Long-term outcome of vein of Galen malformation

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ABBREVIATIONS

KOSCHI	King's Outcome Scale for Childhood Injury
MCA	Middle cerebral artery
TOP	Termination of pregnancy
VGAM	Vein of Galen aneurysmal malformation

AIM To describe the long-term outcomes of children by the time they reached school age with vein of Galen aneurysmal malformation (VGAM).
METHOD This was a retrospective observational study on a consecutive cohort of patients with VGAM. We included patients with at least one Francophone parent, aged between 6 and 11 years at the time of long-term evaluation. The neurological outcome was assessed with the King's Outcome Scale for Childhood Injury score and eight neurological and behavioural items from the Rivermead Postconcussion Symptoms questionnaire.
RESULTS All 52 patients (17 females, 32 males [data missing for *n*=3]) with at least one Francophone parent (5 fetuses and 47 children) were included. At the long-term evaluation time-point, 33 patients were alive and 19 patients had died. Risk of postnatal death was associated with severe neonatal cardiac failure (p=0.007) or isosystemic or suprasystemic pulmonary hypertension (p=0.014). Among survivors, 19 had a good outcome with normal schooling and 14 had a poor outcome. Moreover, among the good outcome patients, a large proportion had neurodevelopmental alterations.
INTERPRETATION Long-term outcome of patients with VGAM appears to be less favourable than outcome described at the short- and medium-term, even in the absence of encephalomalacia at birth. Even patients with good outcome often have neuropsychological disorders that may have repercussions on learning and requiring appropriate rehabilitation or medical management.

Vein of Galen aneurysmal malformations (VGAMs) have an estimated incidence of 1 per cent of all cerebrovascular malformations but are the most frequent cerebral shunts in neonates and infants.[1–3] VGAMs are choroidal malformations that drain into the median prosencephalic vein (Markowski vein), the embryonic precursor of the vein of Galen,[1,4] associated with arteriovenous fistulas between the embryonic choroidal arteries and the Markowski vein.[1,2] Recently, a landmark publication demonstrated that a loss of function mutations in *EPHB4* was responsible for true VGAM in 10 per cent of cases.[5] This was followed by a second study, which identified a similar mutation in approximately 30 per cent of vein of Galen malformations.[6]

In the absence of treatment, these malformations are fatal in almost 100 per cent of cases because of multiple organ failure in the first weeks of life or complications from hydrocephalus in the first years of life. There are two types of VGAM. The choroidal form consists of a network of choroidal arteries that drain into the dilated precursor of the vein of Galen. This form may or may not be high flow. It is described as having poorer clinical course and neurological prognosis.[1] The mural form of VGAM presents as one or more high flow arteriovenous fistulas that drain into one or more location of the Galen vein precursor. This form is less common and has better prognosis, mainly because endovascular treatment is easier as there are fewer fistulas to treat.[1]

Endovascular treatment has significantly improved the prognosis of children with this malformation, although long-term clinical evaluation of this therapy remains unclear.[2] According to some studies, neurocognitive development was typical in over 60 per cent of surviving patients; however, follow-up was limited to about 3 years for most of them or not specified.[2,7–13] Essentially, most of the literature has focused on neonates or infants. In the Bicêtre Hospital study of 216 patients treated between 1981 and 2002,[2] neurological evaluation was done on neonates (6%) and infants (74%) and only 21 per cent of the patients were assessed at infancy, without specification of average age at assessment. In Berenstein et al.'s recently

published series,[13] a total of 66.6 per cent patients were neurologically and developmentally intact, but patients treated in the neonatal period were excluded, also without specification of average age at last clinical assessment. More recently, in a study from a nationally commissioned centre in the UK treating patients with VGAM since 2006, the clinical results indicated that neurological outcome in a neonatal cohort at long-term evaluation was good in around half of survivors.[14] They mentioned that clinical manifestations and underlying pathophysiology are distinct in older children, notably, certain neurocognitive consequences were not obvious and only detectable by the time they reached school age.

The primary objective of our study was to evaluate the long-term neurological outcomes of children at school age with VGAM. The secondary objectives were to determine the clinical and radiological factors associated with poorer long-term neurological prognosis.

METHOD

This study was performed according to the STROBE statement and in accordance with French legislation. The ethics committee of our institution (Bicêtre Hospital) agreed to the study. The patients' informed consents were waived by our ethics committee because of the retrospective observational nature of the study.

We carried out a retrospective observational study on a consecutive cohort of patients with VGAM in a single referral national centre. We included patients with at least one Francophone parent, born between 1st January 2006 and 31st December 2009, whatever the date of VGAM diagnosis, and aged between 6 and 11 years at the time of long-term evaluation. The clinical-management decision tree used in our department from the moment of discovery of the malformation was as follows. In accordance with French law, termination of pregnancy (TOP) was acceptable any time before birth in cases of severe fetal disease. Therefore, we performed TOP at the request of parents in this situation. The management of fetuses in absence of TOP or of newborn infants depended on the presence of encephalomalacia (defined as locoregional brain parenchyma atrophy and/or hyperintensity on T1-weighted sequence on cerebral magnetic resonance imaging [MRI]), in which case we proposed palliative care. We proposed active management for patients with focal lesions without atrophy, for example punctiform lesions on diffusion weighted imaging, enlargement of ventricles, or subependymal white matter hyper- or hypointensities on T2 spin echo or T2 gradient echo-weighted imaging. This was also the case for patients without abnormal brain imaging.

Clinical variables reported were: clinical characteristics at birth (choroidal or mural VGAM, weight, postnatal gestational age calculated by considering the last menstrual period and the early prenatal ultrasound), presence of brain injury on imaging, presence of severe cardiac failure (requiring assisted ventilation and inotropic drugs) or severe pulmonary arterial hypertension (isosystemic or suprasystemic) in the first week of life, occurrence of symptomatic hydrocephalus during the child's follow-up, and the clinical-management modalities.

What this paper adds

- Long-term outcome appears to be less favourable than described at short- and medium-term follow-up.
- Even patients with good outcome at these time-points often have minor neuropsychological disorders.

Outcome measures

We evaluated the neurological outcome of children using the King's Outcome Scale for Childhood Injury (KOSCHI) score and eight neurological and behavioural items from the Rivermead Postconcussion Symptoms questionnaire[15] in 2015 and 2016 by retrospective analysis of their medical file and by telephone consultation with parents. Items included headaches, fatigue or tiring more easily, being irritable or easily angered, feeling frustrated or impatient, forgetfulness or poor memory, poor concentration, taking longer to think, restlessness, and the type of schooling (normal or specialized schooling). Patients were classified into three groups: good outcome (KOSCHI=5-4b), poor outcome (KOSCHI=4a-2), and deceased (pregnancy termination included).

Radiological endpoints assessed by fetal or MRI at birth were the presence of cerebral parenchymal abnormality (encephalomalacia, white matter focal anomaly on diffusion [decreased apparent diffusion coefficient] or T2 gradient echo-weighted sequence [subependymal hypointensity]). At follow-up MRI, the ventricular volume was estimated by the Evans index (normal if <0.31). Ventriculomegaly was defined as an Evans index of 0.31 or higher without any symptoms of intracranial hypertension other than macrocrania. Hydrocephalus was defined as an Evans index of 0.31 or higher associated with clinical symptoms of intracranial hypertension.

Statistical analysis

We used descriptive statistics to represent the distribution of clinical and radiological factors studied in our population. Variables were presented as medians and interquartile ranges (IQRs). We performed a univariate logistic regression to evaluate the association between clinical and radiological factors and the KOSCHI score. The analysis was performed using Anaconda 3.5 (open-source software in Python programming language), linked to R software (R Foundation for Statistical Computing, Vienna, Austria) using the Rpy2 package. Results were reported as odds ratios (ORs) with 95 per cent confidence intervals (CIs). The statistical significance level for all tests was set at p=0.05. Because of the small sample size, we did not carry out a multivariable analysis.

RESULTS

From 1st January 2006 to 31st December 2009, we treated 127 children or fetuses suffering from a VGAM. Of these,

52 patients with at least one Francophone parent (5 fetuses and 47 children) were included. We present the study patient-management flow chart in Figure S1 (online supporting information). The malformation was found antenatally in 38 patients (73%; median age: 33wks of pregnancy, IQR: 32–34wks) and after birth in 14 patients (27%; median age: 51d, IQR: 2–231d).

At the long-term evaluation time-point (patients 6–11y), 33 patients (63%) were alive and 19 patients (37%) had died. The clinical history of the study population was as following: 17 patients (33%) were female and 32 (62%) male (data missing for 3 of the 5 fetuses after TOP). Twenty patients had a mural and 22 a choroidal VGAM-type (data missing for 10 deceased patients lacking appropriate MRI sequences). The five fetuses with pregnancy interruption had encephalomalacia lesions on imaging and of the 47 live-born patients, nine died during palliative care after detecting encephalomalacia lesions by MRI. Thirty-eight patients without encephalomalacia lesions therefore received acute care. Among them, five died despite or after complications of treatment: four newborn infants from multi-organ failure before embolization and one 2-year-old, with vein of Galen malformation cured, after complications of a ventriculoperitoneal shunt (cerebral venous thrombosis and subdural hematoma). Among the 47 patients born alive, risk of postnatal death was associated with severe neonatal cardiac failure (p=0.007; OR: 19.4; CI: 3.2–374.0) or isosystemic or suprasystemic pulmonary hypertension (p=0.014; OR: 8.3; CI: 1.77–60.2). In contrast, for the 33 survivors these variables were not correlated with poor long-term outcomes. Nineteen children had a good outcome (KOSCHI 5-4b) with normal schooling. Fourteen children had a poor outcome (KOSCHI 4a-2), nine of which had specialized schooling and six had severe psychomotor disability (KOSCHI 3b-3a) with significant motor difficulties. Three of these six children had language delay and two were not toilet trained. Table 1 summarizes the results of the univariate logistic regression.

We noted a higher proportion of the eight neurological and behavioural symptoms from the Rivermead Postconcussion Symptoms questionnaire in the poor outcome patient group. Surprisingly, among the patients with good outcome, over one quarter reported 'fatigue' or 'tiring more easily', 'forgetfulness' or 'poor memory' or 'taking longer to think', and nearly half (47%), had 'poor concentration'. The percentage of symptoms according to the long-term outcome is presented in Figure 1. For hydrovenous disorders seen in follow-up of the children, a majority (66%) had long-term ventriculomegaly and a minority (15%) had hydrocephalus with clinical signs of intracranial hypertension not correlated with the outcome.

Endovascular therapy

All the patients assessed at the long-term time-point had been treated by transarterial embolization under general anaesthesia (median number of embolization sessions: 3; IQR: 2–5). Three of the 34 patients treated with embolization had symptomatic complications from the endovascular treatment; two children had territorial infarctions after reflux of embolization material (Hystoacryl), one into the basilar artery and the other into the posterior cerebral artery. A third child presented acute thrombosis of the dilated vein of Galen with compression of the mesencephalic aqueduct and acute hydrocephalus requiring ventriculocisternostomy. Finally, at the long-term evaluation time-point of the 33 survivors, the vein of Galen was occluded in 18 patients and partial occlusion was performed in 15 patients (median percentage of occlusion: 90%; IQR: 90–95%).

DISCUSSION

The main observation in our series is that the long-term outcome of patients with VGAM appears to be less favourable than the outcome described at the short- and medium-term. Although we excluded patients with antenatal or at-birth encephalomalacia lesions, only half of the non-encephalomalacia patients who received acute care had a good long-term outcome. Indeed, 14 children (37%) had a poor outcome and five patients (13%) died despite or because of treatment. Moreover, among the patients with a good outcome, a large proportion had neurodevelopmental alterations with potential disabilities. Compared to a previously reported series from our service,[2] in which 74 per cent of patients had a good outcome but where the neurodevelopmental evaluation was mainly carried out on neonates and infants (81% of the study population), the long-term evolution described here is much poorer. In a recent review of the literature, Gopalan et al.[16] identified good outcome in 65 per cent of patients treated by embolization but did not determine average time of evaluation. A following publication from this group, however, described longer-term evaluation (median age at testing: 5y 2mo, range: 1–11y) and noted similar results to us: that only half of the surviving patients had a good outcome.[14]

Our aim here was to give a comprehensive overview of outcome by including patients who died from cerebral encephalomalacia lesions after a pregnancy termination or after palliative care at birth. Thirteen patients (25%, four patients after TOP and nine neonates) presented severe cerebral involvement with encephalomalacia seen on imaging before or after birth. These lesions are known to be associated with a significant risk of poor evolution or death and for this reason we do not recommend endovascular treatment of the malformation in antenatal encephalomalacia. If parents decline TOP, we then provide palliative care for these patients after birth. For encephalomalacia lesions discovered after birth, usually caused by severe heart failure, we indicate palliative treatment.

It is noteworthy from our observations that in the absence of encephalomalacia lesion at birth, presence of severe cardiac failure or isosystemic or suprasystemic pulmonary arterial hypertension were risks for short-term death (p=0.007 and p=0.014 respectively), but had no influence on the long-term outcome. Although cardiac

Table 1: Univariate statistical analysis

Variable	Death before 3mo despite or because of treatment (*n*=13)	Still alive after 3mo (*n*=34)	*p*	OR	95% CI
Severe cardiac failure at birth	12	13	**0.007**	19.4	3.2–374.0
Isosystemic or suprasystemic pulmonary hypertension	9	12	**0.014**	8.3	1.77–60.2

Variable	Good outcome (*n*=19)	Poor outcome (*n*=14)			
Isosystemic or suprasystemic pulmonary hypertension	7	5	0.947	0.95	0.2–4
Brain parenchyma limited anomaly	2	3	0.380	2.3	0.33–19.9
Severe cardiac failure at birth	8	5	0.711	0.76	0.18–3.1
Hydrocepahlus and ICHT	2	3	0.396	2.138	0.33–19.851

	Comparison group			
Number of sessions of embolization	1 session increase	0.572	1.124	0.749–1.714
Birthweight	1g increase	0.249	1.001	0.999–1.003
Postnatal gestational age	1wk increase	0.854	1.076	0.493–2.474

Bold type indicates statistical significance. OR, odds ratio; CI, confidence interval; ICHT, intracranial hypertension.

involvement is known to be associated with a high risk of mortality and poorer outcome,[13] our observations suggest encephalomalacia as the main risk factor of poor outcome, regardless of the cardiopulmonary state at birth. Additionally, we recently described middle cerebral artery (MCA) pseudo-feeders seen on MRI as a risk factor for the occurrence of encephalomalacia,[17] which currently is one of the cornerstones of our institute's clinical-management decision tree. They likely reflect impairments in both arterial and venous cerebral blood flow. They appear as flow voids in the sylvian fissure on axial T2 standard error-weighted sequences and easy to detect, while fetal cardiac ultrasound imaging requires a high degree of skill and experience. Figure 2 shows three examples of fetal MRIs with or without MCA pseudo-feeders that match the MRIs after birth. Figure S2 (online supporting information) summarizes our new clinical-management workflow adopted in 2016 that aims to prevent occurrence of these irreversible and serious brain lesions. Of note, we no longer use the 'Bicêtre score', which estimates neurological damage based on clinical and electroencephalographic considerations, for therapeutic decisions in our clinical-management tree. In our view, while this score gives a rapid idea of the general state of the patient, its weakness is that it does not reliably evaluate the cerebral parenchyma, which requires MRI data, an element that seems essential for indicating the type of treatment, especially towards palliative care. If at birth the patient does not present a drug-controllable heart failure but has MCA pseudo-feeders on MRI, we recommend emergency embolization of the malformation to reduce cerebral venous pressure, lift the 'steal' in arterial vasculature linked to the shunt, and thereby prevent risk of encephalomalacia lesions. Similarly, on antenatal MRI, in absence of an encephalomalacia lesion but in the presence of MCA pseudo-feeders, if the weight of the fetus on ultrasound is at least 2kg, we propose an early delivery with emergency embolization of the newborn infant. In this respect, we described that the risk of serious haemorrhagic complications in patients weighing under 5kg depended on the age of the child at the time of embolization, not its weight.[18] Only centres with extensive experience in paediatric endovascular treatment should handle this rare situation. However, we advise cautious interpretation of our decision tree as it is based mainly on our experience and requires confirmation with additional multicentre data.

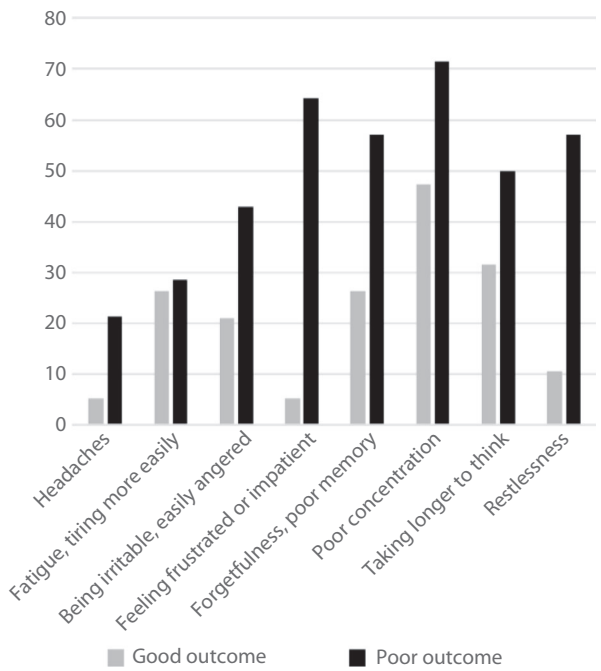

Figure 1: Percentage of symptoms according to outcome at long-term follow-up.

Another finding we observed was that a majority of patients (66%) had ventricular enlargement at long-term evaluation, estimated via the Evans index, that did not affect the long-term outcome whether associated with

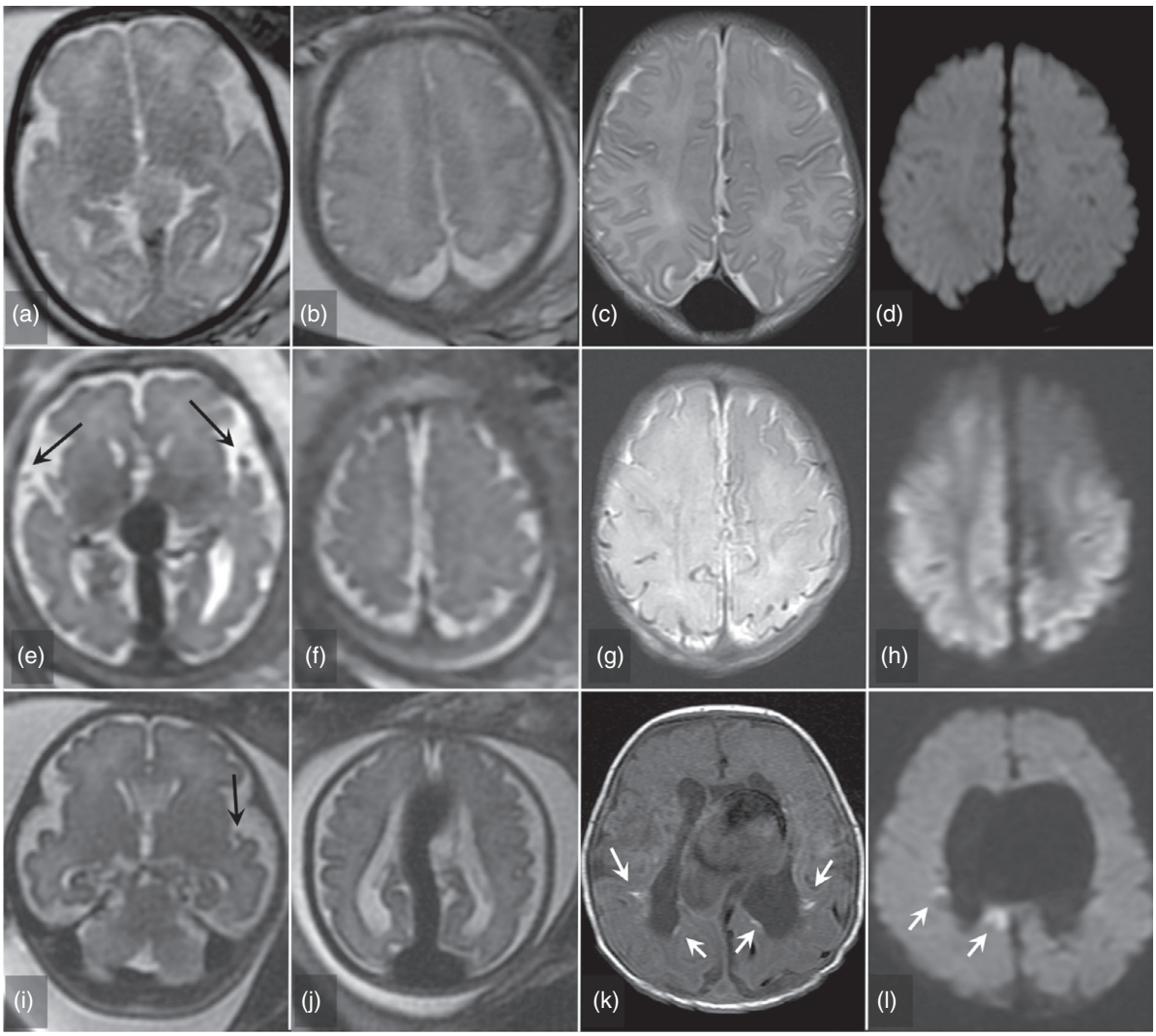

Figure 2: Method for assessing the middle cerebral artery (MCA) pseudo-feeders in three fetuses. In the first fetus no MCA pseudo-feeders were identified (a) on T2 spin echo-weighted sequences. The brain parenchyma was considered normal on fetal magnetic resonance imaging (MRI) (a and b) as well as at birth, 51 days later, on T2 spin echo-weighted (c) and diffusion-weighted imaging (DWI) (d). In the second example, the corresponding MCA pseudo-feeders were identified at the surface of the pia mater as dilated vessels in the sylvian fissure on axial T2 spin echo-weighted sequences (e: black arrows) on fetal MRI. The brain parenchyma was considered normal (e and f). After birth, 9 days later, bilateral encephalomalacia was observed on T2 spin echo-weighted sequences (g: loss of grey-white matter differentiation on both hemispheres) and DWI (h: hyperintensities). In the third example, the MCA pseudo-feeders were seen in the left sylvian fissure on axial T2 spin echo-weighted sequences (i: black arrow) on fetal MRI. However, after birth 42 days later, bilateral focal periventricular lesions were seen on T1 spin echo-weighted sequences (k: white arrows) and DWI (l: white arrows).

intracranial hypertension or simple macrocrania. However, in our treatment protocol, we practise emergency embolization for hydrocephalus with intracranial hypertension sign and semi-urgent within 15 days in cases of breakage of the cranial perimeter with macrocrania greater than 2 standard deviations. Hydrovenous disorders, particularly common in VGAM, result in cerebrospinal fluid accumulation due to increased cerebral venous pressure from the shunt, which may lead to hydrocephalus.[1] For example, Meila et al. saw 48 per cent hydrocephalus cases in their series.[19] To prevent occurrence of irreversible brain damage in symptomatic hydrocephalus, we use embolization treatment to control this complication and have previously described that embolization of at least 80 per cent of the shunt is necessary to control the imbalance.[19] Meila et al. show that, in most cases in their series, embolization of the VGAM as sole treatment is sufficient to decrease high venous pressure.[19] Indeed, the deleterious effects of a ventricular bypass in the absence of embolization of the malformation is well documented and include increased hydrocephalus, subdural hematomas, and cerebral parenchymal lesions[19–21] that strongly contraindicate this

type of first-line treatment. However, once VGAM is corrected, in exceptional cases of hydrocephalus from an etiology other than hydrovenous imbalance (such as siderosis due to intraventricular haemorrhage) ventricular bypass or ventriculocisternostomy may be indicated, as was the case for one of our patients.

Limitations

This was a retrospective study of a relatively small series, so caution is needed in the interpretation of findings and results. In addition, the good/poor outcome dichotomy is questionable. We chose the KOSCHI score to classify the patients; however, among the 14 patients with poor outcome, five had a normal schooling environment. Further case series and research are needed to confirm our findings, but as little data are available for this rare disease, we believe that experience from large paediatric centres will be of assistance towards its understanding and treatment.

CONCLUSION

Patients with VGAM have a higher risk of poor long-term outcome than usually described in the literature, even in the absence of encephalomalacia injury at birth. Even patients with a good long-term outcome often have minor neuropsychological disorders that may have repercussions on learning and require routine testing with appropriate rehabilitation or medical management. Follow-up of particularly frequent hydrovenous disorders in this affection is indicated so that in cases of symptomatic hydrocephalus, urgent embolization treatment may be considered to prevent risk of added brain damage. Finally, the MCA pseudo-feeders seen at MRI, which is a risk factor for the occurrence of encephalomalacia, currently is one of the cornerstones of our present institutional clinical-management decision tree, aiming to prevent future irreversible and serious brain lesions in fetuses and neonates.

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The data supporting the findings of this study are available on request from the corresponding author (GS). The authors have stated that they had no interests that may be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Patient-selection flow chart and long-term outcome

Figure S2: Current institutional clinical-management decision tree

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