital, having covered a 10-year period. Our findings are relevant to the extent that these children have a high risk of alterations in terms of neurodevelopment and a consequent decrease in school performance, requiring close monitoring during their development. It is of utmost importance to provide the necessary support with long-term follow-up, to allow the child to obtain its maximum potential and to advise parents in all phases so that a continuous and adequate approach to the limitations of this children can be obtained.

The present study had the limitations inherent of a retrospective study. Another limitation regards the fact that was only included data from one institution. The present study also had a small size, which limits the extrapolation of results. Similar small studies contribute to a better knowledge of the disease, its treatment and future consequences. As such, it demonstrates the necessity for more such studies from multiple centers to be conducted to arrive at the optimal management protocol for this condition. Furthermore, the clinical assessment of the children at 3 years of age was not blinded, which may imply some bias.

The underlying doubts about the relation between the preexisting CNS damage, the type of therapy that is used in the treatment of PHH and long-term developmental outcomes might be answered by a prospective, multicenter, randomized study.

Conclusion

Preliminary findings in this small group suggests that:

1. CP, epilepsy and developmental delay may have a higher risk of developing in infants where VPS was used as treatment for PHH;
2. no cases of hearing impairment were found, which may indicate that this pathology is not related to the use of VPS;
3. infants treated with VPS for PHH represent an important high-risk group for the development of adverse neurodevelopment outcomes.

Our study highlights the major need for long-term follow-up of infants who had PHH and needed VPS for its treatment and warns of the need for future studies in this area, so that a more targeted approach can be offered to each individual patient.

Declaration of interest

The Authors have no commercial association that might pose a conflict of interest regarding this study. Funding: none.

References

1. Ellenbogen JR, Waqar M, Pettorini B. Management of post-haemorrhagic hydrocephalus in premature infants. J Clin Neurosci. 2016;31:30-4.
2. Diwakar K, Hader WJ, Soraisham A, Amin H, Tang S, Bullivant K, Kamaluddeen M, Lodha A. Long-Term Neurodevelopmental and Growth Outcomes of Premature Infants Born at <29 week Gestational Age with Post-Hemorrhagic Hydrocephalus Treated with Ventriculo-Peritoneal Shunt. Indian J Pediatr. 2017;84(9):662-9.
3. Inder TE PJ, Volpe JJ. Preterm intraventricular hemorrhage/ posthemorrhagic hydrocephalus. In: Volpe JL, Inder TE, Barra BT (Eds.). Volpe's Neurology of the Newborn, 6th ed. Philadelphia (PA): Elsevier, 2018.
4. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, Horwood LJ, Volpe JJ. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed. 2002;87(1): F37-41.
5. Radic JA, Vincer M, McNeely PD. Temporal trends of intraventricular hemorrhage of prematurity in Nova Scotia from 1993 to 2012. J Neurosurg Pediatr. 2015;15(6):573-9.
6. Chumas P, Tyagi A, Livingston J. Hydrocephalus – what's new? Arch Dis Child Fetal Neonatal Ed. 2001;85(3): F149-54.
7. Drake JM, Kestle JR, Milner R, Cinalli G, Boop F, Piatt J Jr., Haines S, Schiff SJ, Cochrane DD, Steinbok P, MacNeil N. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. Neurosurgery. 1998;43(2):294-303; discussion 303-5.
8. Stein SC, Guo W. Have we made progress in preventing shunt failure? A critical analysis. J Neurosurg Pediatr. 2008;1(1): 40-7.
9. Bir SC, Konar S, Maiti TK, Kalakoti P, Bollam P, Nanda A. Outcome of ventriculoperitoneal shunt and predictors of shunt revision in infants with posthemorrhagic hydrocephalus. Childs Nerv Syst. 2016;32(8):1405-14.
10. Brouwer AJ, Brouwer MJ, Groenendaal F, Benders MJ, Whitelaw A, de Vries LS. European perspective on the diagnosis and treatment of posthaemorrhagic ventricular dilatation. Arch Dis Child Fetal Neonatal Ed. 2012;97(1): F50-5.
11. Brouwer MJ, de Vries LS, Kersbergen KJ, van der Aa NE, Brouwer AJ, Viergever MA, Išgum I, Han KS, Groenendaal F, Benders MJ. Effects of Posthemorrhagic Ventricular Dilatation in the Preterm Infant on Brain Volumes and White Matter Diffusion Variables at Term-Equivalent Age. J Pediatr. 2016;168:41-9.
12. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, Whyte HE, Groenendaal F, Kulkarni AV, Han KS, Woerdeman PA, Church PT, Kelly EN, van Straaten HLM, Ly LG, de Vries LS. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology. 2018;90(8):e698-706.
13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-9.
14. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics. 2005;116(3):595-602.
15. Friedman J, Matlow A. Time to identification of positive bacterial cultures in infants under three months of age hospitalized to rule out sepsis. Paediatr Child Health. 1999;4(5):331-4.
16. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986;33(1):179-201.
17. Ahya KP, Suryawanshi P. Neonatal periventricular leukomalacia: current perspectives. Res Rep Neonatol. 2018;8:1-8.
18. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7): 991-9.
19. Volpe JJ. Intracranial Hemorrhage: Germinal Matrix-Intraventricular Hemorrhage. In: Volpe JJ. Neurology of the Newborn, 5th ed. Philadelphia (PA): Saunders Elsevier, 2008.

20. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child. 1981;56(12):900-4.
21. Griffiths R. The Abilities of Young Children. Amersham: Association for Research in Infant and Child Development, 1984.
22. Li HH, Wang CX, Feng JY, Wang B, Li CL, Jia FY. A Developmental Profile of Children With Autism Spectrum Disorder in China Using the Griffiths Mental Development Scales. Front Psychol. 2020;11:570923.
23. Cirelli I, Bickle Graz M, Tolsa JF. Comparison of Griffiths-II and Bayley-II tests for the developmental assessment of high-risk infants. Infant Behav Dev. 2015;41:17-25.
24. Russman BS, Gage JR. Cerebral palsy. Curr Probl Pediatr. 1989;19(2):65-111.
25. Palisano RP, Walter S, Russel D, Wood E, Galuppi B. Develoment and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214-23.
26. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470-2.
27. Boynton BR, Boynton CA, Merritt TA, Vaucher YE, James HE, Bejar RF. Ventriculoperitoneal shunts in low birth weight infants with intracranial hemorrhage: neurodevelopmental outcome. Neurosurgery. 1986;18(2):141-5.
28. Brouwer AJ, van Stam C, Uniken Venema M, Koopman C, Groenendaal F, de Vries LS. Cognitive and neurological outcome at the age of 5-8 years of preterm infants with post-hemorrhagic ventricular dilatation requiring neurosurgical intervention. Neonatology. 2012;101(3):210-6.
29. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics. 2008;121(5):e1167-77.
30. Doctor BA, Newman N, Minich NM, Taylor HG, Fanaroff AA, Hack M. Clinical outcomes of neonatal meningitis in very-low birth-weight infants. Clin Pediatr (Phila). 2001;40(9): 473-80.
31. Sato O, Yamguchi T, Kittaka M, Toyama H. Hydrocephalus and epilepsy. Childs Nerv Syst. 2001;17(1-2):76-86.
32. Gotardo JW, Volkmer NFV, Stangler GP, Dornelles AD, Bohrer BBA, Carvalho CG. Impact of peri-intraventricular haemorrhage and periventricular leukomalacia in the neurodevelopment of preterms: A systematic review and meta-analysis. PLoS One. 2019;14(10):e0223427.