Vein of Galen
Aneurysmal Malformations

ABC 2018

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No conflicts of interest

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Vein of Galen Malformation: Diagnosis and Management


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There was an overall series mortality of 55.6% (no details were available in 33 cases) and a 37.4% mortality for surgically treated cases. After operation, there was a 46.3% incidence of significant morbidity in surviving patients. Neonatal patients fared worst, with an overall mortality of 64 of 70 cases (91.4%) where details were available. The outcome was equally bad for surgically and conservatively treated cases. Operation in the 1- to 12-month age group was more successful, but still had a 41% mortality in the first half of the surviving patients. Over the acce
THE MANAGEMENT OF VEIN OF GALEN ANEURYSMAL MALFORMATIONS

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OBJECTIVE: The vein of Galen aneurysmal malformation (VGAM) is a choroidal type of arteriovenous malformation involving the vein of Galen forerunner. This is distinct from an arteriovenous malformation with venous drainage into a dilated, but already formed, vein of Galen. Reports of endovascular treatment of VGAM in the literature approach the disease from a purely technical viewpoint and often fail to provide satisfactory midterm results. To focus the therapeutic challenge to a strictly morphological goal overlooks the fundamental aspects of neonatal and infant anatomy and fluid physiology. During the past 20 years, our approach to VGAM has remained the same. Our experience, based on 317 patients with VGAM who were studied in Hospital Bicêtre between October 1981 and October 2002, allows us to describe the angioarchitecture, natural history, and management of VGAM in neonates, infants, and children.

METHODS: Of our cohort of 317 patients, 233 patients were treated with endovascular embolization; of these, 216 patients were treated in our hospital. The treatment method of choice was a transfemoral arterial approach to deliver glue at the fistulous zone.

RESULTS: Of 216 patients, 23 died despite or because of the embolization (10.6%). Twenty out of the 193 (10.4%) surviving patients were severely retarded, 30 (15.6%) were moderately retarded, and 143 (74%) were neurologically normal on follow-up.

CONCLUSION: Our data demonstrate that most treated children survive and undergo normal neurological development; an understanding of the clinical, anatomical, and pathophysiological features of VGAM has, therefore, reversed the former poor prognosis. Our level of understanding about the lesion allows us to predict most situations and remedy them by applying a strict evaluation protocol and working within an optimal therapeutic window. Patient selection and timing remain the keys in the management of this condition. It is more important to restore normal growth conditions than a normal morphological appearance, with the primary therapeutic objective being normal development in a child without neurological deficit.

KEY WORDS: Cardiac failure, Clinical outcome, Glue, Hydrovenous disorders, Transarterial embolization, Vein of Galen malformation

What is a vein of Galen malformation?
VEIN OF GALEN MALFORMATION

BY

ARNOLD R. GOLD, M.D.
JOSEPH R. REINSOHOF, M.D.
AND

SIDNEY CARTER, M.D.*

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* The Department of Neurosurgery, New York University, Bellevue Medical Center.

Figure 3 – (Patient 1) – Anteroposterior view of a right common carotid arteriogram, taken at a later phase than in figure 2, showing the vein of Galen as a massive mass of contrast material between the dilated lateral ventricles.

Figure 10 – (Patient 4) – Chest x-ray showing the effect of ligation of the feeding arteries of the malformation on the cardiovascular system. Preoperatively the heart is enlarged with a cardiac thoracic ratio of 0.65, and the postoperative film shows a normal heart size with a cardiac thoracic ratio of 0.57.

Figure 9 – (Patient 4) – Typical skin manifestations showing dilated and tortuous scalp veins and a large telangiectatic lesion above the glabella.
Cardiac Findings in the Fetus with Cerebral Arteriovenous Malformation Are Associated with Adverse Outcome

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*Department of Cardiology, Children’s Hospital Boston, †Department of Pediatrics, Harvard Medical School, and ‡Advanced Fetal Care Center, Boston Children’s Hospital, Boston Mass., USA

Abstract

Cerebral Arteriovenous Malformation (CAVM) impose volume load on the fetal circulation, mainly affecting right heart structures. Though they are thought to comprise up to 30% of pediatric arteriovenous malformations, incidence of approximately 18 per 100,000 adults [1], almost 50% of CAVMs result in perinatal death [2]. Increased right heart dilation and dysfunction are associated with poor outcome, the median cardiothoracic ratio (CTR) among neonatal deaths was 0.40 (0.30–0.48, n = 8). Comparing survivors (n = 5) and nonsurvivors (n = 6), the tricuspid valve (TV) z-score was larger in the nonsurvivor group (Fisher’s exact test p = 0.015). RV dysfunction was also significantly associated with nonsurvival (Fisher’s exact test p = 0.015). A larger difference in combined cardiac output indexed to estimated fetal weight (iCCO) between the TV and mitral valve (MV) z-scores (surrogate for RV dilation, p = 0.052), and CTR >0.38 (p = 0.0762) tended to — but did not reach significance — in nonsurvivors compared with our institutional normal fetal data, the median combined cardiac output indexed to estimated fetal weight (iCCO) was 1020 ml/kg/min (750–1300 ml/kg/min, n = 10). The median gestational age was 36 weeks (range 18–40, n = 10). Prognosis · Cardiac output · Fetal physiology

Methods:

We retrospectively analyzed 120 fetuses referred between October 1999 and August 2015. Fetal echocardiography was performed at 10–28 weeks gestation, when ultrasound was available. Cardiac findings included RV dilation (64%), tricuspid regurgitation (86%), cerebral artery pulsatility index (82%), and right atrial pressure (82%), all more evident in the nonsurvivor group (fig. 1, p = 0.009) when analyzed by Mann-Whitney test. Nonsurvivors had a significantly lower median combined cardiac output indexed to estimated fetal weight (iCCO) compared with our institutional normal fetal data, the median combined cardiac output indexed to estimated fetal weight (iCCO) was 990 ml/kg/min (550–1300 ml/kg/min, n = 3 for nonsurvivors’ hospital patients). A larger difference in combined cardiac output indexed to estimated fetal weight (iCCO) between the TV and mitral valve (MV) z-scores (p = 0.052) and CTR >0.38 (Fisher’s exact test p = 0.076) both tended to — but did not reach significance — in nonsurvivors compared with our institutional normal fetal data. The median combined cardiac output indexed to estimated fetal weight (iCCO) was 1020 ml/kg/min (750–1300 ml/kg/min, n = 10); the median combined cardiac output indexed to estimated fetal weight (iCCO) was 990 ml/kg/min (550–1300 ml/kg/min, n = 3 for nonsurvivors’ hospital patients). The median gestational age was 36 weeks (range 18–40, n = 10). Prognosis · Cardiac output · Fetal physiology

Conclusion:

The median combined cardiac output indexed to estimated fetal weight (iCCO) was 1020 ml/kg/min (750–1300 ml/kg/min, n = 10); the median combined cardiac output indexed to estimated fetal weight (iCCO) was 990 ml/kg/min (550–1300 ml/kg/min, n = 3 for nonsurvivors’ hospital patients). The median gestational age was 36 weeks (range 18–40, n = 10). Prognosis · Cardiac output · Fetal physiology

Fig. 1. a Four-chamber view illustrating dilation of the right atrium and ventricle. b Bicaval view illustrating severe dilation of the SVC (*) relative to the IVC. c Three-vessel view showing the dilated SVC (*) in cross section. d Long axis of the aortic arch showing retrograde flow around the arch from the descending aorta.
Extreme “Melting Brain Syndrome”

5/8/2017 – 1 day old

5/16/2017 – 9 days old
Clinical syndromes with review of the literature

Evaluation of our eight patients and the case reports from the world literature resulted in an arbitrary classification based on age of onset of signs and symptoms. It became apparent that there were three major age groups in whom this arteriovenous malformation became symptomatic: 

- **Early neonatal life**, in which the major signs resulting from the marked effects on the cardiovascular system were progressive hydrocephalus and/or convulsions were prominent features; and
- **Later childhood or adult life**, in which headaches with or without signs of subarachnoid hemorrhage were seen.

The malformations of congenital origin are due either to a failure of maturation with persistence of a more primitive vascular system, or the lack of development of capillaries between the arterial and venous systems. This gives rise to two main types of cerebral arteriovenous aneurysms as demonstrated by Olivecrona and Rives (1948), Hamby (1952) and others. In one type, there is a direct end-to-end anastomosis; in the other, there is a network of poorly differentiated non-capillary vessels between artery and vein forming a mass of dilated and tortuous vessels. This is frequently referred to as an “angioma”, although Virchow (1928) and subsequent investigators have demonstrated the non-neoplastic nature of this condition.

In 1854 or 41 years before Steinheil’s paper, Luschka (1854) described a patient with a cerebral arteriovenous malformation. As DeJong (1957) stated, “we all know that the more thoroughly the literature of any subject is studied, the more difficult it becomes to ascribe priority.”
Endovascular management of vein of Galen aneurysmal malformations: Influence of the normal venous drainage on the choice of a treatment strategy

Monica Pearl · Jose Gomez · Lydia Gregg · Philippe Gailloud

Fig. 1 VGAM classification (adapted from Yasargil [32]). a VGAM Type I: one or several direct arteriovenous shunts are connected to the aneurysmal venous collector of the VGAM. Compression of the cerebral aqueduct by the venous collector is illustrated. b VGAM Type II: an arterio-arterial, “nidus-like” network is interposed between the arterial feeders and the venous collector. Note the presence of typical parasagittal thalamoperforators. c VGAM Type III: Type III is a combination of Types I and II. d VGAM Type IV: in this case, an arteriovenous malformation drains into an enlarged but otherwise normal vein of Galen.
Pediatric intracranial arteriovenous shunts: a global overview

Luca Roccatagliata · Serge Bracard · Staffan Holmin · Michael Sodeman · Georges Rodesch

VGAM

VGAD
Normal Embryology and Development of the Intracranial Vascular System

Charles Raybaud, MD

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doi:10.1016/j.nec.2010.03.011

Fig. 1. Week 4. The neural tube is not closed yet, and the neural plate (pn) receives oxygen and nutrients from the surrounding amniotic fluid (amn) (A). Endothelial vasculogenesis is building up the cardiovascular organ system that already extends toward the cephalic extremity of the embryo (B).

First period of CNS vascular development: extra-embryonal supply, with the open neural tube nurtured by the amniotic fluid...
Normal and Abnormal Embryology and Development of the Intracranial Vascular System

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Fig. 2. Week 5. The neural tube is embedded into a dense connective tissue, the meninx primitiva (mp) (A, B) that contains vascular loops (8) connected to the dorsal aortae and cardinal veins. They are forming the primordial brain vascular meshwork, from which oxygen and nutrients diffuse to the neural tissue.

Fig. 3

Second period of CNS vascular development:
Extrinsic, extraneural, vascularization, with the still avascular brain parenchyma nurtured by diffusion from the surrounding highly vascularized meninx primitiva (a primordial endothelial network), with the choroid plexus developing as extensions of the MP into the ventricles.
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Third period of CNS vascular development:
Intrinsic, intraneural vascularization, with the MP developing into the subarachnoid space. The portion of the MP lying against the neural parenchyma forms sheets of capillaries. Angiogenesis ensues, with capillaries growing from the surface inward and connecting to form primitive arteriovenous loops.
Normal and Abnormal Embryology and Development of the Intracranial Vascular System

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Fig. 8. Weeks 6–11. The choroid stage. The ACA cranially, the ACHA caudally encircle the neck of the hemispheres toward the tela choroidea and the plexuses, together with the PCHA, branch of the midbrain arteries. The tela choroidea and plexuses are drained by a single, median dorsal bridging vein (median prosencephalic vein of Markowski) (mpvm) that antecedes the development of the internal cerebral veins and vein of Galen.

Choroid stage of vascular development:

The first arteries to differentiate are the choroidal and quadrigeminal arteries. A single, midline dorsal vein that drains blood from both left and right choroid plexuses develops on the roof of the diencephalon: the median prosencephalic vein. It has been described as early as 32 days, and no later than the 11th week.

All these vessels are still embedded in the cellular meninx primitiva, with a meningeal capillary network connecting these pial arteries with the MPV. These connections normally disappear when the MP differentiates into the three meningeal layers and into the subarachnoid space. At that point, all direct communication between pial arteries and subarachnoid veins is severed.
On this basis, Raybaud et al. argued that VGAM represents persistent arteriovenous flow to the MPV from the choroidal arteries:

- The venous collector is single, midline, and anterior to the future vein of Galen
- The vein is intra-arachnoidal and extracerebral. Its anatomic extent accords well with the territory of the median prosencephalic vein
- The arteries that supply VGAM are exactly the arteries that were present during the choroidal stage of development
- The underlying arterial pattern of the circle of Willis is usually normal. Even features such as a dense arterioarterial maze are seen in normal anatomical specimens. Given that, the event responsible for the arteriovenous fistula could not have occurred before 41 days (21-22 mm embryo)
- On the other hand, the vein of Galen develops relatively late, and it lacks direct connection to choroidal arteries
- Capillary loops of the meninx primitiva, which are interposed between the arteries of the choroid & quadrigeminal plate and the trunk of the median prosencephalic vein, might be maintained through the stimulus of flow, as persistent meningeal vessels
Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation

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¹ Neuroradiology, Hopital Nord, Marseille, France
² Department of Radiology, University Hospital and Clinics, Madison, Wisconsin, USA
³ Department of Radiology, Rikshospitalet, Oslo, Norway

Normal and Abnormal Embryology and Development of the Intracranial Vascular System

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doi:10.1016/j.nec.2010.03.011

Fig. 19. Vein of Galen aneurysm. The fistulae are extracerebral, in the wall of the venous sac. They are fed by the originally choroidal arteries anteriorly (ACA, ACHA, PCHA) and by the dorsal midbrain arteries posteriorly. The venous sac is single, midline. It may be drained dorsally toward the straight sinus (vein of Galen pattern), or toward a falcine sinus (vein of Markowski pattern), or both (A). On the whole, the vascular pattern of the malformation reflects the anatomy at the choroidal stage (B).
**FIGURE 4.** Late venous phase of vertebral angiogram (A) and three-dimensional angiographic (B) aspect demonstrating the epsilon-shaped deep venous drainage into the superior petrosal sinus (arrows). Because there is no vein of Galen, the deep venous system has to find an alternate route to drain. Thalamostriate veins open into the posterior and inferior thalamic veins, which secondarily join a subtemporal or lateral mesencephalic vein, which then join the superior petrosal sinus, demonstrating a typical epsilon shape on the lateral angiogram.
Normal galenic drainage of the deep cerebral venous system: two cases of vein of Galen aneurysmal malformation

Endovascular management of vein of Galen aneurysmal malformations. Influence of the normal venous drainage on the choice of a treatment strategy

Monica Pearl · Juan Gomez · Lydia Gregg · Philippe Gailloud

Fig. 12 Superselective retrograde injection into the internal cerebral vein demonstrates the normal anatomy of the deep venous system despite the vein of Galen malformation.
Endovascular management of vein of Galen aneurysmal malformations: Influence of the normal venous drainage on the choice of a treatment strategy

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Fig. 5 Baby girl presenting at birth with cardiac and respiratory failure, successfully managed by three sessions of transarterial embolization during the first week of life. After an initially favorable follow-up, she was readmitted emergently at 1 month of age for severe, life-threatening pulmonary hypertension. Transvenous embolization was elected. The pulmonary pressure remained elevated throughout the procedure, decreasing only as the coiling of the venous collector became close to complete. The post-treatment period was favorable, with a neurologically intact baby and resolution of the pulmonary hypertension. She became comatose 72 h after the embolization. A head CT was obtained immediately. a Head CT showing diffuse basal ganglia (arrow) and intraventricular hemorrhage (arrowhead). b Compare the pattern of hemorrhage illustrated in a with this photography depicting the typical postmortem appearance of infarction following deep cerebral venous thrombosis (from [11] with permission).
Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation

C.A. Raybaud¹, C.M. Strohner², and J.K. Hald³

¹ Neuroradiology, Hopital Nord, Marseille, France
² Department of Radiology, University Hospital and Clinics, Madison, Wisconsin, USA
³ Department of Radiology, Rikshospitalet, Oslo, Norway

"Overall, 18 of 20 patients with adequate studies exhibited abnormalities of dural venous drainage, consisting of a falcine sinus, a falcine venous loop or either focal or diffuse lack of opacification of normal dural sinuses"
"Many deep-seated AVMs although having a high flow and draining into the vein of Galen do not create significant ectasia ... Therefore, the VGA does not seem to be the disease, but a consequence of a hemodynamic phenomenon. Therefore, the existence of an obstacle distal to the vein of Galen must be postulated for a better understanding of the ectatic response of the vein to the increased input"

"In all our personal cases and in the published data, whenever careful anatomic analysis has been carried out, a dural venous obstacle could always be demonstrated ... The junction of the vein of Galen and the dural sinus seems to be a critical area. If this junction does not enlarge with the increased flow, it becomes a mechanical obstacle leading to proximal ectasia"

"The embryological development of vascular malformations is unknown. There is, however, definite evidence that it does not correspond to a proliferative disease [52] ... It has been suggested that a venous obstruction could maintain the capillary network at a plexiform stage"

Note – source [52] is John Mulliken and Judah Folkman
The Role of Dural Anomalies in Vein of Galen Aneurysms: Report of Six Cases and Review of the Literature

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Occlusion of Posterior Fossa Dural Sinuses in Vein of Galen Malformation

A. Berenstein, N. Toma, Y. Niimi, and S. Paramasivam


FIG 1. Case 8. A 13-month-old boy was diagnosed with VGM due to macrocrania and prominent scalp and facial veins. Left vertebral artery angiograms before the first embolization demonstrated a VGM in the arterial phase (A and B) and complete occlusion of the left sigmoid sinus and near-occlusion of the right sigmoid sinus in the venous phase (C and D, arrowheads). There was an alternative venous pathway via the emissary vein to the jugular bulb on the right side (C and D, arrowheads). Left vertebral artery angiograms in the midarterial phase (E and F) and the late venous phase (G and H) after subtotal obliteration of VGM achieved by staged transarterial embolization (E and F, arrows) demonstrate the reopened bilateral sigmoid sinuses (G and H, arrows). The patient is developing normally.
The Role of Dural Anomalies in Vein of Galen Aneurysms: Report of Six Cases and Review of the Literature

AJNR 8:185-192, March/April 1987

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- Note – source [52] is from John Mulliken and Judah Folkman
Hemangiomas and Vascular Malformations in Infants and Children: A Classification Based on Endothelial Characteristics

John B. Mulliken, M.D., and Julie Glowacki, Ph.D.
Boston, Mass.

PLASTIC AND RECONSTRUCTIVE SURGERY, March 1982

The beginning of wisdom is to call things by their proper names
-Confucius

<table>
<thead>
<tr>
<th>Hemangiomas</th>
<th>Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferating phase</td>
<td>Capillary</td>
</tr>
<tr>
<td>Involuting phase</td>
<td>Venous</td>
</tr>
<tr>
<td>Endothelial cell proliferation</td>
<td>Arteriovenous</td>
</tr>
<tr>
<td></td>
<td>Lymphatic</td>
</tr>
<tr>
<td>Rapid postnatal growth and slow</td>
<td>Normal endothelial cell cycle</td>
</tr>
<tr>
<td>involution</td>
<td>Grow commensurately with the child</td>
</tr>
<tr>
<td>Female: male, 5:1</td>
<td>Female: male, 1:1</td>
</tr>
</tbody>
</table>
Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies
Michel Wassef, Francine Blei, Denise Adams, Ahmad Alomari, Eulalia Baselga, Alejandro Berenstein, Patricia Burrows, Ilona J. Frieden, Maria C. Garzon, Juan-Carlos Lopez-Gutierrez, David J.E. Lord, Sally Mitchel, Julie Powell, Julie Prendiville, Miikka Vikkula and on behalf of the ISSVA Board and Scientific Committee

*Pediatrics;* originally published online June 8, 2015; DOI: 10.1542/peds.2014-3673

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**TABLE 2** 2014 ISSVA Classification of Vascular Anomalies

<table>
<thead>
<tr>
<th>Vascular Tumors</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple</td>
</tr>
<tr>
<td>Benign</td>
<td>CM</td>
</tr>
<tr>
<td>Locally aggressive or borderline</td>
<td>LM</td>
</tr>
<tr>
<td>Malignant</td>
<td>AVM</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous fistula</td>
</tr>
</tbody>
</table>
What is a Vein of Galen Malformation?

VGAM represents persistence and growth of arteriovenous flow that is intrinsically present during the choroidal stage of cerebrovascular development, when undifferentiated endothelial cell clusters connecting the choroidal arteries with the MPV normally intermingle and interconnect.

The cause for this persistent flow is likely dural sinus stenosis or perhaps an episode of thrombosis. Like other vascular malformations, VGAM is an accident of development.

Corollary: VGAM is fundamentally different from other brain AVM/AVF, which develop after differentiation of the intrinsic vasculature of the brain and which do not derive from the meninx primitiva.
Clinical Interlude:
How are we doing?
THE MANAGEMENT OF VEIN OF GALEN ANEURYSMAL MALFORMATIONS

OBJECTIVE: The vein of Galen aneurysmal malformation (VGAM) is a arteriovenous malformation involving the vein of Galen forerunner. This arteriovenous malformation with venous outflow into a dilated, but all of Galen. Reports of endovascular treatment of VGAM in the literature disease from a purely technical viewpoint and often fail to provide satisfactory results. To focus the therapeutic decision to a strictly morphological parameter, fundamental aspects of neonatal and infant anatomy and fluid physiology are necessary. Over the past 20 years, our approach to VGAM has remained the same. Our experience is that patients with VGAM who were studied in Hospital Bicêtre between October 1981 and October 2002, allow us to describe the angiographic, natural history, and management of VGAM in neonates, infants, and children.

METHODS: Of our cohort of 317 patients, 233 patients were treated with endovascular embolization; of these, 216 patients were treated in our hospital. The treatment method of choice was a transfemoral arterial approach to deliver glue at the fistulous zone.

RESULTS: Of 216 patients, 23 died despite or because of the embolization (10.6%). Twenty-two out of the 193 (10.4%) surviving patients were severely retarded, 30 (15.6%) were moderately retarded, and 143 (74%) were neurologically normal on follow-up.

CONCLUSION: Our data demonstrate that most treated children survive and undergo normal neurological development; an understanding of the clinical, anatomical, and pathophysiological features of VGAM has, therefore, reversed the former poor prognosis. Our level of understanding about the lesion allows us to predict most situations and remedy them by applying a strict evaluation protocol and working within an optimal therapeutic window. Patient selection and timing remain the key in the management of this condition. It is more important to restore normal growth conditions than a normal morphological appearance, with the primary therapeutic objective being normal development in a child without neurological deficit.

KEY WORDS: Cardiac failure, Clinical outcome, Glue, Hydroenous disorders, Transarterial embolization, Vein of Galen malformation


TABLE 2. Therapeutic decision and proposed treatment for patients with vein of Galen aneurysmal malformation

<table>
<thead>
<tr>
<th></th>
<th>Embolization</th>
<th>Abstention</th>
<th>Lost to follow-up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>88 (5)</td>
<td>45</td>
<td>7</td>
<td>140</td>
</tr>
<tr>
<td>Infants</td>
<td>103 (8)</td>
<td>16</td>
<td>6</td>
<td>125</td>
</tr>
<tr>
<td>Children</td>
<td>42 (4)</td>
<td>6</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>233 (17)</td>
<td>67 (21.1%)</td>
<td>17 (5.4%)</td>
<td>317</td>
</tr>
</tbody>
</table>

TABLE 3. Embolization Abstention Lost to follow-up

TABLE 4. Bicêtre neonatal evaluation score

<table>
<thead>
<tr>
<th>Points</th>
<th>Cardiac function</th>
<th>Cerebral function</th>
<th>Respiratory function</th>
<th>Hepatic function</th>
<th>Renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Overload, no medical treatment</td>
<td>Subclinical, isolated EEG abnormalities</td>
<td>Tachypnea, finishes bottle</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Failure: stable with medical treatment</td>
<td>Nonconvulsive intermittent neurologic signs</td>
<td>Tachypnea, does not finish bottle</td>
<td>No hepatomegaly, normal hepatic function</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Failure: not stable with medical treatment</td>
<td>Isolated convulsion</td>
<td>Assisted ventilation, normal saturation FIO₂ &lt; 25%</td>
<td>Hepatomegaly, normal hepatic function</td>
<td>Transient Gurdia</td>
</tr>
<tr>
<td>1</td>
<td>Ventilation necessary</td>
<td>Seizures</td>
<td>Assisted ventilation, normal saturation FIO₂ &gt; 25%</td>
<td>Moderate or transient hepatic insufficiency</td>
<td>Urgent diuresis</td>
</tr>
<tr>
<td>0</td>
<td>Resistant to medical therapy</td>
<td>Permanent neurological signs</td>
<td>Assisted ventilation, desaturation</td>
<td>Abnormal coagulation, hepatic enzymes</td>
<td>—</td>
</tr>
</tbody>
</table>

< 8: Therapeutic abstention
8-12: Urgent embolization
> 12: Embolization at 5-7 months

* EEG, electroencephalogram; FIO₂, fractional inspired oxygen. Maximal score = 5 (cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) + 3 (renal) = 21.
Vein of Galen Malformations in Neonates: New Management Paradigms for Improving Outcomes

**BACKGROUND:** Untreated patients with symptomatic neonatal presentation of vein of Galen aneurysmal malformations (VGAMs) carry almost 100% morbidity and mortality. Medical management and endovascular techniques for neonatal treatment have significantly evolved.

**OBJECTIVE:** To evaluate the clinical and angiographic outcomes of modern management of neonates with refractory heart failure from VGAMs.

**METHODS:** From 2005 to 2010, 16 neonatal patients with VGAM presented to our institution. Medical care from the prenatal to perinatal stages was undertaken according to specified institutional guidelines. Nine patients with refractory heart failure required neonatal endovascular intervention. All patients were treated by transarterial deposition of n-butyl cyanoacrylate into fistula sites. Short- and long-term angiographic studies and clinical outcomes were reviewed.

**RESULTS:** Control of heart failure was achieved in 8 patients. One premature baby died shortly after treatment. Long-term angiographic follow-up shows total or near-total angiographic obliteration in all 8 patients. One patient has a mild hemiparesis from treatment. Another has a mild developmental delay. One patient developed a severe seizure disorder and developmental delay. Overall, 66.7% patients have normal neurological development with near-total or total obliteration of the malformation.

**CONCLUSION:** Treatment of refractory heart failure in neonatal VGAM with modern prenatal, neurointensive, neuroanesthetic, and pediatric neuroendovascular care results in significantly improved outcomes with presumed cure and normal neurological development in most.

**KEY WORDS:** Congenital malformation, Congestive heart failure, Intracranial arteriovenous malformation, Neonate, Therapeutic embolization, Vein of Galen aneurysmal malformation.

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**FIGURE 3.** Frontal (A) and lateral (B) digital subtraction angiograms (DSA) of the left vertebral artery shows multiple tortuous fistulas (black arrow) into the dilated aneurysmal vein (white asterisk). The embryonic falx sinus (white arrow) is visualized. There is no restriction in the venous drainage correlating with severe high-output heart failure.

**FIGURE 4.** A, lateral view of the left vertebral artery DSA in the arterial phase after 4 endovascular embolizations demonstrates complete angiographic obliteration of the VGAM with preservation of all normal arteries. B, the venous phase shows remodeling of a normal appearing venous system, in a baby with normal development.
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KEY WORDS: Congenital malformation, Congestive heart failure, Intracranial arteriovenous malformation, Neonate, Therapeutic embolization, Vein of Galen aneurysmal malformation

TABLE. Clinical Details of Patients Undergoing Neonatal Embolization for VGAM

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cesarean Delivery</th>
<th>Diagnosed</th>
<th>Birth Weight (g)</th>
<th>MRI Pretreatment</th>
<th>Procedural Complications</th>
<th>Postprocedure Hemorrhage</th>
<th>Angiographic Closure</th>
<th>Total Sessions</th>
<th>Developmental Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>Yes</td>
<td>Birth</td>
<td>36</td>
<td>2897</td>
<td>No stroke</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Achieving milestones</td>
</tr>
<tr>
<td>F</td>
<td>Yes</td>
<td>Day 9</td>
<td>34</td>
<td>1810</td>
<td>No stroke</td>
<td>None</td>
<td>Yes</td>
<td>Died</td>
<td>Expired</td>
</tr>
<tr>
<td>M</td>
<td>Yes</td>
<td>In utero</td>
<td>38</td>
<td>4165</td>
<td>No stroke</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Expired</td>
</tr>
<tr>
<td>M</td>
<td>Yes</td>
<td>In utero</td>
<td>36</td>
<td>3409</td>
<td>No stroke</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Achieving milestones</td>
</tr>
<tr>
<td>F</td>
<td>Yes</td>
<td>Birth</td>
<td>39</td>
<td>3400</td>
<td>No stroke</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>Achieving milestones</td>
</tr>
<tr>
<td>M</td>
<td>No</td>
<td>Day 2</td>
<td>38</td>
<td>2930</td>
<td>No stroke</td>
<td>Stroke (microcatheter rupture)</td>
<td>Yes</td>
<td>No</td>
<td>95%</td>
</tr>
<tr>
<td>F</td>
<td>Yes</td>
<td>In utero</td>
<td>37</td>
<td>2386</td>
<td>No stroke</td>
<td>None</td>
<td>No</td>
<td>95%</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>Yes</td>
<td>In utero</td>
<td>38</td>
<td>4204</td>
<td>Occipital infarcts</td>
<td>None</td>
<td>Yes - into stroke</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>M</td>
<td>Yes</td>
<td>In utero</td>
<td>36</td>
<td>2825</td>
<td>Parietal necrosis</td>
<td>None</td>
<td>Yes - into stroke</td>
<td>Yes</td>
<td>3</td>
</tr>
</tbody>
</table>

Correspondence: Johanna T. Fifi, MD, Center for Endovascular Surgery, Roosevelt Hospital, 1000 Tenth Ave, New York, NY 10019. E-mail: jfifi@chpnet.org
Outcome and complications of endovascular embolization for vein of Galen malformations: a systematic review and meta-analysis

Jun Yan, MD, PhD,1 Jing Wen, MD, PhD,2 Roodrajeetsing Gopaul, MD,1 Chao-Yuan Zhang, MD,1 and Shao-wen Xiao, MD1

Departments of 1Neurosurgery and 2Rheumatism, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

- Lasjaunias 2007: 216 patients
  - mortality 10.6%
  - moderate to severe neurological outcome: 26%
  - complete angiographic occlusion: 55%
- Meta-analysis included 34 studies (421 studies screened) with 667 patients, neonates: 44%, infants 41%, children and adults 12%
- Overall cohort result: complete occlusion: 57%
Outcome and complications of endovascular embolization for vein of Galen malformations: a systematic review and meta-analysis

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Departments of 'Neurosurgery and 'Rheumatism, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

- F/U period: mean 63 months, range 0-148 months
- Outcome score: 0 (death), 1 (severe impairment), 2 (moderate impairment requiring significant support), 3 (mild impairment), 4 (normal). Good outcome defined as 3 or 4
- Pooled outcome: 68% good (3-4), 31% poor (0-2)
- Overall mortality: 16%
- Post-embolization complications: 37%
  - Hemorrhage 5%
  - Ischemic injury 6%
  - Developmental delay 12%
  - Leg ischemia 3%
  - Vessel perforation 3%
veins of Galen aneurysmal malformations are arteriovenous malformations of the choroidal system that develop in the early embryonic stage. They represent 30% of vascular malformations in the pediatric age group.

The successful treatment of VGAMs remains a complex challenge. During time intervals of 1980s, 1990s, and 2000s, the mortality rate of embolized patients declined from 17% to 12%. The complication rate dropped from 45% to 35%. The proportion of the poor outcome decreased from 51% to 28%; moreover, the proportion of the good outcome increased from 49% to 70%. The results suggest that advances in endovascular treatment have greatly improved the outcomes of patients with VGAMs. With the development of science and technology, endovascular embolization can result in acceptable rates of mortality, other reasons), and complications (cerebral hemorrhage, cerebral ischemia, hydrocephalus, and developmental delay) (p < 0.05).

As in many retrospective analyses, the limitations of our review included a small number of subjects, mainly cases with individual patient data from large, multicenter, observational studies would be more informative. The goal is not complete occlusion of the lesion, but rather, to a large extent, by staging the embolization procedure. The results of our meta-analysis suggest that vein of Galen malformations with endovascular embolization achieved so much progress that other methods such as Gamma Knife surgery achieved favorable outcomes in the 1980s, 1990s, and 2000s.

FIG. 3. Estimates of the proportion of the poor outcome, including the 95% CI from the random-effects model and the number of patients for each study.
Unblinded assessors in 29/34 studies

Only 19/34 studies were free of selective outcome reporting

Overall quality of the evidence (risk of bias and publication bias induced by study design):

- moderate quality 7
- low quality 1
- very low quality 11

**Methodological Quality**

FIG. 6. Risk of bias graph. Review of our judgment about each risk of bias item presented as percentages across all included studies. Figure is available in color online only.
Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

W. Brinjikji, T. Krings, M.H. Murad, A. Roucaud, and D. Meila

January 1980-January 2017: all studies reporting >=4 patients and reporting angiographic and/or clinical outcomes. Case reports were excluded

Variables tracked: clinical presentation, demographics, embolization technique (venous versus arterial), number of treatment sessions, perioperative complications, complete/near complete embolization rate, long term clinical outcome, mural versus choroidal architecture

“Good” outcome defined as no or minor developmental delay and no permanent disability

Various subgroup analyses were performed as well, including stratification into neonates versus infants versus children
Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

W. Brinjikji, T. Krings, M.H. Murad, A. Rouchaud, and D. Meila

From the Departments of Radiology (W.B.), Neurosurgery, (W.B.) and Center for Science of Healthcare Delivery (M.H.M.), Mayo Clinic, Rochester, Minnesota; Division of Neuroradiology and Neurosurgery (W.B., T.K.), University of Toronto, Toronto Western Hospital and University Health Network, Toronto, Ontario, Canada; Neuroradiology Section (A.R.), Centre Hospitalier Universitaire Bicêtre, Le Kremlin-Bicêtre, France; Department of Radiology and Neuroradiology (D.M.), Klinikum Duisburg, Duisburg, Germany; and Department of Diagnostic and Interventional Neuroradiology (D.M.), Medical School Hannover, Hannover, Germany.

ABSTRACT

Purpose: To identify studies on outcomes of endovascular treatment of vein of Galen malformations.

Methods: The initial literature search yielded 350 unique articles. On re-evaluation, 31 articles were included. These data are pooled across studies with a random-effects meta-analysis.

Results: Outcomes were stratified by age-group (neonate, infant, child). A random-effects meta-analysis was performed. Patients receiving endovascular embolization of vein of Galen malformations experienced good long-term clinical outcomes. Rates of good neurologic outcomes: 1) use of the Bicêtre neonatal shunts that form in utero between the choroidal arteries and the precursor of the vein of Galen, or failure to discriminate between endovascular and surgical outcomes. In total, 31 articles reflective of endovascular treatment of vein of Galen malformations from arteriovenous malformations draining directly into the Vein of Galen or failure to discriminate between endovascular and surgical outcomes.

Limitations: Publication bias.

Conclusions: There were 4 articles with high risk of bias that were excluded from the analysis. The major source of heterogeneity across studies was estimated rate of good neurologic outcomes. Application of a high-quality tool, the Istanbul-Ottawa Scale, was used to assess the quality of the included studies.

Data Extraction and Outcomes

The primary outcome of this study was to assess whether the following variables were associated with:

1. Patient presentation (congestive heart failure, hydrocephalus, brain parenchymal lesions)
2. Type of VOGM (mural versus choroidal)
3. Outcome after embolization (technical success, technical complications, perioperative hemorrhage, technical mortality, all-cause mortality, good neurologic outcomes, poor neurologic outcomes)
4. Follow-up time (months)
5. Subgroup analysis by type of VOGM (mural versus choroidal)

The included articles from the systematic review are as follows:

- 31 articles remained, describing 578 patients
- Yan et al. 2015: 34 studies (out of 421 screened) describing 667 patients
The natural text is: Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

W. Brinjikji, T. Krings, M.H. Murad, A. Rouchaud, and D. Meila


From the Departments of Radiology (A.B.), Neurosurgery (W.B.) and Center for the Science of Healthcare Delivery (A.M.), Mayo Clinic, Rochester, Minnesota; Division of Neuroradiology, Neurosurgery (W.B., T.K.) University of Toronto, Toronto Western Hospital and University Health Network, Toronto, Ontario, Canada; Neuroradiology Service (C.K.), Centre Hospitalier Universitaire Bicêtre, Le Kremlin-Bicêtre, France; and Department of Radiology and Neuroradiology (D.M.), Klinikum Düsseldorf, Düsseldorf, Germany; and Department of Diagnostic and Interventional Neuroradiology (D.M.), Medical School Hannover, Hannover, Germany.

Objective: The purpose of this study was to perform a systematic review of the literature to determine outcomes and predictors of good outcomes following endovascular treatment of vein of Galen arteriovenous malformations (VGAMs).

Methods: We performed a systematic review of the literature from January 1980 to April 2017. Three databases were searched: Ovid MEDLINE, Ovid Embase, and the Web of Science. All articles concerning VGAMs were included if the main outcome was a measure of neurologic outcome. Each study was analyzed by 2 independent reviewers to collect the data. Risk of bias was determined using the Cochrane Collaboration’s tool. Statistical analysis was performed using STATA Statistical Software, Release 14. A random-effects meta-analysis was performed to determine the proportion of children with good neurologic outcomes.

Results: A total of 578 unique patients were included across 44 studies. For all patients, overall good neurologic outcome rates were 80.0% (95% CI, 75.0%– 83.0%). Neonates were significantly less likely to have good neurologic outcomes than children (48.0%; 95% CI, 35.0%– 62.0% versus 77.0%; 95% CI, 70.0%– 84.0%; P < .001). Treatment of neonates was associated with significantly higher rates of good neurologic outcome (78.0%; 95% CI, 68.0%– 87.0% versus 57.0%; 95% CI, 46.0%– 67.0%; P < .001).

Conclusions: Neonates are significantly less likely to have good neurologic outcomes than older infants and children following endovascular treatment of VGAMs. Further research is needed to determine whether these differences are due to a higher incidence of hemorrhage in neonates.
Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

W. Brinjikji, T. Krings, M.H. Murad, A. Rouachaud, and D. Meila

From the Departments of Radiology (W.B.) and Center for the Science of Healthcare Delivery (M.H.M.), Mayo Clinic, Rochester, Minnesota; Division of Neuroradiology and Neurosurgery (W.B., T.K.), University of Toronto, Toronto Western Hospital, and University Health Network, Toronto, Ontario, Canada; Neuroradiology Service (A.R.), Centre Hospitalier Universitaire Bicêtre, Le Kremlin-Bicêtre, France; Department of Radiology and Neuroradiology (D.M.), Klinikum Duisburg, Duisburg, Germany; and Department of Diagnostic and Interventional Neuroradiology (D.M.), Medical School Hannover, Hannover, Germany.

ABSTRACT

Endovascular treatment of vein of Galen malformations has become a widely accepted treatment option for patients with vein of Galen arteriovenous malformations (VOGM). The aim of this study was to perform a systematic review of the literature to determine outcomes and predictors of good outcomes following endovascular embolization or occlusion of VOGMs.

METHODS

We performed a systematic review of the literature to determine outcomes and predictors of good outcomes following endovascular treatment of vein of Galen malformations. We used Ovid MEDLINE, Ovid Embase, and the Web of Science. Our study consisted of all case series with reporting angiographic and/or clinical outcomes following treatment. We did not include case reports, case series with less than 4 patients receiving endovascular treatment of vein of Galen malformations, or studies with overlapping patient populations. We performed a meta-analysis to compare outcomes between different age groups and sex. We performed subgroup analyses by lesion characteristics, type of VOGM (mural versus choroidal), Bicêtre neonatal evaluation score, sex, and age at treatment. We judged each study on 8 items categorized as follows: 1) patient selection, 2) the presence of neurologic symptoms, 3) the presence of developmental delay, 4) the presence of a defining treatment regimen, 5) rates of good neurologic outcome: 1) use of the Bicêtre neonatal evaluation score for patient selection, 2) the presence of neurologic symptoms, 3) the presence of developmental delay, and 4) the presence of a defining treatment regimen, 5) rates of long-term follow-up of children aged 6 years and older, 6) the presence of developmental delay and no permanent disability, 7) the presence of any permanent disability, and 8) the presence of any permanent disability.

DATA SYNTHESIS

Our study consisted of 247 studies, including 10,881 patients. The mean follow-up ranged from 0.5 to 6.8 years (median 2 years). The mean age of the patients was 0.9 years (range 0–23 years). The majority of patients were male (68.7%; sex data available for 252/578 patients). Of the patients, 42% were neonates, 45% were infants, and 13% were children. The most common presenting symptoms were CHF (63%), hydrocephalus (27%), and seizure (11.6%). ICH was present in 8.2% of patients.

DATA ANALYSIS

Analysis of outcomes for children older than 2 years of age could not be performed due to lack of sufficient studies.

Mean follow-up ranged from 0.5 to 6.8 years (median 2 years).

42% were neonates, 45% were infants, and 13% were children. The sex distribution was 68.7% male and 31.3% female.

Presentation (available for 318/578 patients): CHF (63%), hydrocephalus (27%), seizure (11.6%). ICH was present in 8.2%.

CONCLUSIONS

Endovascular treatment of VOGMs is safe and effective. A complete or near-complete occlusion rate of 80% was observed. Overall, the long-term outcome was excellent, with 48.0% of patients having good neurologic outcomes (95% CI, 35.0%–62.0%). The presence of good neurologic outcomes was associated with the Bicêtre neonatal evaluation score, CHF, and sex. The presence of developmental delay was associated with poor neurologic outcomes. The presence of any permanent disability was associated with poor neurologic outcomes. The presence of any permanent disability was associated with poor neurologic outcomes.
Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

From the Departments of Radiology (D.B.), Neurosurgery (W.B.) and Center for the Science of Healthcare Delivery (M.H.M.), Mayo Clinic, Rochester, Minnesota; Division of Neuroradiology and Neurosurgery (W.B., T.K.), University of Toronto, Toronto Western Hospital, and University Health Network, Toronto, Ontario, Canada; Neuroradiology Service (A.K.), Centre Hospitalier Universitaire Bicêtre, Kremlin Bicêtre, France; Department of Radiology and Neuroradiology (D.M.), Klinikum Düsseldorf, Düsseldorf, Germany; and Department of Diagnostic and Interventional Neuroradiology (D.M.), Medical School Hannover, Hannover, Germany.

Yan et al.

- Pooled outcome: 68% good (3-4), 31% poor (0-2)
- Overall mortality: 16%
Studies reporting the use of the Bicêtre neonatal evaluation score for patient selection had higher rates of good neurologic outcome versus those that did not (62% vs 57%).

Patients with CHF were significantly less likely to achieve good neurologic outcome than those without CHF (49.4% vs 66.2%).

Patients with hydrocephalus had similar rates of good outcome as those without it (62%).

There was no association between prenatal diagnosis and good neurologic outcome (66.7% vs 63.1%).
Hidden mortality of prenatally diagnosed vein of Galen aneurysmal malformation: retrospective study and review of the literature

B. DELOISON*, G. E. CHALOUHI*, P. SONIGO†, M. ZERAH‡, A. E. MILLISCHER†, Y. DUMEZ*, F. BRUNELLE†, Y. VILSE* and L. J. SALOMON*

*Department of Obstetrics and Fetal Medicine and SFAPE (Société Française d’Amélioration des Pratiques Échographiques), Paris Descartes University, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants, Paris, France; †Department of Pediatric Imaging, Paris Descartes University, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants, Paris, France; ‡Department of Pediatric Neurosurgery, Paris Descartes University, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants, Paris, France

INTRODUCTION

Vein of Galen aneurysm (n = 21)

‘Isolated’ aneurysm (n = 4)

‘Associated’ aneurysm (n = 17)

Good outcome (n = 3) (3 embolizations)

Poor outcome (n = 1) (1 embolization)†‡

Poor outcome (n = 17)

Termination of pregnancy (n = 9)*

Neonatal death (n = 5) (1 embolization)†

Survived with mental retardation (n = 3) (1 embolization)

DISCUSSION

Figure 3 Outcomes of 21 cases of vein of Galen aneurysmal malformation; see also Tables 3* and 4†. †This infant underwent embolization at 3 months of age but the coil migrated through the venous system, causing fatal thrombosis of the central venous system of the brain.

Literature review: 109 antenatally diagnosed cases between 1994 and 2011. Excluding TOP, outcome was known in 90 cases: 49 perinatal deaths (54%), 13 alive but severely impaired (14%), 29 patients are alive and well (32%)
Vein of Galen aneurysmal malformation (VGAM) in the fetus: retrospective analysis of perinatal prognostic indicators in a two-center series of 49 cases

D. PALADINI¹, B. DELOMUTO², A. ROSSI³, G. E. CHALOUFI², C. GANDOLFO³, P. SONIGO⁴, S. BURATTI⁵, A. E. MIELECHER⁶, G. TUO⁷, Y. VILLE⁸, A. PISTORIO⁷, A. CAMA⁸ and L. J. SALOMON²

¹Fetal Medicine and Surgery Unit, Istituto Giannina Gaslini, Genoa, Italy; ²Maternité, Hôpital Universitaire Necker-Enfants Malades, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, Paris, France; ³Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy; ⁴Radio-Pédiatrie, Hôpital Universitaire Necker-Enfants Malades, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, Paris, France; ⁵Neonatal and Pediatric Intensive Care Unit, Department of Critical Care and Perinatal Medicine, Istituto Giannina Gaslini, Genoa, Italy; ⁶Department of Pediatric Cardiology and Cardiac Surgery, Istituto Giannina Gaslini, Genoa, Italy; ⁷Epidemiology and Biostatistics Unit, Istituto Giannina Gaslini, Genoa, Italy; ⁸Neurosurgery Unit, Istituto Giannina Gaslini, Genoa, Italy

INTRODUCTION

VGAM is a complex malformation, the natural history of which is not yet clearly defined. While the majority of cases present perinatally, a number are detected prenatally and managed at ongoing pregnancies. In the last decade, the natural history and perinatal management of these cases has significantly improved. Two main issues are still under debate: the best timing for vaginal delivery vs. cesarean section and the optimal timing of major neurosurgical intervention. These topics are discussed based on our experience at two referral centers over a relatively limited number of cases, and a comprehensive literature review.

METHODS

This was a retrospective study involving 49 cases of VGAM diagnosed prenatally and managed at two referral centers from 2009 to 2016. The study population included VGAM cases diagnosed at any time during pregnancy with or without major brain lesions. In the majority of cases, the diagnosis was based on fetal ultrasound examination. Major brain lesions were considered as brain damage or symptomatic VGAM with absent/grossly abnormal venous drainage in the straight sinus. The study included all VGAM cases from both centers, with exclusion of a single case that underwent diagnosis at our center after referral from another center with a different echocardiographic examination. All cases were managed at the same center in the postnatal period.

RESULTS

A VGAM-related brain lesion appeared between prenatal diagnosis and birth in 25/49 cases (51.0%). The majority of these cases presented neurological symptoms clinically. In the remaining 24/49 cases (49.0%), VGAM was associated with major brain damage confirmed at postnatal MRI. In this group, brain damage was associated significantly with brain damage (Table 7). A VGAM volume ≥ 20 000 mm³ vs. the remaining cases without progression. Another advantage of this investigation is that it represents the first attempted modeling of perinatal VGAM progression.

Table 8 Relationship according to univariate analysis between different predictors and brain damage in a series of 49 cases of vein of Galen aneurysmal malformation (VGAM)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Brain damage (n/N (%))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain damage</td>
<td>Yes (n = 21)</td>
<td>10/21 (47.6)</td>
</tr>
<tr>
<td>No (n = 17)</td>
<td>1/17 (5.9)</td>
<td>16/17 (94.1)</td>
</tr>
<tr>
<td>VGAM vol ≥ 20 000 mm³</td>
<td>Yes (n = 29)</td>
<td>12/29 (41.4)</td>
</tr>
<tr>
<td>No (n = 13)</td>
<td>1/13 (7.7)</td>
<td>9/29 (31.0)</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>Yes (n = 16)</td>
<td>11/16 (68.8)</td>
</tr>
<tr>
<td>No (n = 33)</td>
<td>7/33 (21.2)</td>
<td>26/33 (78.8)</td>
</tr>
<tr>
<td>Aortic isthmus reversed flow</td>
<td>Yes (n = 14)</td>
<td>6/14 (42.9)</td>
</tr>
<tr>
<td>No (n = 15)</td>
<td>1/15 (6.7)</td>
<td>14/15 (93.3)</td>
</tr>
</tbody>
</table>

*Brain damage defined as development of any kind of brain lesion possibly related to VGAM. †Actual value according to receiver–operating characteristics curve = 19 807.1 mm³. ‡Fischer’s exact test. §Chi-square test. vol, volume.

Figure 3 Box-and-whiskers plot showing relationship between vein of Galen aneurysmal malformation (VGAM) volume measured on magnetic resonance imaging and prenatal progression of lesion. Boxes and internal lines represent median and range, whiskers represent interquartile range and circles represent outliers. Reference line is at 40 000 mm³.
Published Neonatal Outcomes

Outcome and complications of endovascular embolization for vein of Galen malformations: a systematic review and meta-analysis

Jun Yan, MD, PhD,1 Jing Wen, MD, PhD,2 Roodrajeetsing Gopaul, MD,1 Chao-Yuan Zhang, MD,1 and Shao-wen Xiao, MD1


Endovascular Treatment of Vein of Galen Malformations: A Systematic Review and Meta-Analysis

W. Brinjikji, T. Krings, M.H. Murad, A. Rouach, and D. Meila

Neonates:
All small series, short F/U av. 2 yrs, heterogeneous, crude markers of outcome

48% good outcome, 22% poor outcome, 27% mortality

Vijeya Ganesan, Fergus Robertson, Adam Rennie
Paediatric Neurovascular Unit
Great Ormond Street Hospital
London UK
UK VGAM cohort study

- 2006-2016: National service - all UK neonatal VGAMs, 2 centres (GOSH London / Glasgow)
- 87 consecutive neonatal VGAMs, unselected
- 54 survivors, 33 non-survivors (>1/3 untreated)
- Long-term comprehensive neurocognitive assessment study of survivors @ 2017

1/3\textsuperscript{rd} don’t survive
1/3\textsuperscript{rd} good neurocognitive outcome
1/3\textsuperscript{rd} poor neurocognitive outcome

Vijeya Ganesan, Fergus Robertson, Adam Rennie
Paediatric Neurovascular Unit
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London UK
Predictors of poor neurocognitive outcome in survivors:

- Low Bicetre score at presentation
- Abnormal brain scan at outset (esp. white matter volume loss)
- Open AV shunt at follow-up

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Paediatric Neurovascular Unit
Great Ormond Street Hospital
London UK
So, how are we doing?

From the perspective of the pregnant mother, learning that her fetus has a VGAM is no longer analogous to learning that her child has a GBM.

But in terms of the likelihood of (i) surviving to adulthood, and (ii) surviving without major neurocognitive compromise, it is fairly analogous to learning that her child has a medulloblastoma.
What is a Vein of Galen Malformation?

New Horizons
Capillary Malformation–Arteriovenous Malformation, a New Clinical and Genetic Disorder Caused by RASA1 Mutations

Iiro Eerola, Laurence M. Boon, John B. Mulliken, Patricia E. Burrows, Anne Dompmartin, Shoji Watanabe, Ronjan Vanwijck, and Miikka Vikkula

1. A genetic etiology clashes with the idea of malformations as accidents of development
2. VGAM’s privileged status as emerging from the unique choroidal primordial vascular environment is questioned
ACVRL1 gene variant in a patient with vein of Galen aneurysmal malformation

Ayako Chida, Masaki Shintani, Hajime Wakamatsu, Yoshiyuki Tsutsumi, Yuu Iizuka, Nanako Kawaguchi, Yoshiyuki Furutani, Kei Inai, Shigeaki Nonoyama and Toshio Nakanishi

Department of Pediatrics, National Defense Medical College, Tokorozawa-city, Saitama, Japan
Department of Pediatric Cardiology, Tokyo Women’s Medical University, Shinjuku-ku, Tokyo, Japan
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Abstract

A. Chida et al. / ACVRL1 variant in vein of Galen aneurysmal malformation

Received 10 November 2013

Keywords: HHT

3.3. The ACVRL1 R218W variant reduced SMAD 1/5/8 phosphorylation

3.4. Luciferase assay showed impaired BMP signal of ALK1-R218W (Fig. 3A). By densitometry, we found enhanced SMAD1/5/8 phosphorylation in the presence of wild-type ALK1. BMP9 also slightly

4. Discussion

ACVRL1 is a gene encoding endoglin (ENG), a receptor for activin and BMP. This protein is a component of TGF-β receptor complex 2 (TβR-II). AF may be caused by defects in TGF-β signaling. ACVRL1 mutation results in poor development of vascular smooth muscle cells during embryogenesis. The mutation in the ACVRL1 gene leads to reduction of TGF-β signaling. It is possible that the migration of cells is influenced by the reduced TGF-β signaling. Therefore, the vascular smooth muscle cells do not express the expected phenotype. It is possible that the migratory activity of the cells is affected by the reduced TGF-β signaling. In this study, we for the first time, describe one mutation in a VGAM patient. The patient was identified. Immunoblotting revealed that protein expression. A beta-gal expressing plasmid was promoter-reporter activity. The luciferase assay showed impaired BMP signal of ALK1-R218W (Fig. 3A). By densitometry, we found enhanced SMAD1/5/8 phosphorylation in the presence of wild-type ALK1. BMP9 also slightly

Fig. 2. Analysis of images from proband. (A) Axial (left) non-enhanced reconstruction computed tomography on the day of birth demonstrating subarachnoid hemorrhage with a hematoma around galenic cistern. Three-dimensional computed tomography (right) demonstrating bleeding in the parietal superior sagittal sinus, confluence, right transverse sinus, and right sigmoid sinus. (B) Axial (left) and sagittal (right) color Doppler imaging at 3-day-old demonstrating a large hematoma around the median cistern of prosencephalon. There was turbulent flow in the malformation and superior sagittal sinus. (C) Axial (left) and sagittal (right) brain magnetic resonance imaging at 1-day-old demonstrating a hematoma around the median vein of prosencephalon. (D) There was no abnormal arteriovenous shunt in axial (left) and sagittal (right) brain magnetic resonance imaging at 38 d after surgical intervention. There were no scar findings at brain parenchyma.
Eleven AVFs were present in 9 patients; these were typically side, venous reflux or corkscrew-like dilated veins as signs of pial vessels (we encountered only 1 choroidal AVM in this series) location in eloquent cortex. Feeding arteries were almost always...
Molecular genetics of Vein of Galen malformations

Daniel Duran1, Philipp Karschnia1, Jonathan Gaillard1, Jason K. Karimy1, Mark W. Youngblood1, Michael L. DiLuna1, Charles C. Matouk1, Beverly Aagaard-Kienitz2, Edward R. Smith1, Darren B. Orbach3, Georges Rodesch5, Alejandro Berenstein6, Murat Gunel1,7,8, and Kristopher T. Kahle1,8,9

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Authors declare no conflict of interest.

Financing:
Genetics of Vein of Galen Malformations

Table 1. VOGM-associated genetic variants

<table>
<thead>
<tr>
<th>#</th>
<th>Gene</th>
<th>Coding variant</th>
<th>Exon</th>
<th>Type of mutation</th>
<th>Protein variant</th>
<th>Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RASA1</td>
<td>c.2977del</td>
<td>24</td>
<td>frameshift deletion</td>
<td>p.Arg993Valfs</td>
<td>2013</td>
<td>Revencu et al</td>
</tr>
<tr>
<td>2</td>
<td>RASA1</td>
<td>c.2125C&gt;T†</td>
<td>16</td>
<td>stop gain</td>
<td>p.Arg709*</td>
<td>2013</td>
<td>Revencu et al, Heuchan et al</td>
</tr>
<tr>
<td>3</td>
<td>RASA1</td>
<td>c.3024del</td>
<td>24</td>
<td>frameshift deletion</td>
<td>p.Glu1008Asfs</td>
<td>2013</td>
<td>Revencu et al</td>
</tr>
<tr>
<td>4</td>
<td>RASA1</td>
<td>c.2288A&gt;T</td>
<td>17</td>
<td>missense</td>
<td>p.Glu763Val</td>
<td>2008</td>
<td>Revencu et al</td>
</tr>
<tr>
<td>5</td>
<td>RASA1</td>
<td>c.2532_2536del</td>
<td>19</td>
<td>frameshift deletion</td>
<td>p.Leu845Thrfs</td>
<td>2008</td>
<td>Revencu et al</td>
</tr>
<tr>
<td>6</td>
<td>RASA1</td>
<td>c.2119C&gt;T</td>
<td>16</td>
<td>missense</td>
<td>p.Arg707Cys</td>
<td>2013</td>
<td>Heuchan et al</td>
</tr>
<tr>
<td>7</td>
<td>RASA1</td>
<td>c.2912T&gt;C</td>
<td>23</td>
<td>missense</td>
<td>p.Leu971Val</td>
<td>2013</td>
<td>Heuchan et al</td>
</tr>
<tr>
<td>8</td>
<td>RASA1</td>
<td>c.1678G&gt;T</td>
<td>12</td>
<td>stop gain</td>
<td>p.Glu560*</td>
<td>2013</td>
<td>Chida et al</td>
</tr>
<tr>
<td>9</td>
<td>ACVRL1</td>
<td>c.652C&gt;T</td>
<td>6</td>
<td>missense</td>
<td>p.Arg218Trp</td>
<td>2013</td>
<td>Chida et al</td>
</tr>
<tr>
<td>10</td>
<td>ENG</td>
<td>c.1672_1684del</td>
<td>12</td>
<td>frameshift deletion</td>
<td>p.Gln558fs</td>
<td>2011</td>
<td>Tsutsumi et al</td>
</tr>
</tbody>
</table>

† Reported separately by two publications
Adult Presentation of a Familial-Associated Vein of Galen Aneurysmal Malformation: Case Report

David S. Xu, BS
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Christopher S. Eddleman, MD, PhD
Department of Neurosurgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

= RAS p21 GTPase activating protein 1; RASA1

Fetal MRI demonstrating vein of Galen malformations in two successive pregnancies—a previously unreported occurrence

Yune Kwong1 · Maria Cartmill2 · Tim Jaspan3 · Mohnish Suri4

ACVRL1 gene variant in a patient with vein of Galen aneurysmal malformation

Ayako Chida, Fumasa Shintani, Hajime Wakamatsu, Yoshiyuki Tsutsumi, Yu Ozuka, Nanako Kawaguchi, Yoshiyuki Furutani, Kei Inai, Shigeaki Nonoyama and Toshio Nakanishi

Table 1

Summary of VGAM patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Serial number</th>
<th>Gene mutation or variant</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>History and presentation</th>
<th>Complication and family history</th>
<th>Unique imaging findings</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P3389</td>
<td>-</td>
<td>M</td>
<td>Fetal age of 34 wk</td>
<td>Bradycardia, hypoxia</td>
<td>-</td>
<td>-</td>
<td>Catheter embozolization</td>
<td>Intact</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>P3431</td>
<td>RASA1 (c.1678 G&gt;T E560X)</td>
<td>M</td>
<td>Fetal age of 35 wk</td>
<td>Retractive breathing, patent atrial septal defect</td>
<td>-</td>
<td>-</td>
<td>Catheter embozolization</td>
<td>Mental and motor retardation, epilepsy</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>P3858</td>
<td>-</td>
<td>F</td>
<td>2 d of age</td>
<td>Hypertelorism, macrocrania</td>
<td>Patient’s twin sibling : VGAM suspected</td>
<td>-</td>
<td>Catheter embozolization</td>
<td>Severe mental and motor retardation, epilepsy</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>P3865</td>
<td>ACVRL1 (c.652 C&gt;T R218W)</td>
<td>F</td>
<td>1 d of age</td>
<td>Pale skin, bradycardia, anemia, hypothermia</td>
<td>-</td>
<td>SAH, hematoma around VGAM</td>
<td>Craniotomy for removal hematoma</td>
<td>Intact</td>
<td>This study</td>
</tr>
</tbody>
</table>

VGAM = Vein of Galen aneurysmal malformation; RASA1 = RAS p21 GTPase activating protein 1; ACVRL1 = Activin receptor-like kinase 1; M = Male; F = Female; SAH = Subarachnoid hemorrhage.
• However, phenotypic discordance in monozygotic twins, with one individual presenting with VGAM, has been reported twice. Twin-twin transfusion syndrome ensued in the case from The Netherlands, with the donor twin having VGAM and the recipient twin having transposition of the great vessels and a large VSD.

• We had a case in Boston (unpublished) of monozygotic twins with twin-twin transfusion, where the recipient had a VGAM
REVISED ARTICLE

Parkes Weber Syndrome, Vein of Galen Aneurysmal Malformation, and Other Fast-Flow Vascular Anomalies Are Caused by RASA1 Mutations

Nicole Revencu,1,2 Laurence M. Boom,3,1 John B. Mulliken,4 Odile Enjolras,5 Maria Rosa Cordisco,6 Patrice E. Burrows,1,2 Philippe Clapuyt,7 Frank Hammer,8 José Dubois,6 Eulalia Baselga,9 Francesco Brancati,10 Robin Carder,10 José Miguel Ceballos Quintana,12 Bruno Dallapiccola,12 Nicole Fischer,13 Ilona J. Frieden,14 Maria Garzon,15 John Harper,16 Jennifer Johnson-Patrick,17 Christine Labreze,18 Loreto Martorell,19 Harriet J. Paltiel,4 Annette Pohl,20 Julie Prendiville,21 Isabelle Quere,22 Dawn H. Siegel,23 Enza Maria Valente,24 Annet Van Hagen,25 Lieslott Van Hest,25 Keith K. Vaux,26 Asuncion Vicente,27 Lisa Weibel,26 David Chitayat,26 and Maïkka Vikkula28

HUMAN MUTATION 29(7), 959–965, 2008

RESEARCH ARTICLE

Molecular genetics of Vein of Galen malformations

Daniel Duran1, Philipp Karschnia1, Jonathan Gaillard1, Jason K. Karimy1, Mark W. Youngblood1, Michael L. DiLuna, Charles C. Matouk1, Beverly Aagaard-Kienitz2, Edward R. Smith1, Darren B. Orbach1, Georges Rodesch3, Alejandro Berenstein4, Murat Gunel1,7,8, and Kristopher T. Kahle1,3,9

J Neurosurgery Pediatrics, in press

• Revencu et al.’s initial association of RASA1 with VGAM included a set of monozygotic twins with the identical mutation but VGAM in only one

<p>| Table 2. Phenotype of Individuals With CM-AVM with (I) or Without (II) RASA1 Mutation* |
|----------------------------------|----------------------------------|------------------|------------------|--------------------|
| <strong>RASA1 mutation</strong> |</p>
<table>
<thead>
<tr>
<th>Family</th>
<th>Nucleotide change</th>
<th>Putative effect at amino acid level</th>
<th>Mutation carriersa</th>
<th>CMa</th>
<th>AVM/AVFa</th>
<th>PKWSa</th>
<th>Symptoms and associated featuresb</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>c.2532_2536delTTAA</td>
<td>p.Leu845ThrfsX38</td>
<td>2(dn)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>De novo mutation in monozygotic twins; VGAM and CF in one</td>
</tr>
</tbody>
</table>
A RASA1 somatic mutation in a skin punch biopsy was found in a CM-AVM patient who also harbored a separate germline mutation in RASA1.

This suggests that RASA1 germline mutations may predispose to the development of specific syndromes, with expression due to additional somatic mutations (or epigenetic effects?) arising in target tissue.
Metameres - Cobb Syndrome

Capillary malformation of the skin

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**ANNALS of SURGERY**

Vol. LXII  
DECEMBER, 1915  
No. 6

**Hæmangioma of the Spinal Cord**

*Associated with skin mark of the same metamere*

By Stanley Cobb, M.D.

of Boston, Mass.

Hæmangioma of the spinal cord and its membranes are rare, and in the published lists of cord tumors no record is found of their occurrence (viz., Schlesinger’s list of 400 cases and Plateau’s of 243). A thorough review of the literature, however, brings to light seven cases beside the one here reported.
Metameres - Cobb Syndrome

CASE REPORT

Angiogenic and inflammatory factor expressions in cutaneomeningospinal angiomatosis (Cobb’s syndrome): case report

Peng Gao · Hongqi Zhang · Fengming

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Panels a, b, c, and d represent the AVM-like tissues from skin, muscle, dura, and spinal cord tissues, respectively. HE staining (left column) shows the nidus of the AVM-like structure (d1). Tissues were stained with CD31, SMA, VEGF, and MMP-9, respectively. All the marker stainings have a higher magnification within the boxed area from the H&E staining, respectively. For panels a–d, CD31, SMA, VEGF, and MMP-9-positive signals were all observed in all tissue nidus (brown color indicated by arrows). CD31-positive staining was specifically found in the lumen of the vessel (a2–d2). SMA markers were mainly found within the vessel wall in skin, muscle, dura, and spinal cord (a3–d3). VEGF can be found either on the surface of the lumen or in the vessel wall of the AVM-like nidus or in the parenchymal tissues adjacent to the vascular wall (a4–d4). MMP-9-positive signals can be mainly found in the lumen of the vessel wall (a4–d4), and occasionally in the parenchyma (c4). Sections were counterstained with hematoxylin to show blue nuclei. Scale bar for H&E, 500 μm; for CD31, SMA, VEGF, and MMP-9 staining, 100 μm.
The Sturge–Weber syndrome and port-wine stains are caused by a somatic activating mutation in the GNAQ gene. We identified a nonsynonymous single-nucleotide variant (c.548G→T, encoding p.Gln183Ter) in samples of visibly affected tissue from 88% of the participants (23 of 26) with affected members in 23 of the 25 families (92%) and were able to rule out the presence of the same variant in any of the samples from the 6 controls. The prevalence of the mutant allele in affected tissue was modestly increased (0.017) during transgenic expression of mutant GNAQ in fibroblasts and cells in culture, which supports an oncogenic role for this mutation. The preponderance of affected members, the strong family history, the somatic nature of the mutation, and the clinical features of the disease are consistent with the hypothesis that the Sturge–Weber syndrome and port-wine stains are caused by somatic mutation in GNAQ.

Methods

We performed whole-genome sequencing of DNA from paired samples of visibly affected tissue from 4 participants with an unrelated cerebrovascular malformation or in apparently nonsyndromic port-wine stains, but not in any of the samples of affected tissue from 88% of the participants (23 of 26) with the Sturge–Weber syndrome, a port-wine stain, or neither (controls), using standard methods. Details of sequencing strategies, primers, barcodes, and primer sequences are provided in the Supplementary Appendix.

The New England Journal of Medicine

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DOI: 10.1056/NEJMoa1213507

Figure 1. Representative Photographs and Magnetic Resonance Imaging (MRI) Scans from Study Participants with the Sturge–Weber Syndrome or Isolated Port-Wine Stains.

Photographs of participants with the Sturge–Weber syndrome (B and C) show thatbirthmarks tend to be flat and red without evidence of hypertrophy or cobblestoning or other localizing signs and symptoms. Representative MRI scans (D and E) show findings associated with the Sturge–Weber syndrome, including leptomeningeal enhancement (yellow arrows), an enlarged and enhancing left-sided choroid plexus (red arrow), and the severity and extent of presentation are determined by the developmental time of the cerebral lesion. It has been hypothesized that somatic mosaic mutations disrupting vascular development cause both the Sturge–Weber syndrome and port-wine stains, and the severity and extent of presentation are determined by the developmental time of the cerebral lesion.
Somatic Activating Mutations in GNAQ and GNA11 Are Associated with Congenital Hemangioma

Ugur M. Ayturk, Javier A. Couto, Steven Hann, John B. Mulliken, Kaitlin L. Williams, August Yue Huang, Steven J. Fishman, Theonia K. Boyd, Harry P.W. Kozakewich, Joyce Bischoff, Arin K. Greene, and Matthew L. Warman*

*Correspondence: matthew.warman@childrens.harvard.edu

The American Journal of Human Genetics 98, 789–795, April 7, 2016

Figure S2: Somatic mutations in genes that are associated with congenital vascular tumors and malformations in humans. Mutations in genes encoding several different protein components of MAP kinase and mTOR signaling pathways have been identified in affected tissue from individuals with a vascular tumor or malformation. Relative locations and connections between different components in the signaling pathways are indicated by grey lines (arrowheads indicate a component that normally increases signaling and bars indicate a component that normally inhibits signaling). Colored text indicates the specific disorders and colored arrows point to pathway component(s) that can be responsible for causing the disorder. A condition for which a germline mutation may also be causal is indicated with an asterisk.
Somatic MAP2K1 Mutations Are Associated with Extracranial Arteriovenous Malformation

Javier A. Couto,1,6 August Y. Huang,2 Dennis J. Konczyk,3 Jeremy A. Goss,1 Steven J. Fishman,3 John B. Mulliken,1 Matthew L. Warman,2,4,5 and Arin K. Greene1,*

1Department of Plastic & Oral Surgery, Boston Children’s Hospital, Harvard Medical School, Boston, MA 02115, USA; 2Department of Orthopedic Surgery, Boston Children’s Hospital, Harvard Medical School, Boston, MA 02115, USA; 3Department of Surgery, Boston Children’s Hospital, Harvard Medical School, Boston, MA 02115, USA; 4Department of Genetics, Harvard Medical School, Boston, MA 02115, USA; 5Howard Hughes Medical Institute, Boston Children’s Hospital, Boston, MA 02115, USA.

The American Journal of Human Genetics 100, 1–9, March 2, 2017

- MAP2K1 protein product, MEK1 is involved in the RAS signaling pathway important for cell growth
- Germ-line mutations are associated with Noonan’s Syndrome and cardio-facio-cutaneous syndrome
- Somatic mutations are associated with melanoma and hematopoietic malignancy
- MEK1 inhibitors are currently used for some neoplasms
- MEK1 inhibition as AVM therapy, promoting terminal differentiation to capillaries (?)
Somatic Mosaic Activating Mutations in \textit{PIK3CA} Cause CLOVES Syndrome

Kyle C. Kurek,1 Valerie L. Luks,2 Ugur M. Kurturk,2,9 Ahmad I. Alomari,3,6 Steven J. Fishman,4,6 Samantha A. Spencer,2,6 John B. Mulliken,2,6,9 Margot E. Bowen,2,9 Guilherme L. Yamamoto,7 Harry P.W. Kozakewich,1,6 and Matthew L. Warman2,6,8,9,*

Congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies (CLOVES) is a sporadically occurring, nonhereditary disorder characterized by asymmetric somatic hypertrophy and anomalies in multiple organs. We hypothesized that CLOVES syndrome would be caused by a somatic mutation arising during early embryonic development. Therefore, we employed massively parallel sequencing to search for somatic mosaic mutations in fresh, frozen, or fixed archival tissue from six affected individuals. We identified mutations in \textit{PIK3CA} in all six individuals, and mutant allele frequencies ranged from 3% to 30% in affected tissue from multiple embryonic lineages. Interestingly, these same mutations have been identified in cancer cells, in which they increase phosphoinositide-3-kinase activity. We conclude that CLOVES is caused by postzygotic activating mutations in \textit{PIK3CA}. The application of similar sequencing strategies will probably identify additional genetic causes for sporadically occurring, nonheritable malformations.

The American Journal of Human Genetics 90, 1108–1115, June 8, 2012
Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain


RESULTS

We detected somatic activating KRAS mutations in tissue samples from 45 of the 72 patients and in none of the 21 paired blood samples. In endothelial cell–enriched cultures derived from arteriovenous malformations of the brain, we detected KRAS mutations and observed that expression of mutant KRAS (KRAS<sup>G12V</sup>) in endothelial cells in vitro induced increased ERK (extracellular signal-regulated kinase) activity, increased expression of genes related to angiogenesis and Notch signaling, and enhanced migratory behavior. These processes were reversed by inhibition of MAPK (mitogen-activated protein kinase)–ERK signaling.
Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling

BACKGROUND: Most arteriovenous malformations (AVMs) are localized and occur sporadically. However, they also can be multifocal in autosomal-dominant disorders, such as hereditary hemorrhagic telangiectasia and capillary malformation (CM)-AVM. Previously, we identified RASA1 mutations in 50% of patients with CM-AVM. Herein we studied non-RASA1 patients to further elucidate the pathogenicity of CMs and AVMs.

METHODS: We conducted a genome-wide linkage study on a CM-AVM family. Whole-exome sequencing was also performed on 9 unrelated CM-AVM families. We identified a candidate gene and screened it in a large series of patients. The influence of several missense variants on protein function was also studied in vitro.

RESULTS: We found evidence for linkage in 2 loci. Whole-exome sequencing data unraveled 4 distinct damaging variants in EPHB4 in 5 families that cosegregated with CM-AVM. Overall, screening of EPHB4 detected 47 distinct mutations in 54 index patients; 27 led to a premature stop codon or splice-site alteration, suggesting loss of function. The other 20 are non-coding variants that result in amino acid substitutions. In vitro expression of several mutations confirmed loss of function of EPHB4. The clinical features included multifocal CMs, telangiectasias, and AVMs.

CONCLUSIONS: We found EPHB4 mutations in patients with multifocal CMs associated with AVMs. The phenotype, CM-AVM2, mimics RASA1-related CM-AVM1 and also hereditary hemorrhagic telangiectasia. RASA1-encoded p120RASGAP is a direct effector of EPHB4. Our data highlight the pathogenetic importance of this interaction and indict EPHB4-RAS-ERK signaling pathway as a major cause for AVMs.

CM-AVM2

- CM-AVM: AD with high penetrance and variable expression. AVMs seen in ~30% of patients, in the brain, spine, face, neck, or extremities
- 50% of patients with CM-AVM have heterozygous LOF mutations in RASA1
- Studying families with phenotypic CM-AVM but no RASA1 mutation using linkage and whole-exome sequencing, a new mutated gene was identified as EPHB4. These were LOF mutations
Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling

CONCLUSIONS:

EPHB4-RAS-ERK signaling pathway as a major cause for AVMs.

Figure 3. Phenotypic spectrum associated with EPHB4 mutations.

- Penetration was high (102/110)
- All affected individuals had CM (102), and 92 had >1 CM. ~25% had a surrounding white halo. CMs could be present at birth or could develop during childhood or adolescence, and ranged from pinpoint to 15 cm
- 20 individuals had fast-flow lesions (cutaneous, subcutaneous, muscular and bony AVMs in the face/neck/extremities, Parkes Weber, CNS)
Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling

3/20 fast-flow lesions were in the CNS: 2 VGAM and one perimedullary spinal AVF. One additional VGAM was seen in a fetus whose father carried an EPHB4 mutation.

Differences between CM-AVM and CM-AVM2:
- Perioral and thoracic telangiectasias in CM-AVM2 (similar to HHT, but no pulmonary or hepatic AVM seen in CM-AVM2)
- Some CM-AVM2 patients had epistaxis (unlike CM-AVM)
- Overall lower frequency of fast-flow lesions in CM-AVM2 (18% vs 31%)
- Overall lower frequency of associated CNS AVMs in CM-AVM2 (3% vs 10%), but all brain cases were VGAM.
Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling

Conceptually, this molecular pathway sheds light on the long-standing clinical observation that AVM is a disease of the proximal vein.

Modulating the activity of the Ephrin signaling pathway may be a novel therapeutic strategy.

Figure 4. Role of EPHB4 in AVM formation. Artery-fated angioblasts (red) express EphrinB2 and inhibit expression of venous markers (EPHB4 and Chicken ovalbumin upstream promoter transcription factor II, COUP-TFII). Venous-fated endothelial cells (blue) express COUP-TFII, and thereby the EphrinB2 receptor EPHB4, and upregulate expression of Notch signaling. EphrinB2-EPHB4 interaction responsible for suppression of RAS-MEK-ERK and RAS-AKT-mTORC1 pathways. Lack of EPHB4 or p120RASGAP in venous endothelial cells of patients with capillary malformation-arteriovenous malformations 2 (CM-AVM2) and CM-AVM1, respectively (light green) results in constitutive activation of RAS-MEK-ERK and RAS-AKT-mTORC1 pathways, leading to abnormal differentiation of endothelial cells and disorganized vascular development.
Next generation sequencing of VGAM

- International **collaborative** effort
  - Initiated in 2016

- NIH-financed - Centers for Mendelian Genomics

- Current participants:
  - Kristopher T. Kahle (**Principal Investigator**), Richard P. Lifton, Murat Gunel, Daniel Duran – **Lead genomics team** (Yale)
  - Darren B. Orbach, Edward R. Smith (Boston Children’s Hospital)
  - Alejandro Berenstein, (Mount Sinai Hospital)
  - Andrew Ducruet, Joseph Zabramski (Barrow Neurological Institute)
  - Bevery Aagaard-Kienitz (University of Wisconsin)
  - Georges Rodesch (Hôpital Foch)
  - Masaki Komiyama, (Osaka City General Hospital)
Goal – define the genomic landscape of VGAM

- Patient recruitment – REQUIRES MULTICENTER, COLLABORATIVE EFFORT → Over 50 radiographically-confirmed VGAM patients and their parents have been exome sequenced to date.
- Hassle-free DNA collection through buccal swabs → Pipeline allows for international shipments through certified mail.
- Large-scale, unbiased variant discovery.
- Promising results involving key developmental endothelial control pathways.

Workflow

Patient and family recruitment → Sequencing / bioinformatic analysis → Functional validation

*mutation discovery*
**Salient findings**

- Exome sequencing identifies all damaging mutations present in DNA coding regions of VGAM patients and their parents.
- Gene burden analysis (binomial test) detected **significant enrichment** in protein-damaging, transmitted mutations in *EPHB4*.

**EPHB4**

**Quantile-quantile plot depicting significant enrichment of EPHB4 mutations in VGAM when compared to expected, natural mutation rate by gene size.**

**VGAM EPHB4 mutants display:**

1. Reduced or absent tyrosine phosphorylation
2. Reduced or absent binding to RASA1

Representative immunoblots from HEK293 cells harboring transiently transfected constructs of VGAM-associated *EPHB4* mutations discovered through exome sequencing.
Additional findings

- Damaging mutations in 5 other genes of the ephrin family.
- Exome-wide significant mutational enrichment has been found in 2 more, novel genes.
- Study findings are currently in final stages of preparation for publication.

Goals

- **Continued sequencing** of VGAM patients and parents.
- Study is **ongoing and open to enrollment**.
  - A cohort of 50 VGAMs has yielded significant results, hence, **further sequencing is warranted**
  - **Full funding** for VGAM exome sequencing through NIH-Centers for Mendelian Genomics at Yale
- **All collaborators are welcome** – strength through numbers!
- **If you are interested in participating** feel free to touch base with Dr. Kristopher Kahle at kristopher.kahle@yale.edu or come find me after the talk for further details.
What about the dural sinuses, stenosis, flow-mechanistic explanations of VGAM, etc.?
Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

Max A. Tischfield,1,4,5 Caroline D. Robson,2,6 Nicole M. Gillette,1 Shek Man Chim,3 Folassade A. Sofela,1,4 Michelle M. DeLisle,1,4 Alon Gelber,1 Brenda J. Barry,1,4 Sarah MacKinnon,3 Linda R. Dagi,3,7 Jeremy Nathans,9,10,11,12

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A MRV

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C
Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

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Figure 2. CV Growth and Remodeling Is Temporally and Spatially Coupled with Skull Development

(A–C) Wax-plate reconstructions of human fetuses depicting growth and remodeling of the dural CV (Streeter, 1921). (A) Three plexuses (1 = anterior [antPlexus], 2 = middle [midPlexus], 3 = posterior [posPlexus]) drain into the primitive head vein (PHV) adjacent to the eye and trigeminal ganglia (tg). (B) First remodeling step results from an anastomosis between the antPlexus and midPlexus to form the transverse sinus (TVS, blue lines and arrows). The PHV regresses. (C) Second remodeling step results from an anastomosis between the midPlexus and posPlexus to form the sigmoid sinus (SgS, red line and arrows), located above the temporal bone (tempBone, tb) (TVS, blue line and arrows).

(D–F) Z stacks of E11.5 (D), E12.75 (E), and E13.75 (F) mouse embryos stained with endomucin. Growth and remodeling of the CV are highly conserved with humans. Blue and red arrows indicate TVS and SgS, respectively.
Humans with Twist1 mutations and craniosynostosis have dural venous sinus abnormalities

The investigators developed tools that allowed specific spatial manipulation of the Twist1 pathway within specific cell types (skull, dura, pia/arachnoid, endothelial cells)

Surprisingly, Twist1 is dispensable in endothelial cells, but required for specification of osteoprogenitor cells that differentiate into preosteoblasts that produce bone morphogenetic proteins (BMPs)

Twist1 loss in osteoprogenitor cells and dura causes skull and vascular defects

Bmp2/4 loss from mesoderm-derived preosteoblasts/dura causes skull and venous sinus defects

Venous endothelium has receptors for BMP

The effect on the venous sinuses must be paracrine!
Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

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INTRODUCTION

Twist1 appears normal, suggesting that morphogens in proximity to the coronal suture and osteogenic front of the parBone. (Bottom) High levels of Twist1 expression occur in osteo-PCs within the coronal suture and periosteum (white dashes), but protein levels are low in Runx2/ALP+ Pre-OB.

(F) E12.5 transverse section through the head at the level indicated in the top panel of (H). High levels of Twist1 expression co-localize with Runx2 in the frontal and parietal bone periosteum (frBone [fb] and parBone [pb]) and in the coronal suture (corSuture [cs]). Weaker expression is seen in periosteal dura (periDura [pd]) and inner dura (iD), and the arachnoid mater/pia (meninges, m). TVS and antPlexus grow and remodel in periDura underlying the corSuture and parBone.

(H) Top) E12.75 mouse head showing endogenous ALP activity in frBone and parBone pre-OB. (Middle) Transverse section, adjacent to (G). The TVS remodels in proximity to the corSuture and osteogenic front of the parBone. (Bottom) High levels of Twist1 expression occur in osteo-PCs within the corSuture and periosteum (white dashes), but protein levels are low in Runx2/ALP+ Pre-OB.
Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

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SUMMARY

Twist1 mutants (n = 3). a, arterial.

Figure 3. Twist1 Mutants Have Perturbed CV Development Despite Normal Arterial Growth and Remodeling

(A–C) Z stacks of the venous plexuses stained with endomucin detailing the growth and remodeling of the CV. (A) Primitive head vein (PHV, green arrows) and antPlexus (ap, outlined in red) in an E11.75 control. The antPlexus in Twist1CKO−/--;Pdgfrb-cre (n = 4) and Twist1CKO−/--;Sm-Cre (n = 5) embryos have a significant reduction in vessel branching and more empty space (lacunarity, right graphs). (B) By E12.75, the TVS (blue arrows) has remodeled in controls, but the PHV is still present in Twist1CKO−/--;Pdgfrb-cre (n = 5) and Twist1CKO−/--;Sm-Cre (n = 6) embryos. antPlexus branching remains reduced. (C) By E13.75, the SgS remolds in control (F) E12.75 whole-mount smooth muscle actin staining of the arterial head vasculature. Arterial growth and remodeling and smooth muscle coverage appear normal in Twist1CKO−/--;Pdgfrb-cre embryos (n = 5).
Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

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Figure 4. Wild-Type Mice Have TVS Morphogenetic Variation that Is Skewed toward Unilateral Regression in Twist1 Mutant Mice

(A) Top: superior sagittal sinus (SSS, paired arrows) and paired TVS (arrows) meeting at the sinus confluence (SC) on the dorsal surface of control and mutant E13.75 brains. The antPlexus is boxed. Middle: magnified images of the boxed areas detail TVS regression (single arrows) and poor development of the antPlexus (double arrows) in Twist1CKO/WT;Pdgfrb-Cre and Sm22a-Cre mutants. Bottom: unilateral regression of the TVS (arrow) is fully penetrant and complete by E15.5 in Twist1CKO/WT;Pdgfrb-Cre and Sm22a-Cre mutants.

(E) Top: E18.5 Twist1CKO/WT;Sm22a-Cre embryo. The left TVS is tortuous and hypoplastic and the right TVS has regressed (asterisk). A persistent occipital vein is present and drains into the SgS (arrowheads). Middle and bottom: the remaining TVS is hypoplastic in E18.5 Twist1CKO/WT;Sm22a-Cre embryos and the right side is

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Cerebral Vein Malformations Result from Loss of Twist1 Expression and BMP Signaling from Skull Progenitor Cells and Dura

Figure 6. BMP2 and BMP4 Are Required for CV Growth and Remodeling
(C) Top: E18.5 dorsal views of the head depicting the SSS and paired TVS and SgS in controls and three- and four-allele-loss Bmp2/4;Pd-Cre embryos. Bottom: the mean width of the dominant TVS is significantly smaller in all Bmp2/4;Pd-Cre mutant genotypes, and the major vessel is hypoplastic or absent. The SSS is often hypoplastic, truncated, and/or split (arrows).
• Venous sinus malformations result from primary or secondary loss of paracrine BMP signaling from preosteoblasts and dura
• Dural venous sinus angiogenesis is strongly dependent on the development of neighboring tissue, and likely upon the growth environment of each fetus
• Arterial development is unaffected. High levels of NOTCH, found in arterial endothelium, antagonize BMP, while veins are primed to respond to BMPs
• Thus, venous sinus angiogenesis is isolated from arterial angiogenesis and is an independent process
• In terms of VGAM, we may conclude that the malformation itself, induced by its own genetic pathway, is overlaid in each patient onto a separately determined venous sinus drainage architecture, potentially leading to drastically different clinical evolution across patients
Summary

- Clinical presentation of VGAM has been well delineated for >50 years
- VGAM develops in a unique embryological environment characterized by arteriovenous endothelial loops, during a developmental stage where the dominant arteries are the choroidal vessels and the dominant vein the MPV
- Mechanical/developmental hypotheses have dominated thinking about VGAM etiology for >30 years (e.g., VGAM resulting from an episode of in utero thrombosis, VGAM resulting from venous sinus outlet stenosis, venous sinus stenosis being a consequence of high flow)
- While endovascular treatment has no doubt improved prognosis, the prenatal diagnosis is still devastating, and there remains much room for improved therapeutic approaches
- Major areas of clinical uncertainty: how much treatment is enough? What to do for the older child/adult with a newly diagnosed asymptomatic VGAM?
- Very recent genetic / cell biological developments herald a new era in our understanding of VGAM (and arteriovenous lesions more broadly). From a genetic perspective, the classical distinction between vascular tumors and vascular malformations is not as rigid as had been believed
Summary

• These recent developments are likely to lead to completely novel therapeutic approaches, with drug targets in the RAS/ERK/mTOR pathway.

• The relationship between germline and somatic mutations in VGAM remains unclear.

• Interestingly, development of the venous sinuses is dependent not on the above intrinsic genetic factors, but rather results from paracrine effects of pathways related to skull and meningeal development. Individual idiosyncrasies of a given embryo’s environment may play a key role.

• Thus the VGAM itself, induced by its own genetic pathway, is overlaid onto a separately determined sinus drainage architecture, potentially leading to drastically different clinical evolution across patients. The independently-developed venous sinus architecture may serve as the “second hit” or “developmental accident” required to activate a potential VGAM into a clinical VGAM in vulnerable patients.

• Many of our “intuitive” mechanistic hypotheses are being upended and more are likely to be upended by new cellular/genetic developments. We need to be comfortable expecting the unexpected.
It snowed in one of the hottest places in the world

By AJ Willingham, CNN

Updated 12:33 PM ET, Tue January 9, 2018

On Sunday, Ain Sefra, a desert town in Algeria known as the "Gateway to the Sahara," experienced a substantial amount of snow for reportedly the third time in 40 years.

Some reports say parts of the area got nearly 15 inches of snow, but Ain Sefra officially reported less than one inch.

It was enough to provide some otherworldly visuals from an area that routinely sees some of the hottest temperatures on earth during the summer.
Thank You