Antenatal Post-hemorrhagic Ventriculomegaly: A Prospective Follow-up Study

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Key words
- Ventriculomegaly
- post-haemorrhagic status
- antenatal status
- outcome

Abstract

Objective: The aim of this study was to evaluate the presence and the severity of neurological and cognitive impairment at 2 years of age in 16 infants (9 term born, 7 preterm of mean gestation 33.6 weeks) with cerebral ventriculomegaly of antenatal onset associated with intraventricular haemorrhage.

Methods: Ventricular dilatation, with or without associated lesions, was, with one exception, not identified on the antenatal routine scan at approximately 22 weeks but was obvious on the scans performed between weeks 27 and 33. In 8 of the 16 cases there were signs of parenchymal involvement or of abnormalities of the corpus callosum or cerebellum. In all patients the diagnosis of antenatal IVH was confirmed by early neonatal imaging. Outcome was measured using the Hammersmith infant neurological examination and the Griffiths developmental scales at 2 years.

Results and Conclusions: At 2 years, 8 infants had normal motor outcome and 8 had cerebral palsy. The presence and severity of cerebral palsy or neurodevelopmental delay was not always related to the magnitude or symmetry of the ventricular dilatation per se. The presence of associated lesions was a negative prognostic marker. The early development of epilepsy was also associated with an abnormal outcome.

Introduction

Intraventricular haemorrhage (IVH) is a common event in preterm infants but can also occur in utero with a suggested incidence of 1–5 in 10000 pregnancies [2]. A number of predisposing conditions, such as accidents or trauma during gestation or maternal alloimmune thrombocytopenia have been reported [5,16], but the cause is not always identified. The presence of haemorrhage is also not always recognised in utero due to the isoechogenicity of blood and choroid plexus and is often confirmed after birth on neonatal ultrasound scan (US) and MRI, that better identify the intraventricular clots or the periventricular venous infarction progressing towards cavitation [7].

The aim of this prospective study was to evaluate the presence and the severity of neurological and cognitive impairment in infants with antenatal IVH and post-haemorrhagic ventriculomegaly (PHVM) or post-haemorrhagic hydrocephalus (PHH) prospectively followed for at least 24 months. More specifically, we wished to establish whether the presence and the severity of neurodevelopmental sequelae can be related to the antenatal ultrasound findings or to the extent of the lesion observed on neonatal ultrasound.

Subjects and Methods

Study entry criteria

All infants born at the Catholic University of Rome between January 2000 and December 2003 with the ultrasound antenatal diagnosis of ventricular dilatation (VD) were selected and enrolled when the following criteria were fulfilled:

1) Evidence of antenatal post-haemorrhagic ventriculomegaly or antenatal post-haemorrhagic hydrocephalus on cranial US performed within six hours of birth and on neonatal brain MRI. The diagnosis was based on the persistence of ventricular dilatation and at least one of the following findings [2]:

- residual intraventricular clots,

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- unilateral porencephalic cyst in the periventricular white matter communicating with the ipsilateral ventricle,
- periventricular venous infarction partially cavitated.

2) No evidence of intrauterine infections, congenital malformations, chromosomal abnormalities and metabolic disorders at clinical and laboratory investigations routinely performed in the neonatal period in this group of patients.

The study was approved by the Research Ethical Committee of the Catholic University.

Antenatal US methods

Ultrasound examinations were always performed transabdominally using a multiplanar approach with 3.5–5 MHz. probes. Screening antenatal ultrasonography includes, in all cases and at all gestational ages, a measurement of foetal cerebral ventricular size, at the level of the atrium of lateral ventricles (AW) [1]. Ventriculomegaly (VM) is diagnosed when AW is ≥ 10 mm in the II and III trimester of pregnancy: "mild" VM if AW is between 10 and 15 mm; "severe" VM if AW is >15 mm. All examinations were performed and analysed by two expert sonographers (LM and MDS). The time of scanning was in all cases part of routine assessments.

Neonatal ultrasound

Cerebral US scans were always performed within six hours after birth and repeated at least once at the end of the first week. This was in all cases followed by a cerebral MRI also performed at the end of the first week. Neonatal US were always performed by the same investigator (RL) using a Hewlett-Packard Image Point equipped with a multifrequency beam (5–7.5 MHz). Lateral ventricles were measured on the basis of ventricular index and ventricular height [9]. We also measured the vertical depth of the frontal horn of the lateral ventricles immediately anterior to the thalamo-caudate notch to define the ventricular dilatation as mild, moderate and severe when this dimension exceeded respectively 3, 5 and 10 mm [7]. Brain MRI were performed using a 1.5 Tesla magnet with standard T_1 and T_2 sequences.

Ventricular dilatation was defined as not hypertensive ventriculomegaly or as hydrocephalus on the basis of neuroimaging and clinical data. All neonates were evaluated by a paediatric neurosurgeon consultant in order to establish treatment indications.

Neonatal assessment

All neonates enrolled in the study were submitted to clinical and laboratory investigations including a standardised neurological assessment, ophthalmological evaluation, auditory brain stem responses (ABR), TORCH, and karyotype. A complete blood cell count and clotting tests were obtained on the first day after birth. A detailed history was taken from the parents and analyses of maternal charts were performed to investigate the presence of predisposing risk factors.

Follow-up evaluation

All infants have been regularly followed until the age of 24 months with a standardised assessment. This included serial cranial US evaluations at least at 1 and 3 months and structured neurological examination and neurodevelopmental scales at least at 6, 12 and 24 months.

The neurological examination consisted of a structured assessment evaluating cranial nerve function, posture, movements, tone, reflexes/saving reactions and visual behaviour. Cerebral palsy, if present, was classified according to the criteria proposed by Himmelmann et al. [6]. All the infants also underwent a neurodevelopmental assessment, using the Griffiths' Mental Developmental Scales [8]. The assessment includes motor, personal and social, language, hand and eye and performance scales.

Neurodevelopment was classified as: normal, when DQ was >85; borderline, when it was between 70 and 85; mildly delayed between 55 and 70; moderately delayed between 35 and 55; severely delayed less than 35.

Neurological examination and neurodevelopmental assessments were performed by trained paediatric neurologists (DR, GB, EM) blinded to details of the imaging findings.

Results

During the study period a total number of 16 neonates (8 males, 8 females) fulfilled the inclusion criteria (**Table 1**). Nine of the 16 were born at term and 7 before term (33–36 weeks). All 9 term neonates were born after an elective Caesarean section. Of the 7 preterm infants five had an elective Caesarean section, 3 of the 5 because of ventriculomegaly. The remaining two children had an emergency Caesarean section for foetal distress. The Apgar score at 1 and 5 minutes was >7 in all neonates but one born at 33 weeks GA who needed resuscitation. All neonates but 2 had a birth weight (BW) >3rd centile for GA according to the Italian neonatal growing curves (mean BW 2733 ± 704 g). Head circumference was >97th centile in 4 cases, being otherwise appropriate for GA [13].

Risk factors possibly related to intracranial bleeding were identified in 4 cases, 1 with a car accident one week before ventriculomegaly was seen on US, 1 with an episode of maternal hypotension prior to US identification of intracranial haemorrhage, 1 with cerebral arterial vasodilatation observed in the foetus of a pre-eclamptic mother with previous negative antenatal US and 1 with severe alloimmune thrombocytopaenia. There was no evidence of any other coagulation disorder or traumatic antenatal event. Maternal pre-eclampsia was diagnosed in 3 of the 16 patients (19%).

Antenatal scans

With one exception, none of the patients had any evidence of ventricular dilatation or of any other CNS abnormality on the antenatal US routinely performed around 22 weeks. In all cases the diagnosis of foetal cerebral ventriculomegaly was made at 33 ± 3.7 weeks. The ventricular dilatation was asymmetrical (**Table 2**) in 9 of the 16 (56.25%). In 6 patients the US findings were suggestive of IVH with cystic parenchymal lesions in 3 of the 6 (**Tables 1, 3**).

In another 5 scans there were other signs of CNS involvement (**Table 3**) suggesting abnormal development of the corpus callosum and/or cerebellum, or parenchymal cystic lesions.

Neonatal scans

In all cases neonatal US performed soon after birth showed signs of antenatal IVH with intraventricular clots and in 10 cases (62.5%). a haemorrhagic porencephalic cyst. The US diagnosis was in all cases confirmed by MRI performed in the first week (**Fig. 1**).

Eleven of the 16 children had associated lesions to the IVH ranging from parenchymal haemorrhage or subdural haematoma, to ischaemic lesions, such as periventricular leukomalacia or arte-

Table 1 Antenatal, neonatal, brain MRI and clinical findings at 2 years

	Sex	Antenatal risk factors	Antenatal findings	GA at US diagnosis	GA at birth	BW (g)	HC at birth cm (perc)	VD	Shunt	Parenchymal haemorrhage	Subdural haematoma	PV WM	BGT	epilepsy	Motor outcome	Develop-mental outcome
1	F	–	VM	36	38	2990	32 (<10)	moderate	–	–	–	–	–	–	○	○
2	F	pre-eclampsia	VM	32	33	1680	29 (10)	moderate	–	–	–	–	–	–	○	○
3	M	–	PHVM	30	36	2630	34 (75–90)	severe	–	–	–	–	–	–	○	○
4	F	–	VM	27	37	2830	35 (90)	severe	–	–	–	–	–	–	○	○
5	M	–	VM	35	36	2780	41.8 (>90)	severe	X	–	X	loss	–	–	○	◉
6	M	–	VM + mega-cisterna magna + CC agenesis	22	38	3250	35 (50)	moderate	–	–	–	loss	–	generalised 2nd year	◒	◉
7	M	–	VM	36	37	3100	35.5 (>90)	severe	X	–	–	–	–	–	○	○
8	M	car accident	VM	35	39	4100	37 (90)	severe	–	X	–	–	X	–	◐	○
9	M	–	PH-VM6 + PVI	35	37	3180	37 (>90)	moderate	–	X	–	–	–	–	○	○
10	F	pre-eclampsia	VM	33	33	1650	30 (25)	moderate	X	X	–	–	–		○	○
11	M	hypotension	PHVM	30	35	2090	34 (90)	severe	X	X	–	loss	X		◐	○
12	F	–	VM + - arachnoid cyst	34	37	3300	37 (>90)	severe	X	X	–	–	–	early partial	◙	●
13	F	alloimmune trombocyto-paenia	PHVM + PVI	31	38	2310	32 (<10)	severe	X	X	–	–	–	west	◙	●
14	M	pre-eclampsia	VM + CC agenesis	33	33	1900	32 (90)	severe	X	X	–	–	–	west	◙	●
15	F	–	PHVM + - mega-cisterna magna	35	37	3630	40 (>90)	severe	X	X	–	cPVL	–	west	◙	●
16	F	–	PHVM + PVI	32	33	2300	34.2 (>90)	severe	X	X	–	loss	–	west	◙	●

○ = normal, ● = abnormal, ◐ = hemiplegia, ◒ = diplegia, ◙ = tetraplegia, ◉ = mild developmental delay

BGT = basal ganglia and thalamus; BW = birth weight; HC = head circumference; perc = percentile; CC = corpus callosum; cPVL = cystic periventricular leukomalacia; F = female; GA = gestational age (in weeks); M = male; Perc = Percentile; PHVM = posthaemorrhagic ventriculomegaly; PVI = periventricular infarction; PV WM = periventricular white matter; VD = ventricular dilatation; VM = ventriculomegaly

rial infarction, or abnormalities of the posterior fossa or corpus callosum. ▶ **Table 1** shows details of these findings.

Seven infants had ultrasound evidence of rapidly progressive ventricular dilatation and increased intracranial pressure and underwent surgical intervention during the first month. The other 9 did not require ventriculoperitoneal shunting before discharge from the hospital but 2 of the 9 required a ventriculoperitoneal shunt after the first month. Two children had post-shunt infections (cases 14 and 16). ▶ **Table 1** shows details of neonatal US and MRI.

Table 2 Correlation between ventricular dilatation on antenatal scans and motor and developmental outcome

Antenatal scans	Neuro exam	Neurodevelopmental outcome
VD both sides >15 symmetrical	○○○◒■■■	○○○◉●●●
VD both sides >15 asymmetrical	○○○◐◐	◉○○○○
Asymmetrical VD, one side >15, one side <15	○■	○●
Asymmetrical VD, 1 side >15, other side not measurable because of cyst	○	○
Asymmetrical VD, 1 side <15, other side not measurable because of cyst	■	●

○ = normal; ● = abnormal; ◐ = hemiplegia; ◒ = diplegia; ■ = tetraplegia; ◉ = mild developmental delay. VD = ventricular dilatation

Neurological follow-up

At 2 years, 8 infants had normal motor outcome and 8 had cerebral palsy, 2 with hemiplegia, 1 with diplegia and 5 with tetraplegia. Six of the 16 children also developed epilepsy, 5 in the first year (West syndrome and partial seizures) and 1 in the second year (generalised seizures) (▶ **Table 1**).

Neurodevelopmental outcome at 2 years

At 2 years, 9 of the 16 infants had neurodevelopmental outcome within normal range. In the remaining 7 infants, neurodevelopmental delay was mild in 2, moderate in 3 and severe in 2 patients (▶ **Table 1**). Patients were also assessed using a struc-

Table 3 Correlation between associated lesions on antenatal scans and motor and developmental outcome

Antenatal scans	Neuro exam	Neurodevelopmental outcome
Venous infarct	■○■	●○●
Abnormal corpus callosum	◒* ■	◉*●
Abnormal posterior fossa	◒* ◐■	◉*○●
Cystic formations	■	●
No associated lesions	◐○○○○○○○	○○○◉○○○○

○ = normal; ● = abnormal; ◐ = hemiplegia; ◒ = diplegia; ■ = tetraplegia; ◉ = mild developmental delay

* Same child, showing both abnormal corpus callosum and abnormal posterior fossa

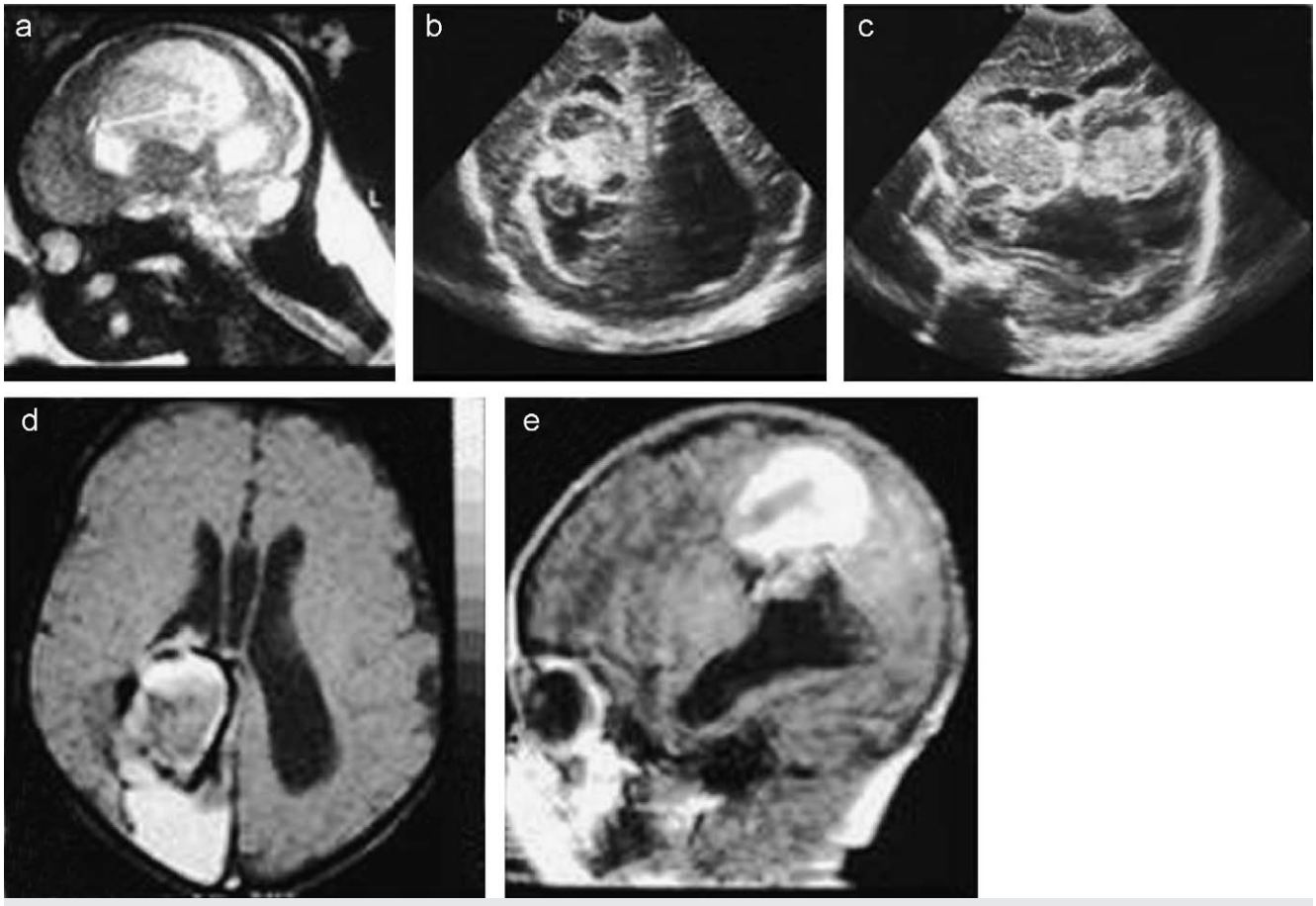

Fig. 1 Patient No. 9: Prenatal T_2-weighted MRI image at 36 weeks of gestation (**a**), neonatal coronal and sagittal cranial ultrasound (**b**, **c**) and neonatal axial and sagittal T_1-weighted MRI images (**d**, **e**). Images show the prenatal intraventricular haemorrhage complicated by a periventricular venous infarction partially cavitated communicating with the ipsilateral ventricle.

tured evaluation of visual function; the results of visual assessment have already been published [15].

Correlation between antenatal US findings and neurodevelopmental outcome

All infants had severe or moderate VD but there was not a consistent association between the magnitude or the asymmetry of the VD and the presence or severity of neurological sequelae (**Table 2**).

Eight infants had associated lesions on antenatal scans and all but one had some sequelae at follow up, irrespective of the type of associated lesion (**Table 3**).

Correlation between neonatal brain imaging and neurodevelopmental outcome

All neonates had moderate/severe not hypertensive ventriculomegaly or hydrocephalus requiring shunt insertion in 9 of the 16 and endoscopic third ventriculostomy in one.

Six of the 16 infants had ventricular dilatation without parenchymal haemorrhage or any other associated haemorrhage (only 1 of them requiring shunting): 5 had normal neurological and developmental outcome, 1 had diplegia and mild developmental delay. Ten infants also had parenchymal haemorrhage (periventricular venous infarct in 9, cerebral haematoma in 1 associated with subdural haematoma), all but 2 requiring shunting; 7 of them had cerebral palsy, associated with neurodevelopmental delay in 5 of the 7, 1 had normal motor outcome but mild delay and 2 normal neurological and neurodevelopmental outcome.

All the 6 children who developed epilepsy had abnormal neurological and cognitive outcome that was more severe in the infants who had early epilepsy in the first year. They all had some associated brain lesions beside ventriculomegaly.

Discussion

A few studies have reported that developmental outcome in children with post-haemorrhagic ventricular dilatation is strongly associated both with the extent of haemorrhagic parenchymal injury and with the white matter involvement [3, 19]. Most of the previous studies, however, mainly included preterm infants with postnatal onset of haemorrhages and less has been reported about the neurological and cognitive outcome in infants with post-haemorrhagic ventricular dilatation of antenatal onset. A few studies have recently reported outcome in antenatally diagnosed intracranial haemorrhage [4, 5, 18], but few details are given on neurodevelopmental outcome and no systematic prospective studies using structured neurological and neurodevelopmental assessments have been so far reported.

In our cohort 7 of the 16 infants (43.75 %) with antenatal post-haemorrhagic ventricular dilatation had normal neurological and neurodevelopmental outcome and another 1 only had a mild neurodevelopmental delay. With one exception, there was no evidence of lesions on the antenatal scans routinely performed around 22 weeks. In all cases, in contrast, ventricular dilatation and the other associated lesions were found on the subsequent scan performed between 27 and 36 weeks. When we correlated the presence and severity of lesions on the antenatal scans with outcome, we found that neither the magnitude of the ventricular dilatation nor the asymmetry of ventricular dilatation could, alone or in combination, predict the presence or the severity of neurological sequelae as both normal and abnormal outcomes could be found in infants who had antenatal evidence of mild and severe ventricular dilatation. The presence of associated lesions was, in contrast, more often related to abnormal outcome, irrespective of whether the signs detected on the antenatal scans were suggestive of abnormal development of the corpus callosum or the cerebellum or related to cystic formations. Only 1 of the 8 infants with isolated ventricular dilatation on antenatal scans developed cerebral palsy and only one had a mild developmental delay. These findings are in partial agreement with previous studies [4, 5] reporting abnormal outcome in a significant proportion of infants with antenatal evidence of grade 3 and 4 IVH. In a recent review, Özduman et al. reported the outcome in infants with foetal stroke, most of them with haemorrhages. Over half of the infants suffered neonatal or foetal death and an additional 25 % were handicapped at follow-up [12]. Our data, however, cannot easily be compared to the previous studies because of different inclusion criteria. In our study we only included infants who survived and who had evidence of haemorrhage at birth, therefore excluding the foetuses dying in utero and, at the other end of the spectrum, those who had an antenatal resolution of haemorrhage who were both included in the previous studies.

A similar association between normal outcome and isolated ventriculomegaly was also found on postnatal ultrasound findings. Patients with venous infarcts or other ischaemic lesions, such as white matter loss and periventricular leukomalacia, had more often unfavourable outcome, but this did not always hold true for individual cases, as normal outcome was found in a proportion of patients with parenchymal haemorrhages and/or shunted hydrocephalus. The presence of epilepsy, particularly in the first year, was, in contrast, always associated with the most severe neurodevelopmental outcome. These findings are in agreement with our previous observation of visual abnormalities in a smaller cohort with antenatal posthaemorrhagic VD [15] suggesting that epilepsy may be an additional risk factor for the development of neurodevelopmental abnormalities. As the number of infants in this study is too small to allow any meaningful multivariate analysis, further studies in a larger cohort are needed to demonstrate whether the epileptic disorder is per se responsible for neurodevelopmental impairment, or whether the presence of epilepsy is only a marker of a more severe underlying lesion that is responsible for both epilepsy and abnormal neurodevelopmental outcome.

In conclusion, our results suggest that post-haemorrhagic ventricular dilatation of antenatal onset is not always associated with abnormal outcome, even when it appears to be moderate or severe. The presence of associated lesions, in contrast, increases the risk of abnormal outcome. Our study, however, also suggests that routine ultrasound scans often fail to identify the presence of haemorrhage in utero and that other techniques should be considered when a ventricular dilatation is observed on routine US examinations. As recently suggested by various papers, transvaginal sonography [11, 17] and antenatal MRI [10, 14] will probably increase the identification of intracranial haemorrhages in utero and provide further diagnostic and prognostic information.

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