Neurodevelopmental outcome of post-hemorrhagic ventricular dilatation at 12 and 24 months corrected age with high-threshold therapy

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ABSTRACT

Background: The management of post-hemorrhagic hydrocephalus remains a discussion.

We describe the neurodevelopmental outcome at the corrected age of 12 and 24 months of infants with PHVD treated with high-threshold therapy.

Objective: To describe, and compare the neurodevelopmental outcome of a cohort of premature infants with grade III or IV intraventricular hemorrhage with or without development of PHVD.

Methods: Retrospective chart and image review of all IVH grade III and IV infants admitted to the department of Neonatology of the Academic Medical Center, Amsterdam, the Netherlands between January 1999 and December 2006. A standardized neurodevelopmental examination was performed at the corrected ages of 12 and 24 months.

Results: In total, 118 cases with IVH were identified. IVH grade III: *n* = 63, mean gestational age (GA): 28 weeks (SD 2.3), median birth weight (BW): 1130 g (range 908-1460g); IVH IV: *n* = 31, mean GA: 28 weeks (SD 2.4), median BW: 1105g (range 925-1230g). Grade III and IV cases developed PHVD in 75% versus 42% respectively. Abnormal outcome in IVH III patients mainly occurred in cases with PHVD (12 months: 47% abnormal, 24 months: 64% abnormal). In the IVH IV cases, outcome was comparable with or without PHVD. Developmental delay was more pronounced at 24 months.

Conclusion: Mainly IVH III cases developed PHVD. Comparing our results with the literature neurodevelopmental outcome was poorer with our high-threshold therapy.

1. INTRODUCTION

Intraventricular hemorrhage (IVH) and post-hemorrhagic ventricular dilatation (PHVD) still pose major treatment dilemmas for neonatologists in the Neonatal Intensive Care Unit (NICU). Although the incidence of IVH and PHVD is decreasing, [1], [2] and [3] it remains a frequently encountered clinical problem as more pre-and immature infants survive. [4], [5] and [6] Intraventricular hemorrhage, either alone or in combination with cerebral parenchymal injury, is associated with adverse neurodevelopmental outcome. [7], [8], [9] and [10] The severity of the neurological impairments is determined by the severity of the IVH as well as the complication of ensuing PHVD. [7], [11], [12] and [13] Recently, the onset of PHVD in 78% of IVH grade III cases was demonstrated, compared to 53% of the children with a grade IV hemorrhage.[14]

The pathogenesis of PHVD is a complex one determined by compromise of the normal cerebrospinal fluid (CSF) flow by obstructing blood clots and deposition of extracellular matrix proteins in the foramina of the third ventricle, fourth ventricle and the subarachnoid space. [15] and [16] As the development of PHVD is determined by multiple factors, the timing and choice of treatment both remain a matter of debate. [17], [18] and [19] We are still awaiting the results of a randomized controlled trial concerning long-term outcome in infants with PHVD undergoing high- versus low-threshold treatment by CSF drainage.

There is much debate on the issue if treatment for PHVD should be initiated only in patients with symptoms of raised intracranial pressure or in cases with head growth exceeding twice the normal rate. [20] and [21] Unfortunately symptoms may be very nonspecific in premature infants and cerebral damage may already develop in asymptomatic cases. [1] and [22] On the other hand it is not evidence-based to treat every case with invasive procedures as prophylactic CSF drainage by lumbar puncture (LP) and ventricular reservoir placement does not reduce the risk of shunt dependence, morbidity or mortality. [18] and [23] Non-invasive diuretic therapy with acetazolamide and furosemide during PHVD even demonstrated adverse effects on the long-term outcome.[24] Administration of thrombolytic therapy and the Drainage Irrigation and Fibrinolytic Therapy (DRIFT) trial were both unsuccessful or led to severe complications. [25], [26] and [27]

CSF drainage at the right time will probably improve long-term outcome, but when is the right time? In this study we describe the neurodevelopmental outcome at the corrected age of 12 and 24 months of a cohort of premature infants with either a grade III or grade IV hemorrhage without the development of PHVD versus a grade III or grade IV hemorrhage with PHVD. As our treatment protocol has consisted of a routine *high*-threshold therapy (with a Ventricular Index > the p97 + 4 mm curve on the Levene normal value graph) we hope our results will contribute to the discussion on timing of treatment for PHVD.

2. PATIENTS AND METHODS

2.1. Patients

This study is a retrospective study based on chart reviews. To identify eligible cases with IVH grade III or IV and PHVD, the clinical database of the department of neonatology of the Emma Children's Hospital, Academic Medical Center, Amsterdam, the Netherlands was searched. The study period was between January 1999 and December 2006.

First diagnosis of IVH was usually made during routine screening of cerebral ultrasound sessions. The cerebral ultrasound screening protocol consisted of scans carried out on the 1st, 4th, 7th, and 28th day of life. Records and images of all infants with either IVH grade III or IV, according to the classification of Papile,[28] were retrieved. Grade III was defined as massive IVH with blood filling > 50% of the ventricular volume associated with acute dilatation of this ventricle. Grade IV was defined as an IVH with an associated ipsilateral parenchymal echo density present. All cases with ensuing PHVD were identified.

Cases with antenatally diagnosed hydrocephalus, congenital cerebral malformations or signs of congenital infection were excluded. In all cases with IVH, the ventricular index (VI) was measured in a coronal view at the level of the foramen of Monroe, according to the criteria of Levene.[29] When the ventricular index (in mm) crossed the 97th percentile line the diagnosis PHVD was made and cranial ultrasound scans were performed every other day to evaluate progression of the ventricular dilatation. Scans were repeated every day when necessary (i.e. highly progressive increase in VI). In our NICU the current policy is to start CSF drainage treatment in PHVD when the VI crosses the p97 + 4 mm line (which is considered high-threshold treatment). If CSF drainage by lumbar puncture was unsuccessful (dry tap or repeatedly < 10 ml/kg CSF drained per session with increase of the VI) or when PHVD persisted for >14 days despite repeated daily lumbar punctures, an intraventricular Omaya reservoir was placed. When the infant appeared dependent on continuous CSF drainage, a ventricular-peritoneal drain was inserted.

The neurodevelopmental outcome was studied at 12 and 24 months of corrected age by a trained pediatric neonatologist or pediatric neurologist during planned outpatient clinic visits. Assessment of long-term outcome was based on a standardized clinical neurological examination according to the manual written by Touwen.[30] Due to the retrospective nature of this study assessing pediatricians were not blinded by the infants' history. The neurodevelopmental outcome was classified according to definitions stated by B. Resch[12]:

Group 1: Normal for corrected age, no neurological abnormalities.

Group 2: Slight developmental delay, mild neurological abnormalities including mild hypertonia or hypotonia, abnormal coordination, isolated hyperreflexia, nystagmus, or strabismus.

Group 3: Handicaps like mono-, di-, and hemiparesis, mild visual or hearing impairment, well-controlled seizures and/or slight mental retardation.

Group 4: Severe handicaps like tri- or quadriparesis, blindness, deafness, poorly controlled seizures, and/or severe mental retardation.

2.2. Analysis

All data were obtained by retrospective chart review. To evaluate if outcome parameters of patients with IVH III and IVH IV could be compared, important clinical parameters of these patients possibly influencing outcome were compared using the *T*-test, Mann–Whitney *U* test, Chi-square test or Fisher Exact Test, as appropriate. The effect of PHVD treatment on outcome was tested using the test for linear-by-linear association. A *p*-value <0.05 was considered significant. Statistical analysis was done using SPSS 16.1 for Windows.

3. RESULTS

3.1. IVH

In total, 118 cases with either grade III or IV intraventricular hemorrhage were admitted. Four infants were excluded from this cohort because the IVH probably originated antenatally, making exact diagnosis of the IVH grade unfeasible. Five cases were excluded because of additional congenital cerebral malformations or multiple congenital abnormalities. There were no cases identified with congenital infectious diseases in this cohort. Ten term infants with IVH were excluded, as the pathophysiology of IVH in term infants can probably not be compared to that of preterm infants. Five children were excluded because they received low-threshold therapy (before the p97 + 4 mm line was exceeded) due to extreme rapid progression of the ventricular index and/or clinical signs of raised intracranial pressure (increase in head circumference, unexplained apnea).

After excluding the former children a total of 94 children with an IVH III or IV were able to be included in this study. 63 children (67%) had been diagnosed with a grade III hemorrhage and 31 (33%) with a grade IV hemorrhage.

The clinical characteristics of the groups of patients with an IVH III and IV are shown in Table 1. The IVH III infants needed inotropic support significantly more often (*p*: 0.002) and had received antenatal corticosteroids less frequently (*p*: 0.015) than IVH IV infants.

[TABLE 1]

3.2. Mortality

17 of the 63 children (27%) in the grade III group died. In the grade IV group 18 of the 31 children (58%) died. In 79% of the cases death occurred in the first 14 days of life. More infants in the grade IV group (10/31, 29%) died before possible development of PHVD compared to the IVH III group infants (8/63, 13%). In the majority of cases, infants died due to withdrawal of intensive care therapy following multidisciplinary and ethical discussions on quality of life and severe neurological prognosis (based on ultrasound scan results, neurophysiological data (EEG) and a poor clinical status).

3.3. PHVD and intervention (Fig. 1)

Of all 94 included infants with IVH, PHVD developed in 60 cases (64%). Grade III IVH led to PHVD in 47/63 cases (75%) compared to 13/31 cases (42%) in grade IV IVH cases. 22 (37%) of the 60 children with PHVD needed intervention because of progression.

[FIGURE 1]

In all infants treated for PHVD, primary intervention with lumbar punctures to decrease intracranial pressure and hydrocephalus was successful in 16/22 cases with PHVD (73%). Five of the 22 children died within 14 days after initiation of CSF drainage therapy. LPs resulted in dry tap in 1/22 cases, necessitating early placement of an Omaya reservoir for CSF drainage. A total of 5/22 (23%) infants with PHVD finally needed permanent ventricular-peritoneal shunt (VPD) placement. In the grade III group 3 children needed a VP shunt (3/17, 18%), which was less often than in the grade IV group (2/5, 40%). Shunt revision was eventually needed in 3 patients.

3.4. Neurodevelopmental outcome

Neurodevelopmental outcome at the corrected age of 1 year is shown in Table 2. Of the 46 surviving children in the IVH III group, 4 children were not assessed at one year of age. In the IVH IV group also, 4 of the 13 surviving children were lost to follow-up.

[TABLE 2]

In the IVH III group, 23 out of 42 assessed infants (55%) had a normal neurodevelopmental outcome at the corrected age of one year (Table 2). Abnormal outcome in this group was mainly seen in patients who had developed PHVD. Comparing outcome results in IVH III infants with or without PHVD this difference however did not reach a statistically significant level ($p = 0.68$).

In the IVH IV group, 3 children (33%) had normal development at one year of age. Infants in this group with PHVD or without PHVD had a comparable outcome ($p = 0.46$).

The neurodevelopmental outcome at two years of age is shown in Table 3. In the IVH III group only one child was lost to further assessment. In the grade IV group two children were missing.

[TABLE 3]

In the IVH III group at two years of age 16/45 (36%) patients had a normal development. Abnormal development was seen in 64% of infants. Again abnormal development was seen mainly in cases with IVH III and PHVD. Comparing outcome results in IVH III infants with or without PHVD this difference did again not reach a statistically significant level ($p = 0.67$). In the IVH IV group the occurrence of PHVD did not seem to influence outcome as at the corrected age of 1 year, again results were not significant ($p = 1.00$).

It is a striking fact that, at the corrected age of one year and at two years of age, only patients with a grade III hemorrhage and PHVD were classified in group 4. The state of developmental delay was also more clinically pronounced at the corrected age of two years.

The need for VP shunt placement was associated with severe developmental delay. Only 2/8 (25%) of these patients had a normal development.

Complications of treatment were noted as follows. Five children developed meningitis or ventriculitis following CSF drainage by lumbar punctures or the use of a ventricular reservoir. Of these 5 infants, 2 died and 2 children were classified in group 4 at the corrected age of two years.

Cystic periventricular leukomalacia was diagnosed by cerebral ultrasound in six patients (6/94, 6%). Two of these children had a grade III hemorrhage and four had a grade IV hemorrhage. One of these patients died after withdrawal of therapy. At two years of age, four of these patients were classified into group 3 and one patient was classified in group 2.

4. DISCUSSION

In this study we investigated if the development of PHVD influenced the neurodevelopmental outcome of patients with grade III and IV IVH at the corrected age of 12 and 24 months. Up until now we have used a high-threshold for therapy in these cases.

Our data suggests that infants with IVH III and IV who develop PHVD have a worse neurodevelopmental outcome than those who do not develop PHVD, although we did not find a significant difference probably due to a lack of power. Other reports concluded that the extent of cognitive and motor impairments is far more determined by the presence- or extent of periventricular white matter injury than by the hydrocephalic process itself. [9], [11] and [19] At the time of this study period it was not the standard of care to perform magnetic resonance imaging in these infants. It is therefore impossible to make clear statements on the extent of white matter injury in our patients.

The results of this study were comparable to a study performed by Brouwer et al.[14] In their study, 78% of the children with a grade III hemorrhage developed PHVD compared to 75% in this study. In the grade IV group PHVD-development was seen in 42% compared to 53% in the report by Brouwer et al. Mortality rates were also comparable for the IVH III infants, 25% versus 28% in the study by Brouwer et al. In the IVH IV infants the mortality was higher in the current study, 58% versus 37%.[14] Because both studies were performed in tertiary neonatal intensive care units in the Netherlands, both treatment regiments and patient characteristics were highly comparable. The only significant difference between these two reports is the fact

that Brouwer et al. studied patients who received *low* -threshold therapy (after the VI exceeded the p97 curve of Levene) compared to *high*- threshold therapy in our report (therapy after the VI exceeded the p97 + 4 mm curve of Levene).

Comparing the neurodevelopmental outcome with the results from Brouwer et al.,[14] where 86% of the IVH III and 45% of the IVH IV infants had a normal neurodevelopmental outcome, our data suggests a poorer neurodevelopmental outcome with *high*-threshold therapy. When comparing neurodevelopmental outcome in infants with a grade III or grade IV IVH it has to be taken into account that because of our ethical policy withdrawal of intensive care is more frequent in the IVH IV group. Consequently, the IVH III group is naturally supposed to have the highest incidence of the major deficits. Brouwer et al. also suggest that PHVD and the subsequent need for intervention might influence neurodevelopmental outcome. Our results suggest the same, although it did not reach a significant level.

De Vries et al.[17] already discussed the issue as to whether the children receiving low-threshold therapy would ever exceed the P97 + 4 mm line. De Vries et al. also reported less requirement of shunt placement in infants with low-threshold therapy. As the need for shunt placement was associated with a worse neurodevelopmental outcome in our report, this should be taken into account.

Resch et al.[12] described a cohort of premature infants with IVH and PHVD-development stating that only 15% of the infants with either an IVH III or IV developed normally at the corrected age of one year. The results of this study can hardly be compared to our results as gestational ages in our cohort exceed those in the cohort of Resch. At the time of our study, intensive care treatment was usually not started in infants with a gestational age <25 weeks. Also differences in medico-legal and ethical practice will have influenced differences in outcome. This could explain the worse neurological outcome described by Resch et al. Our outcome results will have been influenced by the fact that withdrawal of intensive care was more frequent in the IVH IV group infants.

In conclusion we state that low-threshold therapy for PHVD in premature infants might be more beneficial to long-term outcome than high-threshold therapy. As our study describes a relatively small cohort of cases, and data was collected retrospectively, we hope the current Dutch randomized controlled trial comparing low-threshold versus high-threshold therapy will answer questions on treatment timing for PHVD.

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TABLES AND FIGURES

Table 1 – Characteristics of study population.

	IVH III	IVH IV	*p*-value
	n = 63	*n* = 31	
Gender, male/female	40/23	19/12	NS
Birth weight [a], grams	1130 (908–1460)	1105 (925–1230)	NS
Gestational age[b], weeks	28 (±2,3)	28 (±2,4)	NS
Apgar score at 5 min[a]	7 (6–8)	8 (7–9)	NS
Antenatal steroids, *n*	36 (57%)	26 (84%)	0.015
Mechanical Ventilation[a], days	7 (3–12)	6 (3–10)	NS
Inotropic support[a], days	3 (0–4)	0 (0–2)	0.002
Steroids postnatal, *n*	16 (25%)	3 (10%)	NS
Infection[c], *n*	29 (46%)	12 (39%)	NS

For analysis of differences between groups: Continuous variables: Students-T-test (independent samples), Dichotomic variables: Chi-square test.
a median (iqr).
b means (sd).
c sepsis and/or meningitis.

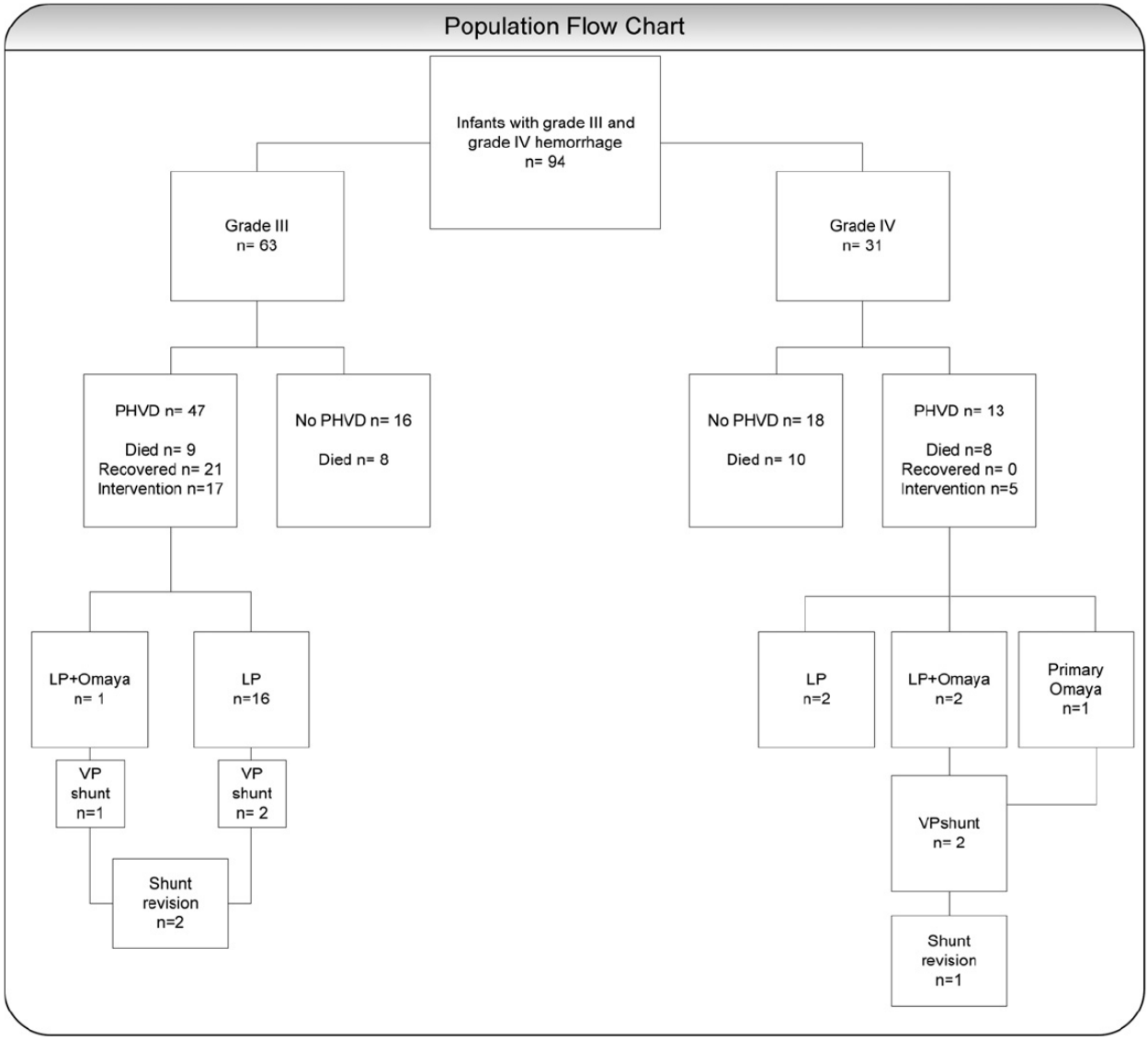

Fig. 1 – Population flow chart.

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Table 2 – post-hemorrhagic ventricular dilatation and neurodevelopmental outcome at 1 years.

IVH			Neurodevelopmental outcome 1 year				
			Group 1	Group 2	Group 3	Group 4	Total
IVH 3	post-hemorrhagic ventricular dilatation	yes	19	7	5	5	36
		no	4	2	0	0	6
		Total	23	9	5	5	42
IVH 4	post-hemorrhagic ventricular dilatation	yes	1	1	2		4
		no	2	1	2		5
		Total	3	2	4		9

Table 3 – post-hemorrhagic ventricular dilatation and neurodevelopmental outcome at 2 years.

IVH			Neurodevelopmental outcome 2 years				
			Group 1	Group 2	Group 3	Group 4	Total
IVH 3	post-hemorrhagic ventricular dilatation	yes	13	13	6	6	38
		no	3	3	1	0	7
		Total	16	16	7	6	45
IVH 4	post-hemorrhagic ventricular dilatation	yes	0	1	4		5
		no	2	1	3		6
		Total	2	2	7		11