

DR. ALESSANDRO PARODI (Orcid ID : 0000-0002-3463-3004)

DR. LAURA COSTANZA COSTANZA DE ANGELIS (Orcid ID : 0000-0002-0201-257X)

DR. CARLO BELLINI (Orcid ID : 0000-0002-4199-7412)

Article type : Brief Report

Post-haemorrhagic hydrocephalus management: delayed neonatal transport negatively affects outcome

Alessandro Parodi¹, Ilaria Giordano¹, Laura De Angelis¹, Mariya Malova¹, Maria Grazia Calevo², Deborah Preiti¹, Marcello Ravegnani³, Armando Cama³, Carlo Bellini¹, Luca A. Ramenghi^{1,4}.

¹ Neonatal Intensive Care Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy.

² Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy.

³ Paediatric Neurosurgery Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy,

⁴ Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), University of Genoa, Genoa, Italy.

Short title: Hydrocephalus in transported preterm infants

Corresponding author:

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/APA.15604](https://doi.org/10.1111/APA.15604)

This article is protected by copyright. All rights reserved

Alessandro Parodi, MD

Neonatal Intensive Care Unit, IRCCS Istituto Giannina Gaslini, Via Gaslini 5,

16148 Genoa, Italy

E-mail: alessandroparodimail@gmail.com

Phone: +39 01056362218

Post-haemorrhagic ventricular dilatation (PHVD) remains a major cause of brain injury in preterm infants. Cerebrospinal fluid drainage is often needed to decrease dilatation and prevent further damage (1). Like most European neonatal intensive care units (NICUs), we treat infants once the ventricular index (VI) has crossed the 97th percentile (p97) and 4mm line (2,3), as recently recommended (1,4).

We had noticed that neonates transferred to our level-four NICU had extremely severe PHVD frequently surpassing the treatment threshold. Our aim was to assess the degree of ventricular dilatation, the timing of surgery and neurodevelopmental outcome in inborn and outborn patients. The hypothesis was that infants were being referred to our centre later than recommended.

The clinical database at the Gaslini Institute of Genoa, Italy, was retrospectively searched for all preterm infants treated for postnatal-onset PHVD from January 2012 to December 2018. Our NICU has a longstanding practice to treat PHVD once the VI has crossed the p97+4 mm line according to Levene (3) by external ventricular drain (EVD) placement. This temporary drain progressively reduces ventricular dilatation by continuously draining 10-15 ml/kg of cerebrospinal fluid daily, according to ventricular size changes and aiming for VI <p97 over the next two weeks. Once the cerebrospinal fluid protein concentration is below 1 g/L, EVD is removed and ventricular size is closely monitored to identify patients with recurrent progressive dilatation who require a permanent ventriculo-peritoneal shunt.

Study patients were divided into outborn infants transferred to the unit for PHVD treatment and inborn infants admitted before PHVD onset. Outborn infants who had already received PHVD treatment were excluded.

The clinical data collected included the admission age of outborn patients, the age when EVD placement was decided and provided and any need for a ventriculo-peritoneal shunt. The ultrasound data included the prospectively measured VI in each lateral ventricle on the day that we decided to treat inborn and outborn infants. VI was retrospectively plotted on Levene's graph to calculate the difference between the VI and the p97 (VI-p97), according to postmenstrual age (3).

Neurodevelopmental outcome was assessed using the Vineland Adaptive Behavior Scales II (VABS-II), a parental questionnaire investigating four domains of adaptive behavior (communication, daily living skills, socialization, and motor skills) and overall adaptive functioning. Developmental delay was defined as a score <70 (-2 SD or less).

Demographic, clinical and ultrasound data were compared between the two groups. Measurements of non-dilated lateral ventricles were excluded if there was unilateral hydrocephalus.

Parameters were compared using the Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical variables. The statistical analysis was performed using SPSS for Windows, version 20 (IMB Corp, New York, USA).

Of the 27 preterm infants treated for postnatal-onset PHVD, 12 were outborn and 15 were inborn. Decisions about EVD treatment were made the same day that outborn infants were admitted. They were significantly older than inborn infants at the time of the decision and actual surgery (Table 1).

We included 47/54 lateral ventricle measurements for 21 outborn and 26 inborn patients: six measurements were missing due to porencephaly involving the frontal horn, following periventricular haemorrhagic infarction, and we excluded a non-dilated lateral ventricle in

one patient with unilateral PHVD. The VI-p97 values were significantly higher in the outborn group (Table 1).

A ventriculo-peritoneal shunt was inserted in 66.7% of outborn and 40.0% of inborn patients ($p=0.18$). A higher rate of developmental delay in all domains was observed in outborn patients compared to inborn patients, although statistically not significant (Table 1). A similar trend was observed after excluding subjects with parenchymal lesions (3 patients with infarction in each group and 1 inborn patient with cystic periventricular leukomalacia), reaching statistical significance for overall adaptive functioning (66.7% of outborn vs 18.2% of inborn patients with VABS-II composite score <70 , $p=0.04$).

Infants transferred from other centres with progressive PHVD were treated later and reached more severe ventricular dilatation than inborn infants. Their ventricular measurements were significantly higher before surgery and most widely exceeded the p97+4 mm cut-off commonly used in Europe (2). Interestingly, our follow-up data showed a trend towards a higher rate of permanent shunt and developmental delay in outborn than in inborn patients, although the sample was too small to reach statistical significance for most outcomes. These results agree with data showing impaired neurodevelopmental outcomes for EVD treatment after 25 days of life compared to earlier treatment (5). Furthermore, the p97+4 mm treatment threshold is supported by evidence suggesting that early PHVD management (i.e. based on ventricular measurements) results in improved neurodevelopmental outcome and in reduced shunt rate when compared to late treatment (i.e. based on clinical signs of increased intracranial pressure) (1,4).

Delays in transferring infants to our centre may have been due to their poor clinical conditions related to extreme prematurity and local deficiencies in the regionalisation of perinatal care. Transporting an unstable preterm infant is challenging, but delayed transport means delayed treatment.

Our findings suggest that patients with progressive PHVD should be transferred to specialist care by skilled neonatal emergency transport services when ventricular dilatation is approaching the intervention threshold: it might be reasonable to plan

transport once VI has reached the p97, following a progressive increase over the last week. The risk of subsequent neurological disabilities caused by delayed PHVD treatment and the risk to move unstable preterm infants should be carefully weighed.

FUNDING

No external funding.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABBREVIATIONS

PHVD, post-haemorrhagic ventricular dilatation; VI, ventricular index; p97, 97th percentile; NICU, neonatal intensive care unit; VABS-II, Vineland Adaptive Behavior Scales II.

References

1. Leijser LM, Miller SP, van Wezel-Meijler G, et al. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? *Neurology*. 2018;90(8):e698-e706.
2. Brouwer AJ, Brouwer MJ, Groenendaal F, et al. European perspective on the diagnosis and treatment of posthaemorrhagic ventricular dilatation. *Arch Dis Child Fetal Neonatal Ed*. 2012;97: F50–55.
3. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. *Arch Dis Child*. 1981;56:900-4.
4. De Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(1):F70-F75.
5. Bassan H, Eshel R, Golan I, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. *Eur J Paediatr Neurol*. 2012;16:662-70.

Table 1. Comparison of demographic characteristics, clinical characteristics, neurodevelopmental outcome and ventricular measurements between inborn and outborn groups (EVD: external ventricular drain; VABS-II: Vineland Adaptive Behavior Scales II; VI-p97: difference between the Ventricular Index and the 97th percentile according to postmenstrual age).

Means and standard deviations (\pm) unless otherwise stated	Inborn patients (n=15)	Outborn patients (n=12)	P value
Birth weight (grams)	1157 \pm 402	1359 \pm 575	0.37
Gestational age (weeks)	28.4 \pm 2.1	28.2 \pm 3.4	0.87
Male sex, n (%)	8 (53.3)	8 (66.7)	0.70
Admissions age (days)	-	30.3 \pm 20.5	-
Age at decision about EVD surgery (days)	16.1 \pm 5.4	30.3 \pm 20.5	0.04
Age at EVD surgery (days)	17.4 \pm 5.4	31.6 \pm 20.2	0.03
Days between decision for surgery and EVD surgery	1.3 \pm 0.8	1.3 \pm 0.9	1
Post-menstrual age at EVD surgery (weeks)	30.9 \pm 2.0	32.8 \pm 3.7	0.07
Age at VABS-II administration (years)	5.9 \pm 1.7	5.2 \pm 1.8	0.30

Communication score <70, n (%)	5 (33.3)	7 (58.3)	0.18
Daily Living Skills score <70, n (%)	5 (33.3)	6 (50.0)	0.31
Socialization score <70, n (%)	3 (20.0)	4 (33.3)	0.36
Motor Skills score <70, n (%)	9 (60.0)	9 (75.0)	0.34
Composite (overall) score <70, n (%)	6 (40.0)	9 (75.0)	0.08

	Inborn lateral ventricles (N=26)	Outborn lateral ventricles (N=21)	p-value
Right VI-p97 (mm)	5.1 ± 0.9	7.7 ± 1.5	<0.0001
Left VI-p97 (mm)	5.1 ± 1.1	10.0 ± 3.6	<0.0001