Brain Injury in Fetuses with Vein of Galen Malformation and Nongalenic Arteriovenous Fistulas: Static Snapshot or a Portent of More?

C. Jaimes, F. Machado-Rivas, K. Chen, M.A. Bedoya, E. Yang and D.B. Orbach

AJNR Am J Neuroradiol 2022, 43 (7) 1036-1041
doi: https://doi.org/10.3174/ajnr.A7533
http://www.ajnr.org/content/43/7/1036
Brain Injury in Fetuses with Vein of Galen Malformation and Nongalenic Arteriovenous Fistulas: Static Snapshot or a Portent of More?

C. Jaimes, F. Machado-Rivas, K. Chen, M.A. Bedoya, E. Yang, and D.B. Orbach

ABSTRACT

BACKGROUND AND PURPOSE: Brain injury in fetuses with vein of Galen malformations and nongalenic AVFs is a rare complication whose appearance, course, and prognosis are poorly studied. We sought to characterize the MR imaging features and examine associations with postnatal outcome.

MATERIALS AND METHODS: This was a retrospective analysis of fetal MRIs of subjects with vein of Galen malformation and nongalenic arteriovenous fistulas. Two pediatric neuroradiologists independently reviewed examinations to determine the presence of abnormalities on structural imaging (T1 volumetric interpolated breath-hold examination and T2-HASTE), DWI, and T2*-weighted images; discrepancies were adjudicated by a third reviewer. Radiologic progression of injury was determined by additional fetal or neonatal MRIs. A simple composite score evaluating poor neonatal clinical outcome as either intubation or death by postnatal day 2 was also queried. A body fetal imager evaluated the presence of systemic findings of right heart strain.

RESULTS: Forty-nine fetal MR imaging examinations corresponding to 31 subjects (27 vein of Galen malformations and 4 nongalenic AVF cases) were analyzed. Injury was observed in 8 subjects (26%) with 14 fetal examinations; the mean gestational age at identification of injury was 32.2 (SD 4.9) weeks. Structural abnormalities were present in all subjects with injury; restricted diffusion, in 5/7 subjects with available data; and T2* abnormalities, in all subjects with available data (n = 7). Radiologic progression was documented in all cases with follow-up imaging (n = 7). All subjects with fetal brain injury had a poor neonatal clinical outcome.

CONCLUSIONS: Brain injury in fetuses with vein of Galen malformation and nongalenic AVFs shows a combination of structural abnormalities, restricted diffusion, and blooming on T2* images. Injury appears to portend a poor prognosis, with relentless progression and a likely association with adverse neonatal outcomes.

ABBREVIATIONS: NG-AVF = nongalenic AVF; VOGM = vein of Galen malformation; VIBE = volumetric interpolated breath-hold examination

Congenital AVMs are a rare group of disorders that result from either persistent primitive anastomoses or formation of pathologic connections in the early embryonic and fetal stages. The most common of these conditions is a vein of Galen malformation (VOGM), which results from persistent communication between the embryonic choroidal arteries and the median prosencephalic vein of Markowski. Other lesions, such as pial arteriovenous fistulas, occur more rarely and are collectively referred to as nongalenic AVFs (NG-AVFs). These conditions are increasingly identified prenatally and are referred to subspecialized centers for counseling and treatment planning.

VOGMs and NG-AVFs result in direct communication between the arterial and vascular beds, creating high-flow intracranial shunts and secondary high-cardiac-output states. Even though the hemodynamic repercussions of a high-output state do manifest prenatally, end-organ injury is rare. For example, most fetuses will show an elevated volume load in the right heart chambers, but only rarely will overt cardiac failure ensue. Parenchymal brain injury, while also rare in utero, is, nevertheless, sometimes identified in fetuses that undergo MR imaging. Due to the overall low incidence of VOGMs and NG-AVFs and the challenges associated with serial imaging in fetal life, little is known about the evolution and significance of
Table 1: Fetal brain parenchymal injury and progression

<table>
<thead>
<tr>
<th>MRI Feature</th>
<th>% (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal brain parenchymal injury (n = 8)</td>
<td>26 (8/31)</td>
</tr>
<tr>
<td>Structural abnormality (n = 8)</td>
<td>100 (8/8)</td>
</tr>
<tr>
<td>Low volume</td>
<td>88 (7/8)</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>50 (4/8)</td>
</tr>
<tr>
<td>Signal abnormality (T1WI or T2WI)</td>
<td>88 (7/8)</td>
</tr>
<tr>
<td>DWI abnormality (n = 5)</td>
<td>71 (5/7)</td>
</tr>
<tr>
<td>DWI data available for only 7 of 8 subjects</td>
<td>100 (7/7)</td>
</tr>
<tr>
<td>T2* Abnormality (n = 5)</td>
<td>100 (5/5)</td>
</tr>
<tr>
<td>T2* data available for only 5 of 8 subjects</td>
<td>100 (5/5)</td>
</tr>
</tbody>
</table>

*Repeat scan data are available for only 7 of 8 subjects.

parenchymal injury in fetuses with high-flow intracranial vascular shunts.

The purpose of this study was to characterize the MR imaging features of parenchymal injury in fetuses with VOGM and NG-AVF, to investigate their clinical context, and to explore its prognostic significance. We hypothesized that parenchymal injury would show relentless progression and that it would be associated with poor neonatal outcomes.

MATERIALS AND METHODS

Sample Recruitment

We performed a retrospective institutional review board-approved and Health Insurance Portability and Accountability Act–compliant study. We queried the institution’s electronic health record for cases of VOVM or NG-AVFs between 2007 and 2021 that had fetal brain and body MR imaging. We excluded cases with nondiagnostic image quality or cases with other CNS/body abnormalities nonattributable to the VOVM or NG-AVF. For each subject, we recorded gestational age and sex. Additionally, we reviewed postnatal records and classified the outcome into good and adverse outcomes; the adverse outcome was defined as a composite measure derived from the patient’s need for intubation or emergent embolization or death by postnatal day 2.

Fetal Brain Evaluation

Cases were reviewed independently by 2 board-certified pediatric neuroradiologists with experience in fetal neuroimaging. The discrepancies were adjudicated by blinded and independent review of the images by a third, board-certified neuroradiologist/Committee on Advanced Subspecialty Training (CAST)-credentialed neurointerventional radiologist with 15 years of experience in pediatric endovascular interventions, including VOVM management.

Images were reviewed to confirm the diagnosis of VOVM or NG-AVF. The studies were additionally reviewed to determine the presence of parenchymal injury. Sequences available were reviewed, including structural images (T2 HASTE, steady-state free precession, and T1–volumetric interpolated breath-hold examination [VIBE]), diffusion-weighted images (or diffusion tensor images), and T2* gradient-echo sequences. All images were scored in a binary manner as having either normal or abnormal findings. For structural images, the radiologists evaluated the following: 1) signal abnormality (T2 hyperintensity, T2 hypointensity, and T1 hyperintensity), 2) low volume, and 3) ventriculomegaly. DWI was evaluated for the presence of restricted diffusion, and the T2* gradient-echo imaging was evaluated for the presence of abnormal parenchymal blooming.

Progression of the brain injury was evaluated in all subjects with a repeat fetal scan by a single reviewer. If no fetal scan was available, an immediate postnatal MR imaging was evaluated to assess chronic changes. The increased extent of the injury that was documented prenatally or development of new areas of parenchymal injury was regarded as progression.

Fetal Body Evaluation

Images were reviewed by a board-certified pediatric radiologist with expertise in fetal imaging. Only structural images were analyzed (T2 HASTE, steady-state free precession, and T1–VIBE). The radiologist evaluated the presence of the following: 1) ascites, 2) pleural effusion, 3) pericardial effusion, 4) cardiomegaly, 5) scalp edema, 6) body wall edema, and 7) anasarca.

Statistical Analysis

Measures of central tendency were used to describe the population. Percentages were used to describe the scoring of brain parenchymal injury and progression. To evaluate associations between fetal brain parenchymal injury and fetal body MR imaging in a cross-sectional fashion, we estimated the prevalence odds ratio for each variable. To evaluate associations between brain parenchymal injury and postnatal clinical outcomes at 2 days of life in a retrospective cohort, we estimated the relative risk. All statistical analyses were performed in STATA (StataCorp) with an α threshold of .05.

RESULTS

Study Sample

A total of 49 fetal MR imaging examinations were analyzed. Of these, 46 (94%) had T2 HASTE sequences, 39 (80%) had steady-state free precession, 37 (76%) had T1 VIBE, 34 (69%) had DWI, and 31 (63%) had T2* images. The examinations corresponded to 31 subjects (27 with VOVM and 4 with AVFs), of which 18 were male and 13 female. The mean gestational age for the first examination was 32.3 (SD 4.7) weeks (minimum, 20.4 weeks; maximum, 37.6 weeks), and 14 subjects underwent at least 1 additional fetal MR imaging examination (mean interval, 3.9 [SD, 3.2] weeks; minimum, 0.9 weeks; maximum, 12.7 weeks).

Brain Injury

Findings consistent with brain injury were observed in 8 subjects (26%) in 14 individual fetal MR imaging examinations. The mean gestational age at the time of identification of brain injury for each subject (presenting MR imaging) was 32.2 (SD 4.9) weeks. Findings are summarized in Table 1, and a case-by-case outline is presented in Table 2.

Abnormalities on structural imaging were identified in all fetuses with brain injury (n = 8) (Fig 1). Mild or moderate diffuse parenchymal volume loss was identified in 7 subjects (88%) and was noted in the presenting examination in 5 subjects (63%). Ventriculomegaly was present in 4 fetuses (50%) and was
Signal abnormalities, including T2 prolongation, T2 hypointensity in periventricular regions (radiating periventricular abnormalities and/or the germinal matrix), and T1 hyperintensity in the periventricular regions were identified in 7 fetuses (88%) and in the presenting examination in 6 subjects (75%). T2 prolongation was identified in the presenting examination of 50% of subjects; T2 hypointensity, in 50%; and T1 hypointensity, in 25%. An individual fetus often had >1 pattern of signal abnormality on structural images.

Five of the 8 fetuses with brain injury had T2*-weighted sequences available, and abnormalities in T2* were identified in all; in every case, the abnormality was appreciable in the presenting examination. The patterns observed included engorgement of the periventricular (medullary) veins (60%), “blooming” in the germinal matrix (20%), and generalized signal drop throughout the parenchyma (40%) (Fig 2). Subject 8 had both patterns, with generalized blooming ipsilateral to the AVF and contralateral engorgement of the periventricular veins.

Restricted diffusion was identified in 5 of 7 fetuses who had available data (71%) and was identified in the presenting scan in 3 subjects (43%). Four cases showed patchy bilateral areas of restricted diffusion and 1 case (20%) showed generalized restricted diffusion in the gray and white matter of both cerebral hemispheres (Fig 3).

The abnormalities in this cohort of fetuses with brain injury were confined to the supratentorial brain, completely sparing the posterior fossa. In all fetuses with VOGM with injury (n = 6) and in 1 fetus with NG-AVF whose shunt drained to a midline vein (subject 2), the injury was bilateral and symmetric. In a single fetus with a NG-AVF with dominant left-hemispheric drainage (to the vein of Labbe) (subject 8), the pattern of injury was markedly asymmetric, with severe involvement of the left hemisphere and only minimal periventricular changes on structural imaging and T2* in the right periventricular region (Online Supplemental Data).

Progression of Brain Injury
We observed progression of the fetal brain parenchymal injury in all cases that had at least 1 abnormality and for whom a repeat scan was available (Fig 4). The mean interval between examinations for this subgroup was 3.1 (SD 2.1) weeks, including 2 cases of documented progression in the immediate postnatal period.

In subject 8 (NG-AVF with left hemispheric venous drainage), progression included the worsening of the severe injury that was

Table 2: Subject demographics and MR imaging examination findings

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dx</th>
<th>GA (wk)</th>
<th>Structural Abnormality</th>
<th>Low Volume</th>
<th>Ventriculomegaly</th>
<th>Signal Abnormality</th>
<th>DWI Abnormality</th>
<th>T2* Abnormality</th>
<th>Documented Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VOGM</td>
<td>36.9</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fetal</td>
</tr>
<tr>
<td>2</td>
<td>NG-AVF</td>
<td>28.6</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fetal</td>
</tr>
<tr>
<td>3</td>
<td>VOGM</td>
<td>20.4</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fetal</td>
</tr>
<tr>
<td>4</td>
<td>VOGM</td>
<td>23.2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Postnatal*</td>
</tr>
<tr>
<td>5</td>
<td>VOGM</td>
<td>35.3</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Postnatal*</td>
</tr>
<tr>
<td>6</td>
<td>VOGM</td>
<td>29.3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fetal</td>
</tr>
<tr>
<td>7</td>
<td>VOGM</td>
<td>26.7</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fetal</td>
</tr>
<tr>
<td>8</td>
<td>NG-AVF</td>
<td>32.0</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Fetal</td>
</tr>
</tbody>
</table>

Note: – Dx indicates diagnosis; GA, gestational age; wk, weeks.
* Immediate postnatal exam.

![FIG 1. Structural abnormalities in fetuses with brain injury on T2- and T1-weighted images.](image-url)

A. Coronal T2 HASTE in a 35.3-week fetus (subject 5, scan 1) shows localized T2 prolongation (arrow), volume loss, and ventriculomegaly. B. Coronal T2 HASTE in a 21.9-week fetus (subject 3, scan 2) shows T2 hypointensity in the periventricular region (arrow). C. Coronal T2 HASTE shows periventricular cystic change (arrow) in a 29.4-week fetus (subject 2, scan 2). D. Coronal T2 HASTE (D) and coronal T1 VIBE (E) in a 33-week fetus (subject 6, scan 3) show generalized T2 prolongation and cerebral edema (asterisk), periventricular T2 hypointensity (arrow in D), and corresponding T1 hyperintensity (arrow in E).
noted in the left hemisphere on the baseline MR imaging as well as development of subtle areas of injury in the periventricular regions of the contralateral hemisphere.

**Body MR Imaging Associations**

We observed a trend of increased odds of concurrent body abnormalities in subjects who had brain parenchymal injury relative to those without parenchymal injury, but the trend did not reach statistical significance (all $P > .47$) (Online Supplemental Data).

Similarly, we observed a nonsignificant trend of increased odds of fetal body abnormalities in subjects who had an adverse composite outcome compared with those who did not (all $P > .09$) (Online Supplemental Data).

**Postnatal Outcomes**

All subjects (8/8) who had brain parenchymal injury on fetal MR imaging met the composite outcome of death or intubation at 2 days of life, while this was the case for only 30% of subjects (7/23) who did not manifest fetal brain injury. These findings indicate a tripling of the risk of meeting the composite outcome in patients with fetal brain parenchymal injury (relative risk, 3.29; 95% CI, 1.77–6.1; $P < .001$).

**DISCUSSION**

Parenchymal injury in fetuses with high-flow intracranial vascular malformations is a rare complication, as opposed to neonates with these conditions in whom parenchymal injuries frequently accrue. The increase in the use of fetal MR imaging to evaluate patients with VOGM and NG-AVF has led to an increase in the recognition of this form of end-organ damage and its evolution. Our retrospective analysis of fetuses with VOGM and NG-AVF shows that brain injury occurs in a minority of the affected patients; it is limited to the supratentorial space; and it is almost always bilateral and symmetric. Abnormalities were detected in structural images, T2*-weighted images, and DWI. Our results also indicate that parenchymal injury is a marker of an aggressive disease course, with documented radiologic progression in all cases that underwent serial imaging and with a strong association with adverse neonatal clinical outcomes.

Fetal MR imaging is a valuable tool to determine prognosis and counsel parents of patients with VOGM who are diagnosed prenatally. Despite advances in neurointerventional techniques and critical care, up to 40% of patients with VOGM who require urgent embolization die in the neonatal period, and half of the survivors have severe neurologic sequelae. Stratifying the risk of death or disability on the basis of prenatal examinations remains challenging, though the caliber of the venous sinus draining the main varix may be a strong predictor; nevertheless, the strongest prognostic evidence rests on clinical evaluation in the first hours and days after birth. We believe that the presence of prenatal brain injury is a marker of an aggressive pathophysiologic cascade and that this understanding can aid in parental counseling. Lecce et al reported that brain injury on a postnatal MR imaging was a predictor of adverse outcomes, and it would be reasonable to attribute at least a similar if not greater prognostic value to prenatal injury. Furthermore, our results support the likely association between prenatal brain injury and adverse neonatal outcome; this would suggest that these fetuses are likely to present in the neonatal period with low Bicêtre scores and overlap with the populations reported by Lecce et al, as non-survivors or survivors with significant neurologic impairment.
We observed a heterogeneous MR imaging appearance of prenatally diagnosed brain injury that probably reflects a complex pathophysiology with varying degrees of acuity and with cumulative injury. Prior reports have postulated that diffuse and progressive acute injury to the parenchyma in subjects with VOGM, referred to as “melting brain syndrome,” is secondary to elevated venous pressure and chronic hypoxia.7-8 The pattern of MR imaging abnormalities observed in our cohort is consistent with this hypothesis. For example, the areas of periventricular T2 prolongation could be attributable to either venous congestion or injury of varying chronicity, the restricted diffusion could represent acute venous ischemia, and the areas of T1 hyperintensity could represent late subacute areas of injury. Similarly, the T2*-weighted findings are consistent with a venous pattern of injury, including findings of venous congestion in the medullary veins and parenchyma and occasionally areas of hemorrhage. The bilateral and symmetric distribution of injury in patients with drainage via midline veins in contrast to the asymmetric injury in the fetus with lateralized venous drainage of a NG-AVF further supports a venous hemodynamic etiology as a contributing factor or causative mechanism.

Parenchymal injury showed a relentless course toward progression in our cohort of affected fetuses. This finding is consistent with observations in neonates and infants with VOGM; in these patients, the occurrence of even focal brain parenchymal injury is considered an urgent indication for intervention. If an intervention does not alleviate the adverse hemodynamic conditions, the injury may progress to “melting brain,” and the prognosis is poor.9 Recognizing that fetal brain injury differs from a static insult is fundamental to counseling parents and to the subsequent management of the fetus. If the abnormalities are subtle or equivocal, a repeat MR imaging in a short interval can confirm the presence of injury. If the abnormalities are overt, one should expect them to progress during the remainder of the pregnancy and probably result in substantial neurocognitive sequelae if the patient survives. Our results also show that brain parenchymal injury is a relatively rare occurrence (26% of the sample), which differs from the rate (40%) reported by Paladini et al.10 The reason for this discrepancy is difficult to resolve due to the substantial differences between studies including the following: 1) random differences in populations and referral patterns, 2) modalities used, 3) definitions of brain injury, and 4) the duration of time during which the study populations were identified (dating back to 1999 in the study by Paladini et al).

This study has several limitations. First, a small sample size limits the power of the statistical analysis performed and increases the chance of type II error. This also precludes subgroup analysis and exploratory analysis with other demographic variables (sex, morphologic features of the malformation, and so forth). A second limitation is the retrospective design. Use of MRIs acquired at several institutions (outside records) during a 10-year period yields a variable quality of the MR imaging examinations as well as variability in protocols. Follow-up examinations were performed at variable intervals, and data from other outside records that were not uploaded onto the PACS (eg, fetal echocardiograms) may be incomplete or be unreliable. Third, our analysis is limited to neonatal clinical outcomes and does not have longer-term data or structured neurologic testing. Fourth, our sample may be subject to a selection bias. Our hospital is a tertiary referral center for subspecialized pediatric care, possibly resulting in overrepresentation of severe clinical presentations; the observed prevalence of brain injury in 25% of our cases could be overestimated as a result.

Last, for this first study, we chose to focus on the significance of prenatal signs and a limited set of clinical outcomes in the immediate neonatal period (death or intubation within 2 days postnatally due to heart failure). National-level outcome data from the same expert, high-volume center contrasting neonates with VOGM and this degree of heart failure with those who can be treated electively postneonatally (Lecce et al5 compared with Gopalan et al9) makes clear that this distinction represents a major bifurcation in outcome, with high mortality and a high rate of severe neurocognitive injuries in the former group. No doubt, future effort should focus on long-term outcomes and associations with interventions.

CONCLUSIONS
Parenchymal brain injury is a complication seen in a minority of fetuses with VOGM and NG-AVFs. A combination of sequences, including DWI and T1-, T2-, and T2*-weighted sequences can help identify and characterize the injury. Findings of brain injury

FIG 4. Progression of brain injury in 3 patients who underwent serial fetal MRIs. A and B, Subject 3, scan 1 and 2, at 20.4 weeks and then at 21.9 weeks when there is evidence of increased periventricular T2 hypointensity. C and D, Subject 2, scan 1 and 2, at 28.6 weeks and then at 29.4 weeks when there is evidence of a cystic change in the periventricular white matter and worsening of the T2 signal abnormality. E and F, Subject 6, scan 2 and 3, at 31.7 weeks and then at 33 weeks when there is generalized brain swelling and effacement of the extra-axial CSF in a pattern consistent with diffuse injury.
appear to portend a poor prognosis, with relentless progression and a likely association with adverse neonatal outcomes.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

**REFERENCES**