Vein of Galen Aneurysmal Malformations

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Vein of Galen Malformation: Diagnosis and Management

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vessel ligation. Forty-six patients (78.0%) were treated by [illegible]. In 79 patients (22.2%), there was no treatment or no details of treatment were available. 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

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

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What is a vein of Galen malformation?

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VEIN OF GALEN MALFORMATION

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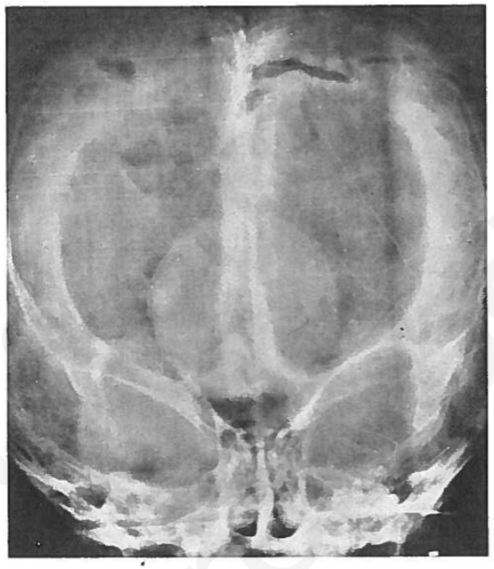

Figure 3 – (Patient 1) – Anterioposterior view of a right common carotid angiogram, taken at a later phase than in figure 2, showing the vein of Galen as a midline mass of contrast material between the dilated lateral ventricles.

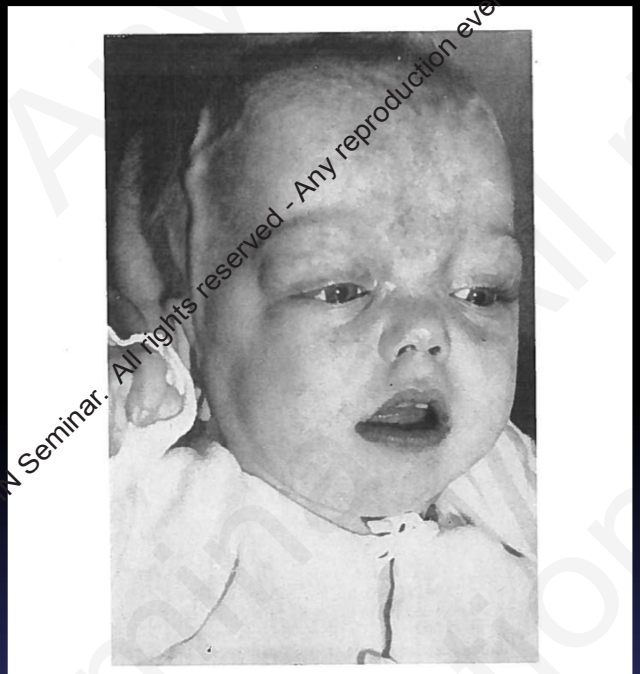

Figure 9 – (Patient 4) – Typical skin manifestations showing distended and tortuous scalp veins and a large telangiectatic lesion above the glabella.

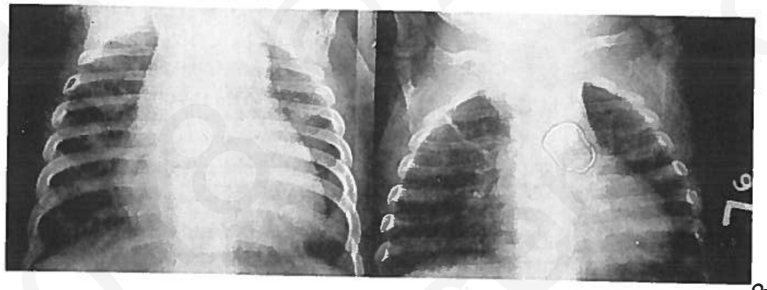

Figure 10 – (Patient 4) – Chest x-ray showing the effect of ligation of the feeding arteries of the malformation on the cardiovascular system. Preoperatively the heart is enlarged with a cardiac thoracic ratio of 0.65, and the postoperative film shows a normal heart size with a cardiac thoracic ratio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

Original Paper

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Cardiac Findings in the Fetus with Cerebral Arteriovenous Malformation Are Associated with Adverse Outcome

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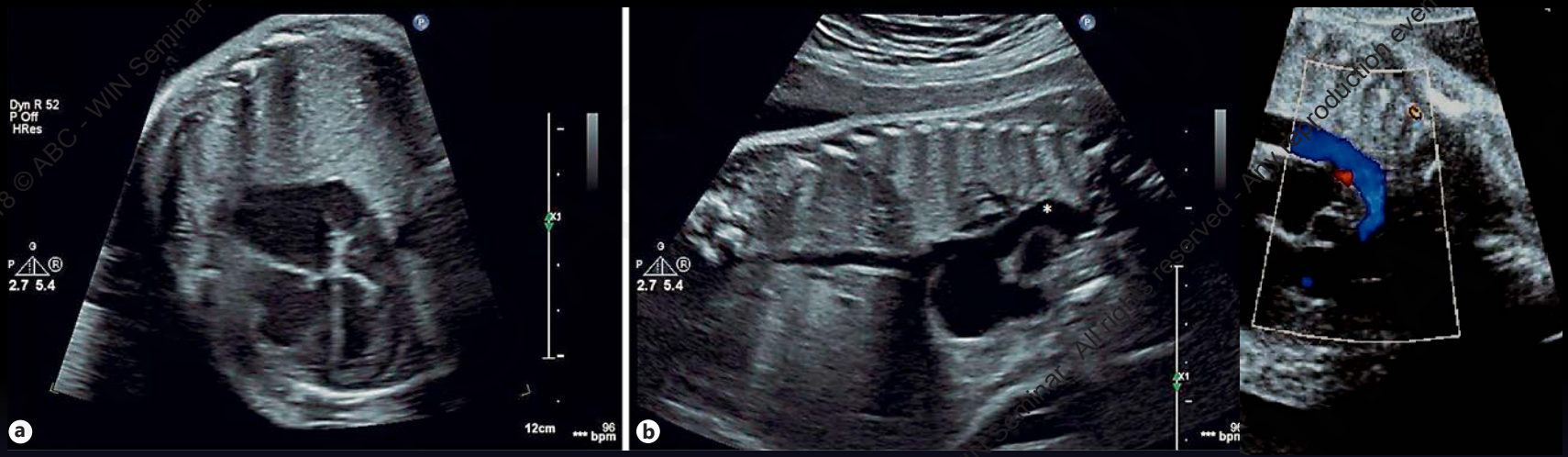
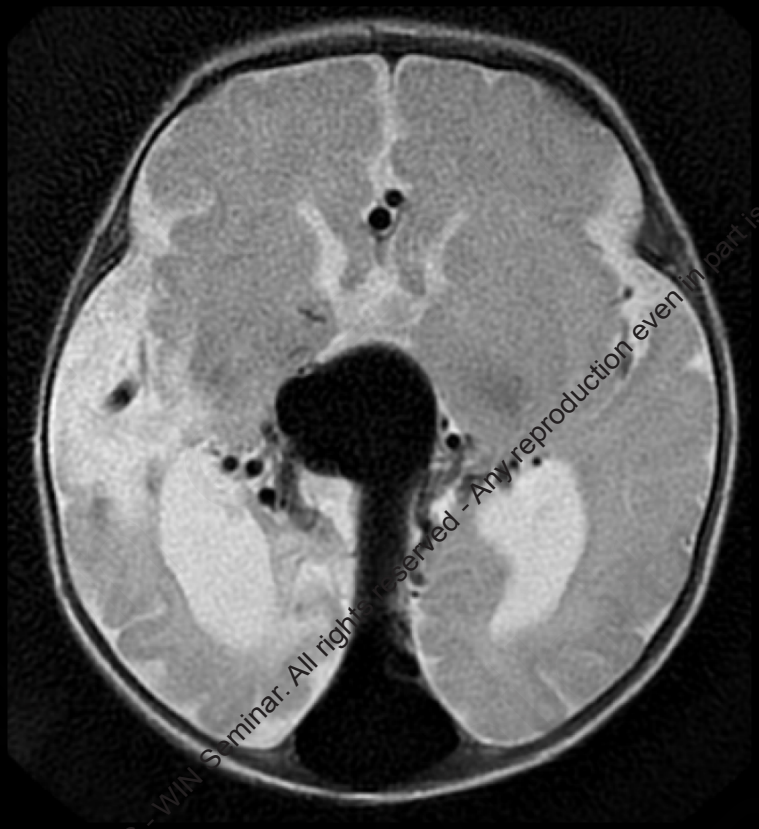
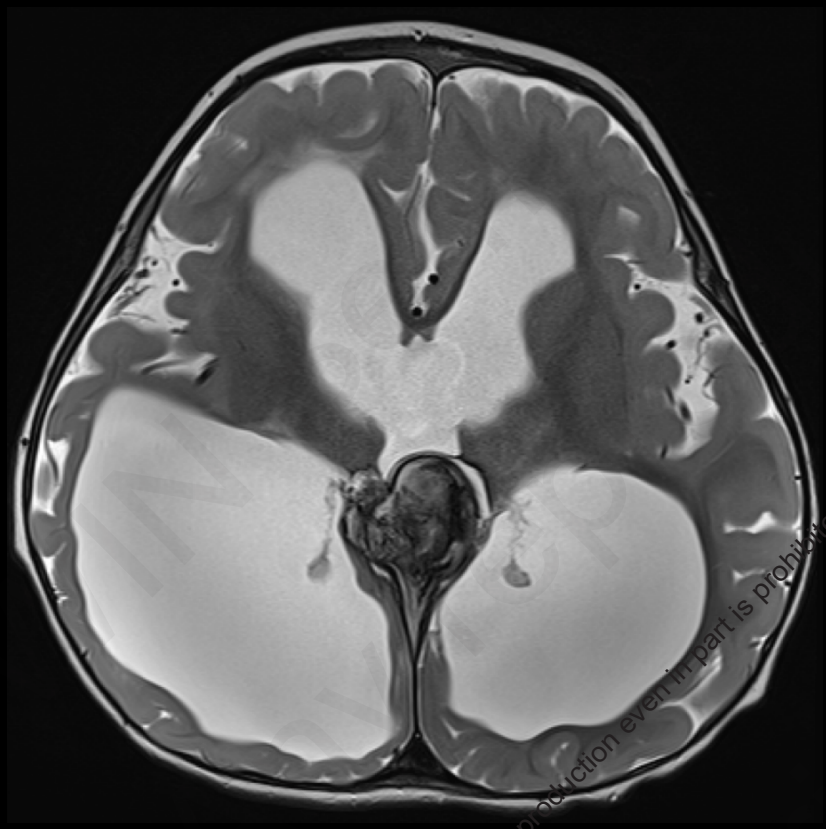


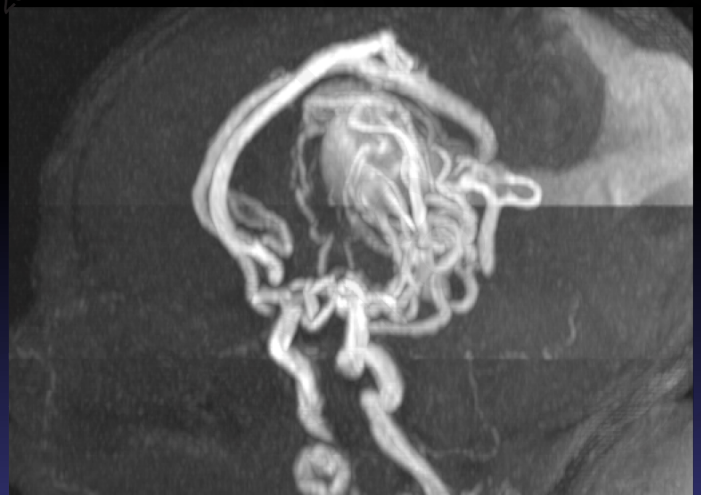
Fig. 1. a Four-chamber view illustrating dilation of the right atrium and ventricle. **b** Bicaval view illustrating severe dilation of the SVC (*) relative to the IVC. **c** Three-vessel view showing the dilated SVC (*) in cross section. **d** Long axis of the aortic arch showing retrograde flow around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

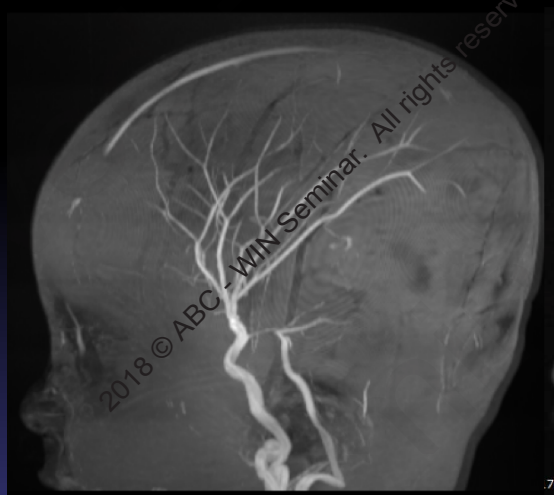


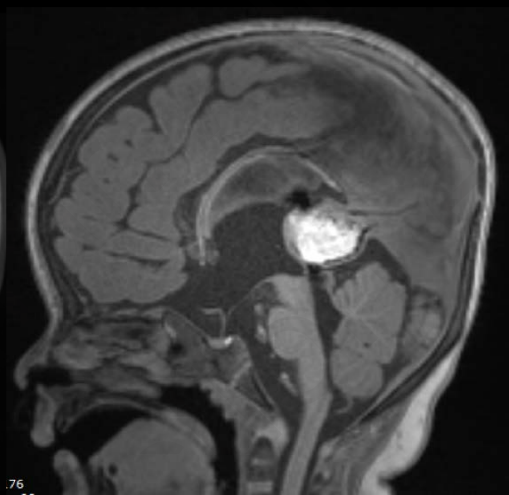


2 days

17 months







Extreme "Melting Brain Syndrome"

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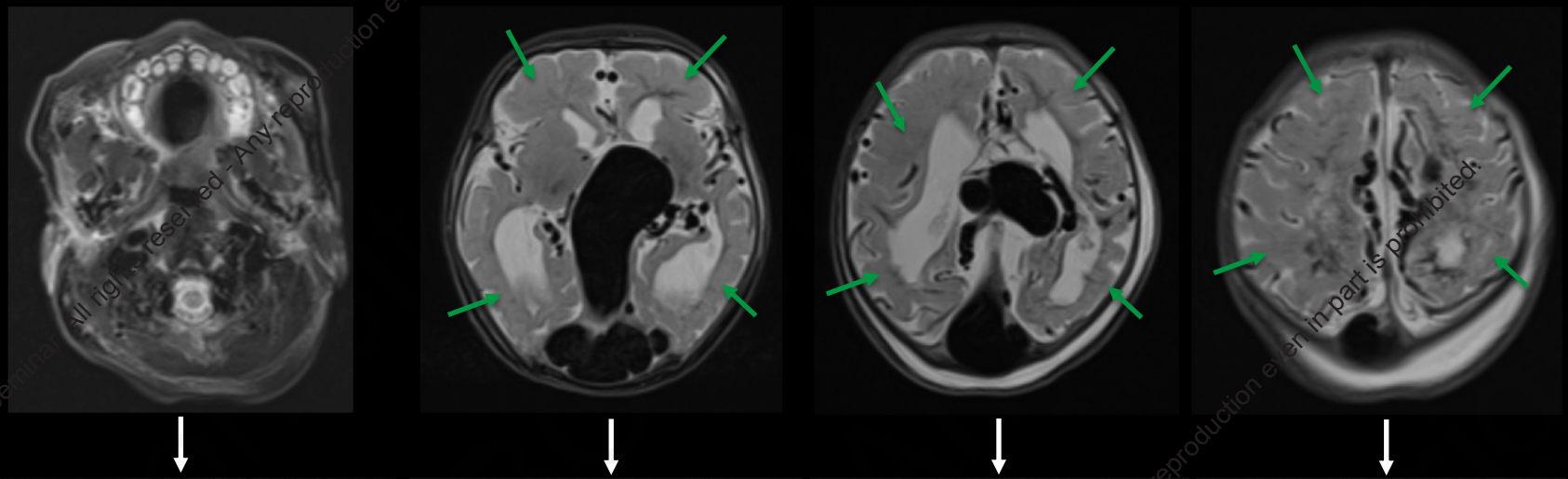
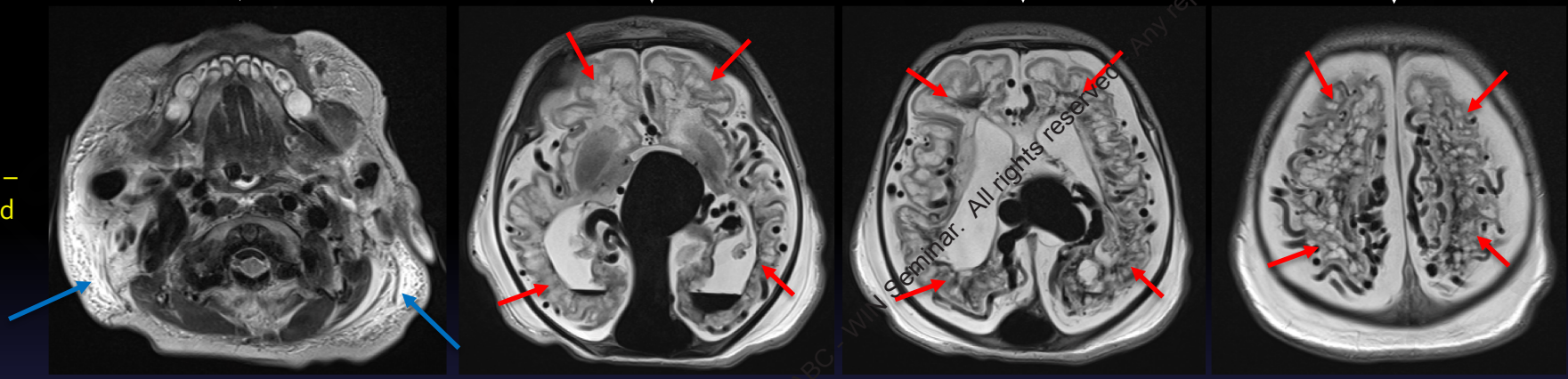
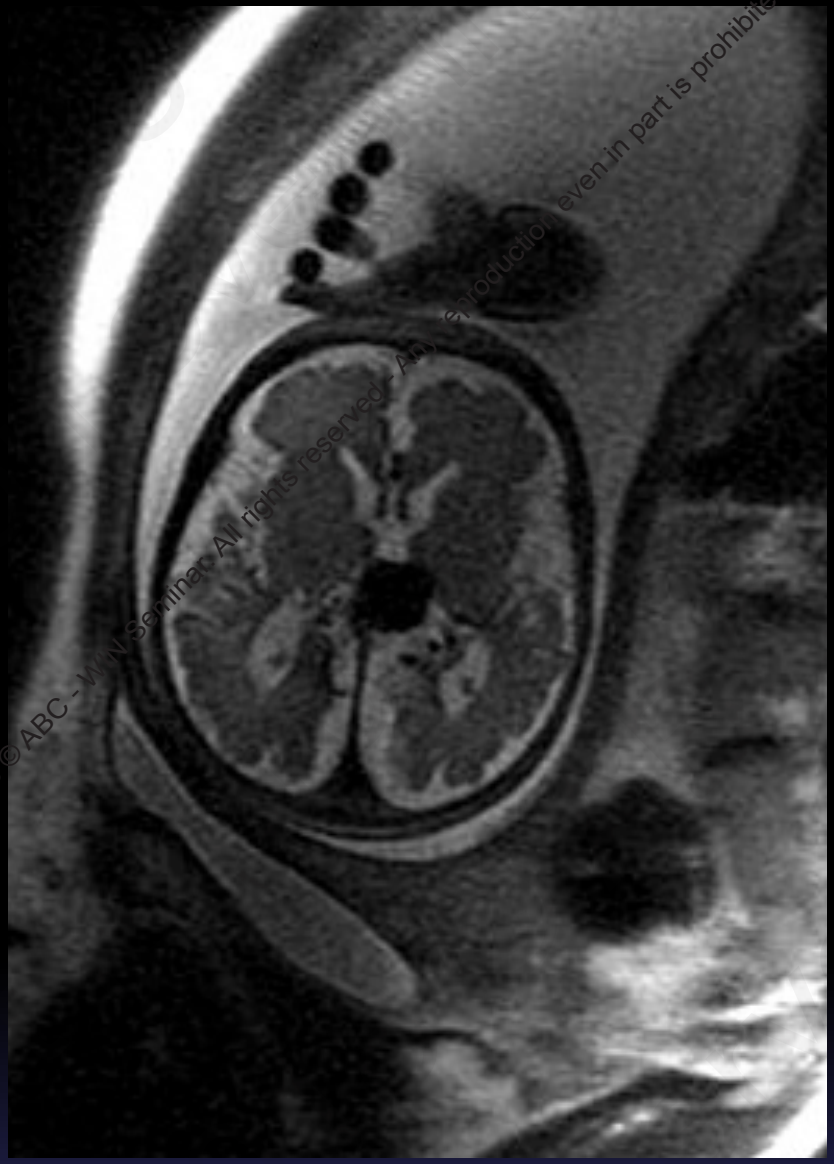
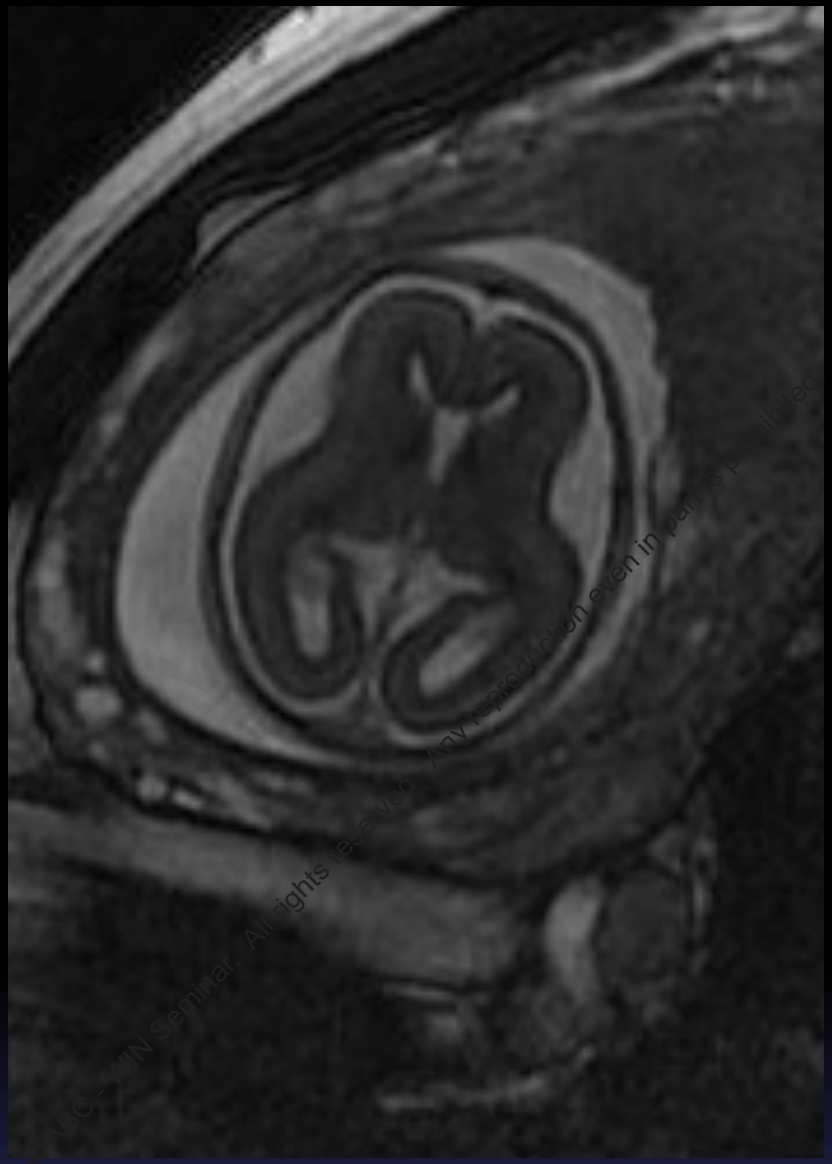
1 day old



5/16/2017 –
9 days old







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VEIN OF GALEN MALFORMATION

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Clinical syndromes with review of the literature

Evaluation of our eight patients and the case reports from the world literature resulted in a 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, with the major signs resulting from the marked effects on the cardiovascular system; during infancy in which 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 Riives (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."

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SPECIAL ANNUAL ISSUE

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

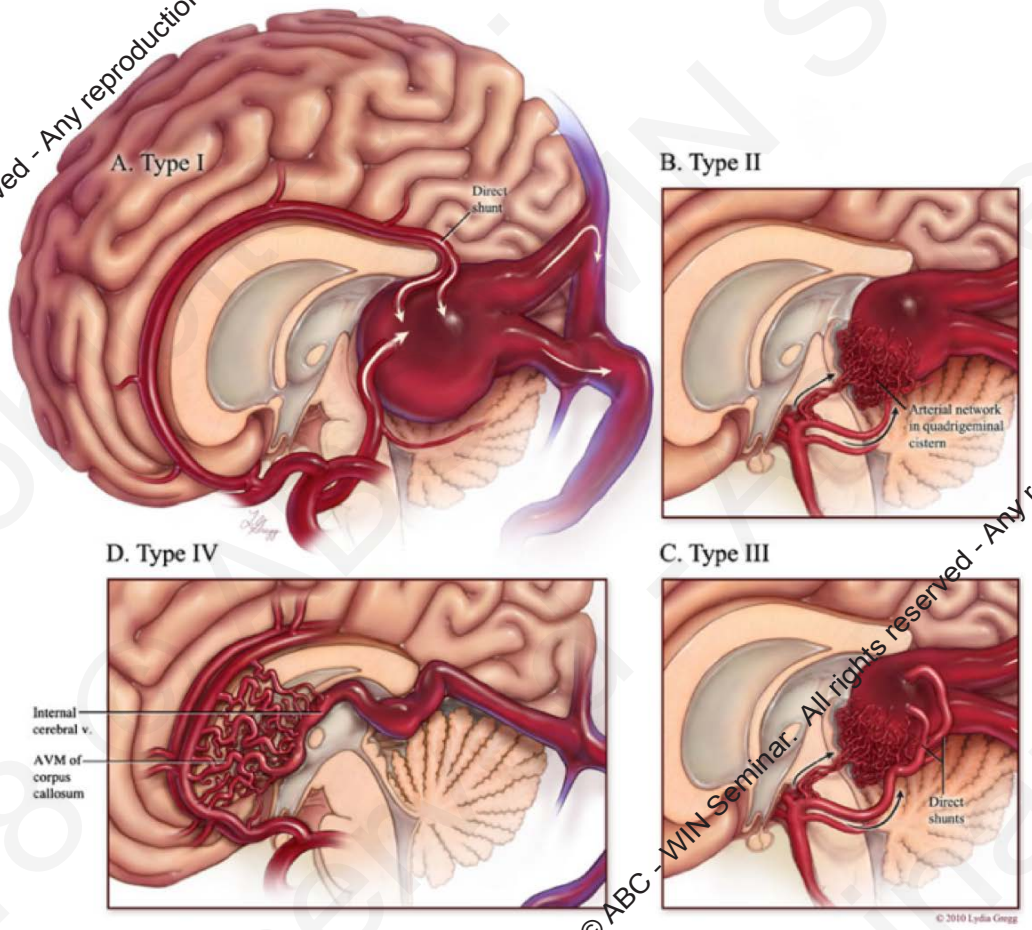

Fig. 1 VGAM classification (adapted from Yasargil [32]). **a** VGAM Type I: one or several direct arteriovenous shunts are connected to the aneurysmal venous collector of the VGAM. Compression of the cerebral aqueduct by the venous collector is illustrated. **b** VGAM Type II: an arterio-arterial, "nidus-like" network is interposed between the arterial feeders and the venous collector. Note the presence of typical transmesencephalic 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

Childs Nerv Syst (2013) 29:907–919
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REVIEW PAPER

Pediatric intracranial arteriovenous shunts: a global overview

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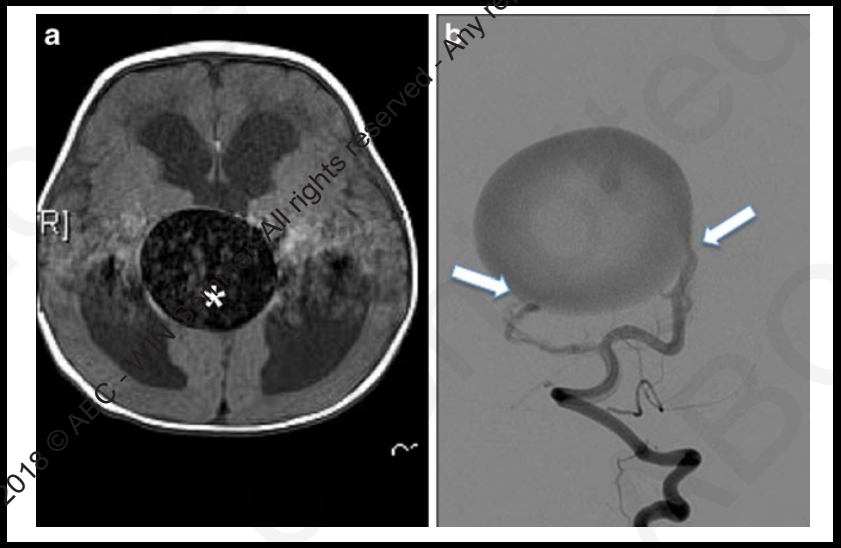

Fig. 2 Mural type of vein of Galen malformation. **a** Axial T1-weighted MRI: note the large venous ectasia of the medial vein of the prosencephalon (*asterisk*). The arterial feeders are not clearly depicted: the picture evokes a direct fistulous aspect of the shunt. Hydrodynamic disorders have occurred with hydrocephalus and subependymal CSF resorption. **b** Angiography with left vertebral artery injection, anteroposterior (AP) view demonstrates the mural type of vein of Galen malformation with two direct shunts in the wall of the venous ectasia vascularized by posteromedial choroidal arteries (*arrows*)

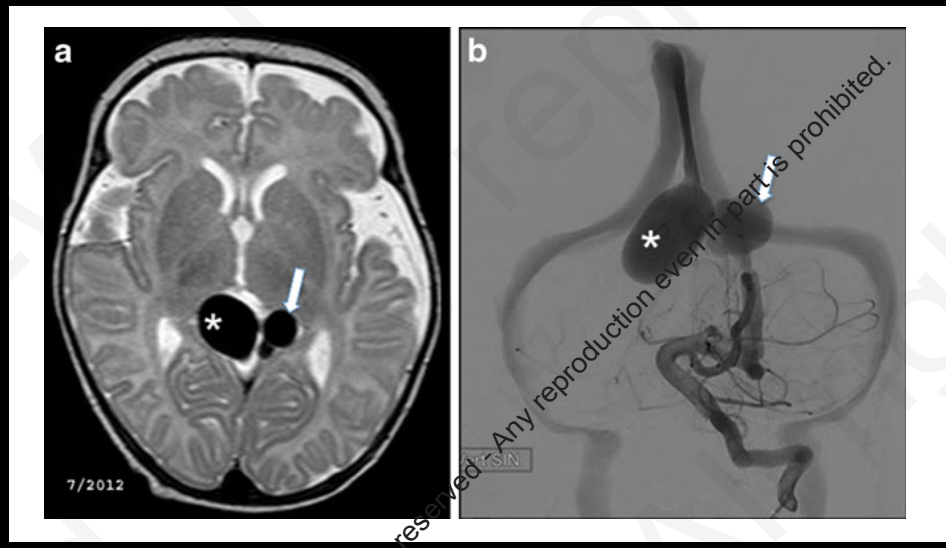

Fig. 4 Vein of Galen aneurysmal dilatation. **a** T2-weighted MRI, axial view: although the vein of Galen is dilated (*asterisk*), another venous ectasia is detected on the left lateral flank of the vein of Galen (*arrow*) but separated from it. This picture is suspected to correspond to a first venous ectasia that drains initially a CAVF, before joining the vein of Galen itself. Note the hydrovenous disorders represented by cortical atrophy with wide sulci in this infant child. **b** Left vertebral angiography, AP view. The choroidal AVF is well depicted, draining first into a choroidal venous ectasia (*arrow*) before joining the vein of Galen (*asterisk*). This lesion corresponds to a "true" CAVM draining into a dilated vein of Galen and not to a vein of Galen malformation

VGAM

VGAD

Normal and Abnormal Embryology and Development of the Intracranial Vascular System

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Neurosurg Clin N Am 21 (2010) 399–426
doi:10.1016/j.nec.2010.03.011

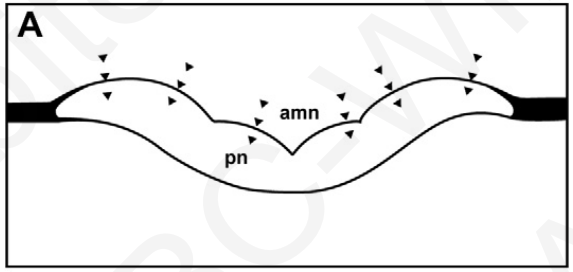
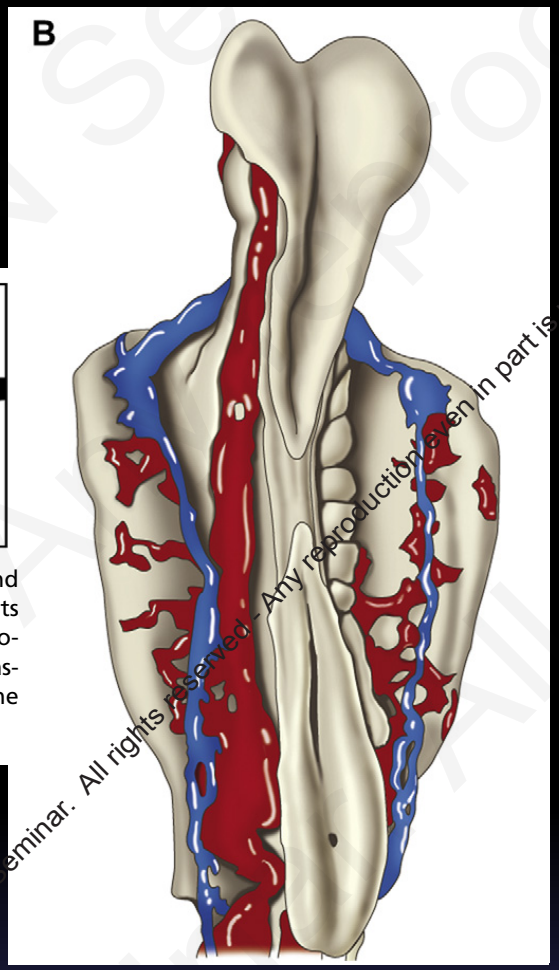


Fig. 1. Week 4. The neural tube is not closed yet, and the neural plate (pn) receives oxygen and nutrients from the surrounding amniotic fluid (amn) (*A*). Endothelial vasculogenesis is building up the cardiovascular organ system that already extends toward the cephalic extremity of the embryo (*B*).



First period of CNS vascular development:
extra-embryonal supply, with the open neural tube nurtured by the amniotic fluid

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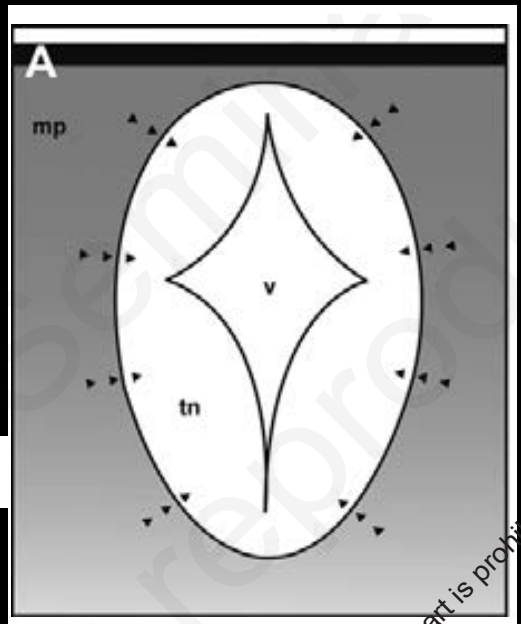
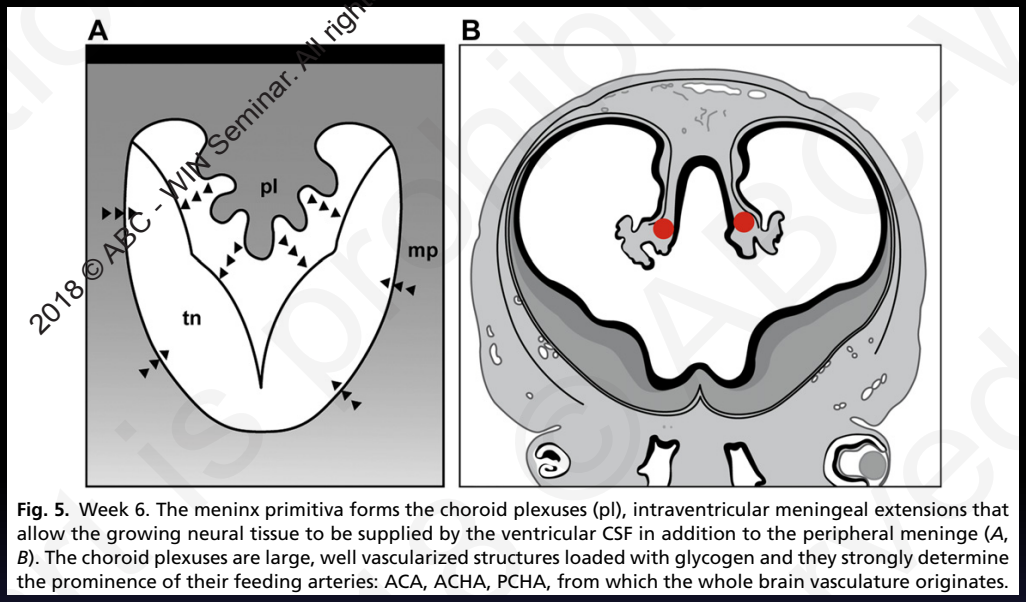


Fig. 2. Week 5. The neural tube is embedded into a dense connective tissue, the meninx primitiva (mp) (*A, B*) that contains vascular loops (*B*) connected to the dorsal aortae and cardinal veins. They are forming the primordial brain vascular meshwork, from which oxygen and nutrients diffuse to the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



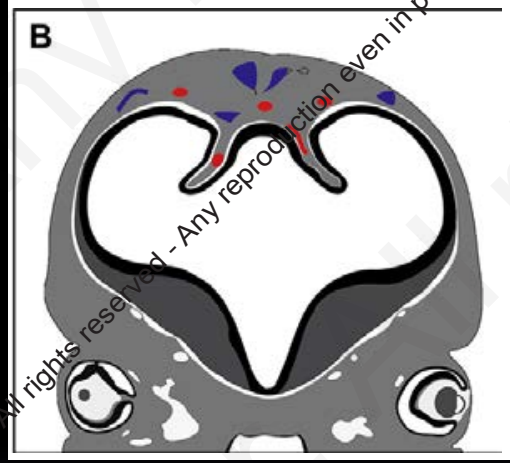


Fig. 5. Week 6. The meninx primitiva forms the choroid plexuses (pl), intraventricular meningeal extensions that allow the growing neural tissue to be supplied by the ventricular CSF in addition to the peripheral meninge (*A, B*). The choroid plexuses are large, well vascularized structures loaded with glycogen and they strongly determine the prominence of their feeding arteries: ACA, ACHA, PCHA, from which the whole brain vasculature originates.

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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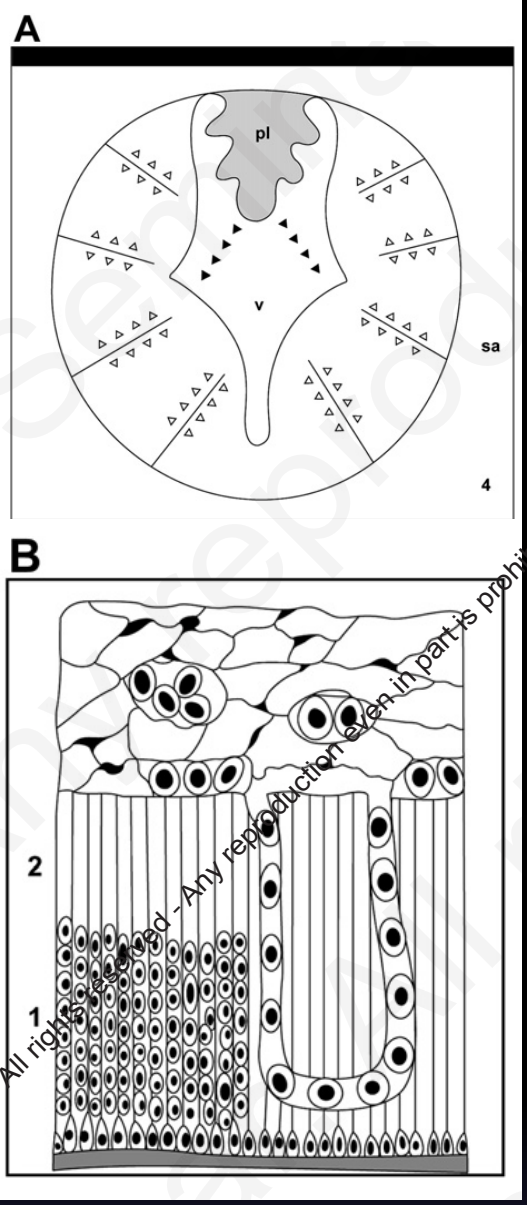

Fig. 7. Week 6 onward. When the neural tissue becomes too thick to be fed by extrinsic diffusion alone and while the germinal matrix develops, the intrinsic vascularization appears (*A*), while the meninx primitiva becomes the subarachnoid space (sa). Intrinsic vessels form by angiogenesis: capillaries grow from the surface and extend toward the periventricular germinal zone where they connect together to form primitive arterio-venous loops (*B*). The cortex itself is not significantly vascularized until well after mid gestation.

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

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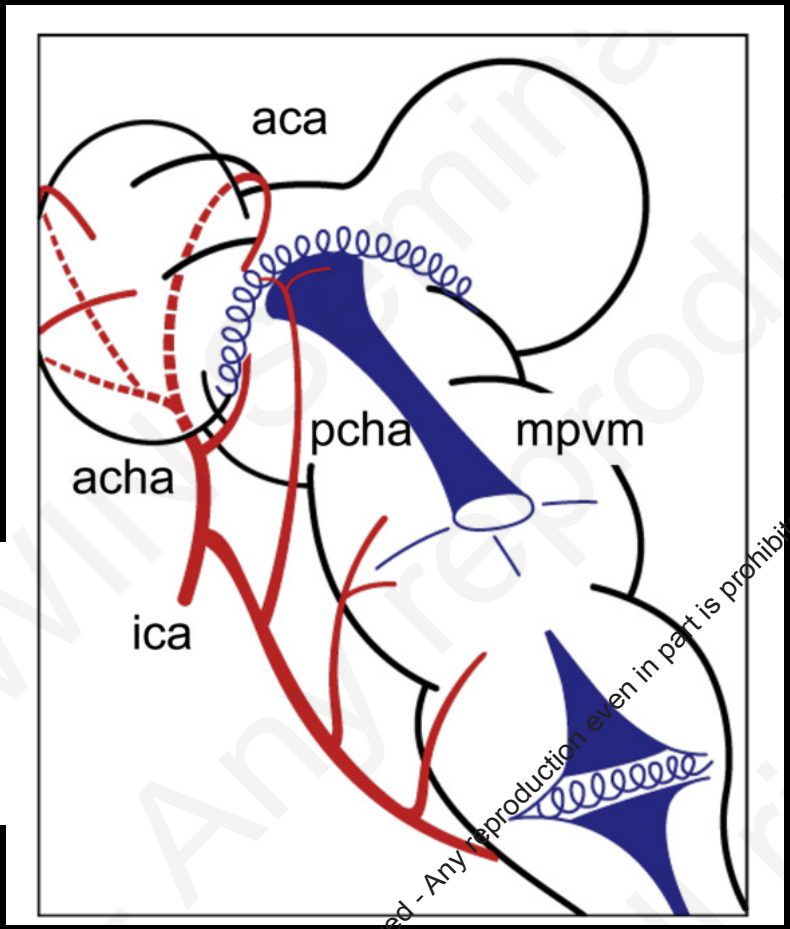

Fig. 8. Weeks 6–11. The choroid stage. The ACA cranially, the ACHA caudally encircle the neck of the hemispheres toward the tela choroidea and the plexuses, together with the PCHA, branch of the midbrain arteries. The tela choroidea and plexuses are drained by a single, median dorsal bridging vein (median 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.

Neuroradiology (1989) 31: 109–128

Neuro radiology

Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation

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- 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

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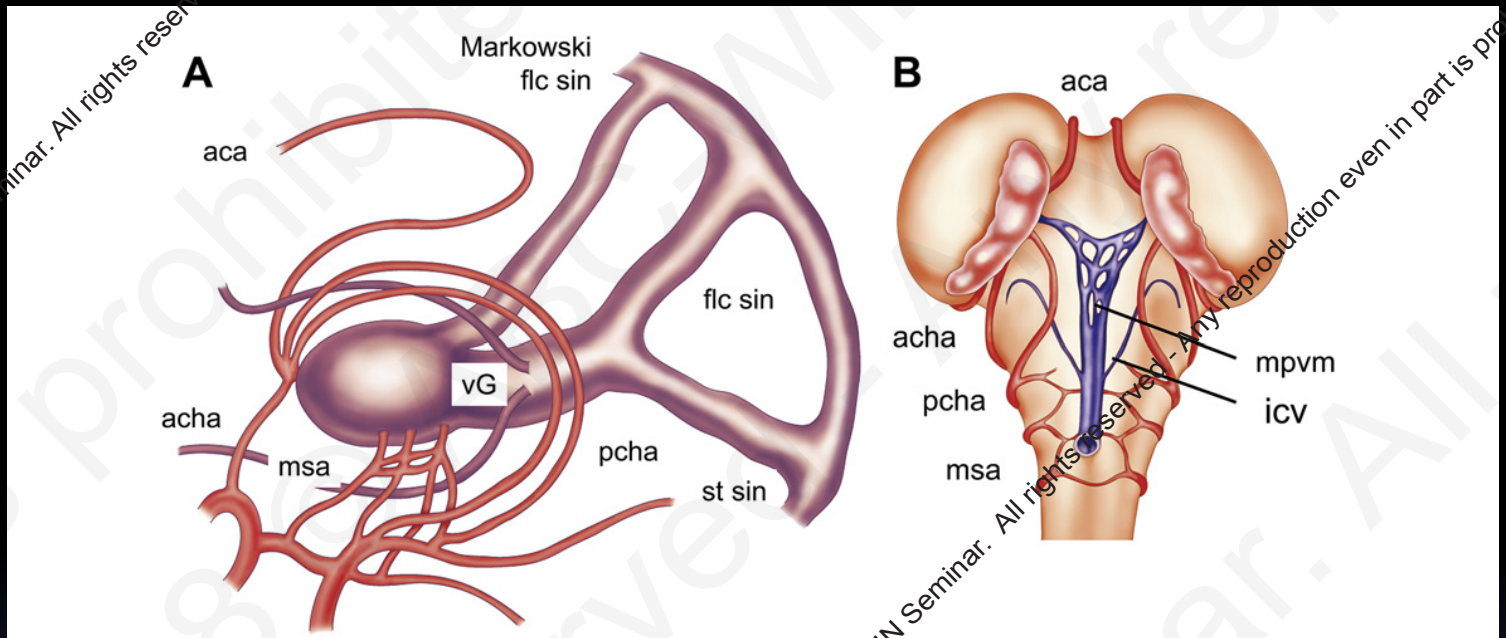

Fig. 19. Vein of Galen aneurysm. The fistulae are extracerebral, in the wall of the venous sac. They are fed by the originally choroidal arteries anteriorly (ACA, ACHA, PCHA) and by the dorsal midbrain arteries posteriorly. The venous sac is single, midline. It may be drained dorsally toward the straight 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*).

The Management of Vein of Galen Aneurysmal Malformations

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Neurosurgery 59:S3-184-S3-194, 2006 DOI: 10.1227/01.NEU.0000237445.[illegible].16

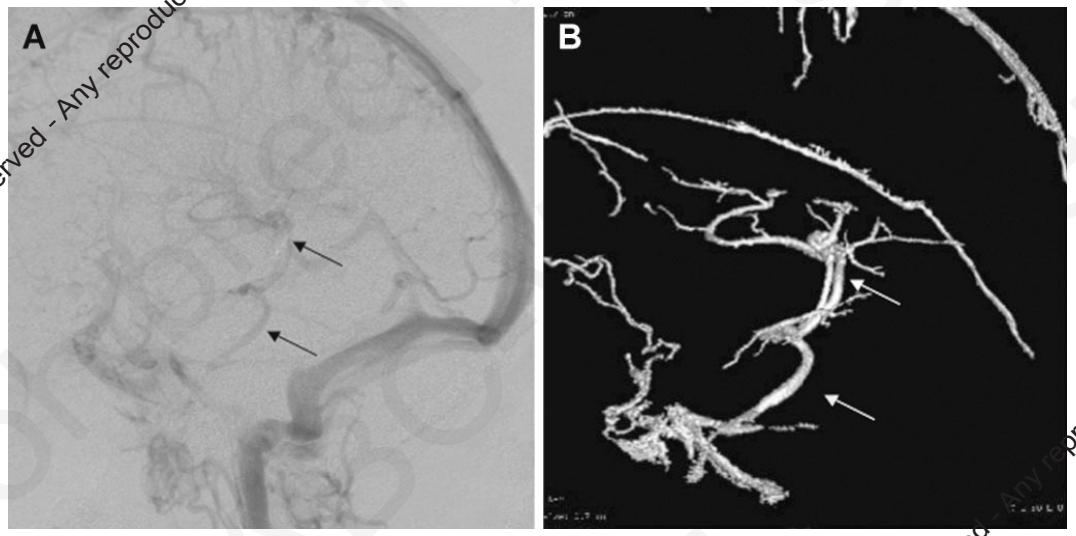


FIGURE 4. *Late venous phase of vertebral angiogram (A) and three-dimensional angiographic (B) aspect demonstrating the ε-shaped deep venous drainage into the superior petrosal sinus (arrows). Because there is no vein of Galen, the deep venous system has to find an alternate route to drain. Thalamostriate 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.*

Childs Nerv Syst (2004) 20:91–97
DOI 10.1007/s00381-003-0841-y

ORIGINAL PAPER

O. Levrier
P. H. Gailloud
M. Souei
L. Manera
H. Brunel
C. Raybaud

Normal galenic drainage of the deep cerebral venous system n two cases of vein of Galen aneurysmal malformation

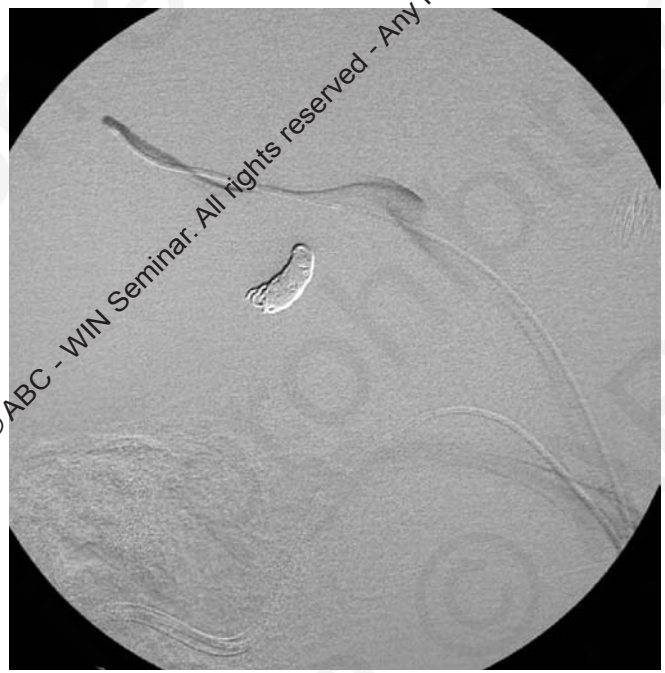


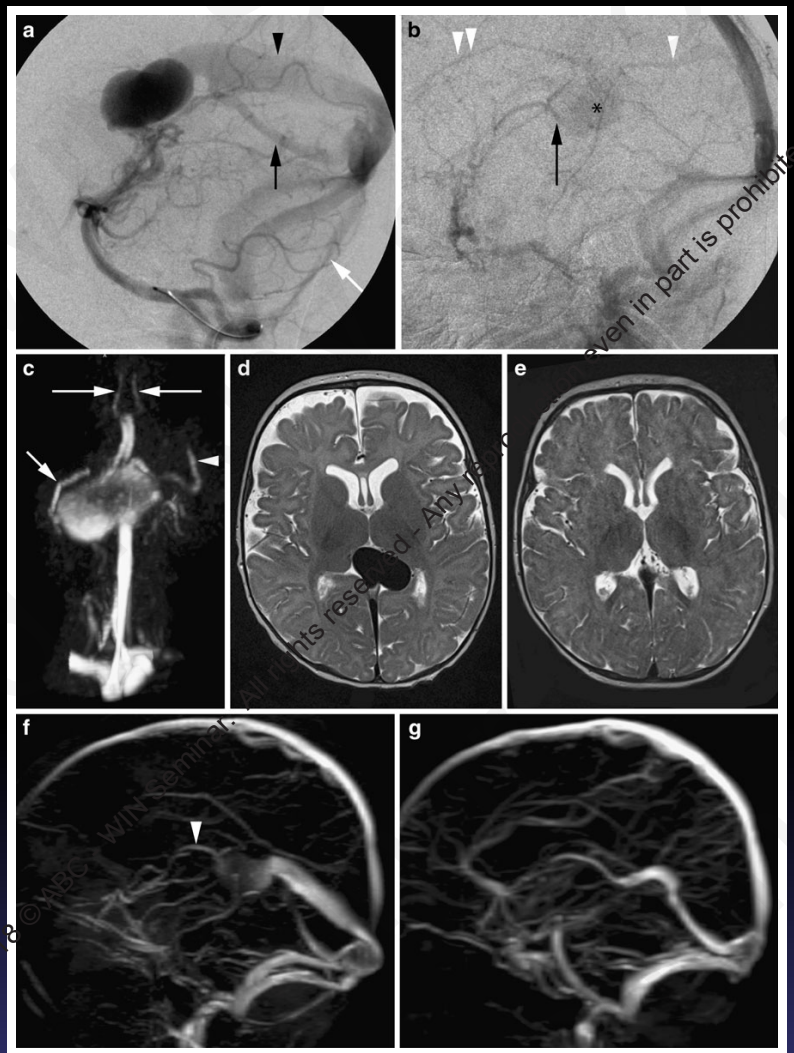
Fig. 12 Superselective retrograde injection into the internal cerebral vein demonstrates the normal anatomy of the deep venous system despite the vein of Galen malformation

Childs Nerv Syst (2010) 26:1367–1379
DOI 10.1007/s00381-010-1257-0

SPECIAL ANNUAL ISSUE

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



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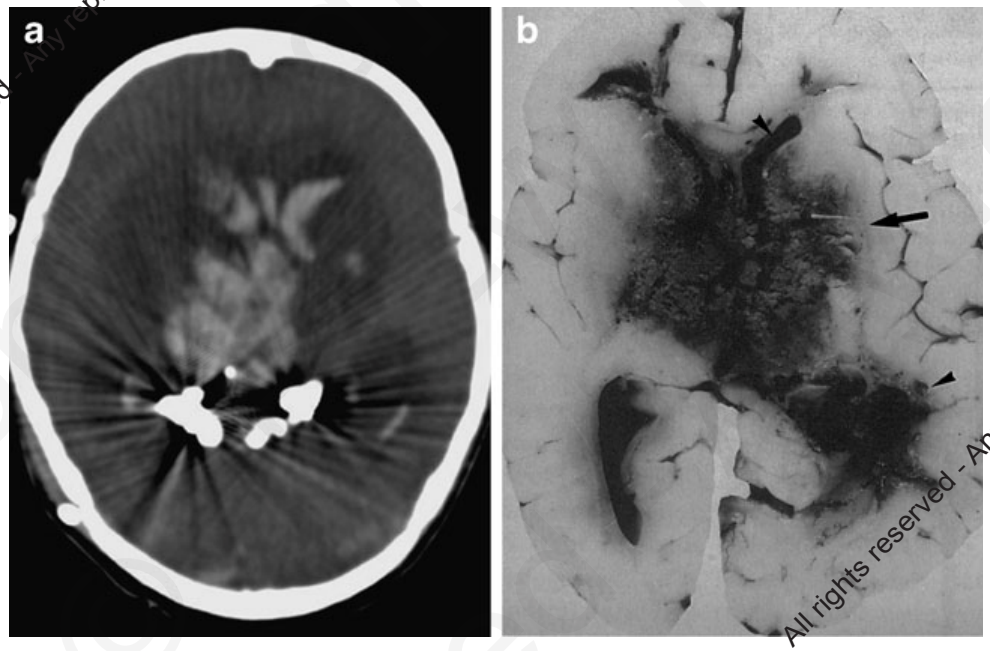

Fig. 5 Baby girl presenting at birth with cardiac and respiratory failure, successfully managed by three sessions of transarterial embolization during the first week of life. After an initially favorable follow-up, she was readmitted emergently at 1 month of age for severe, life-threatening pulmonary 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)

Neuroradiology (1989) 31: 109–128

Neuro radiology

Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation

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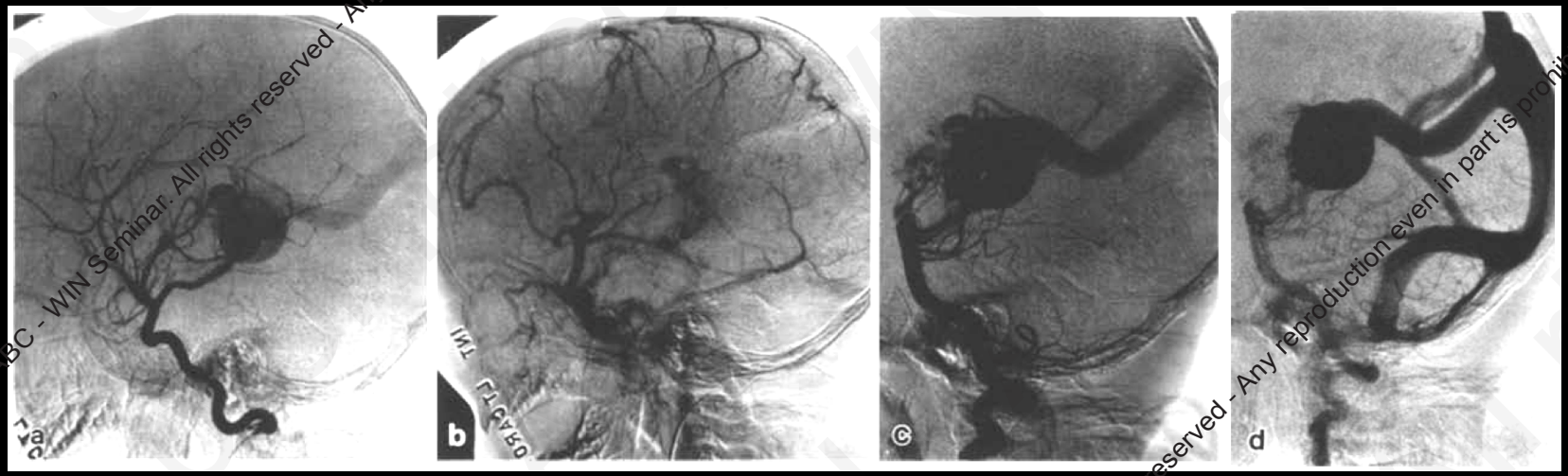

"Overall, 18 of 20 patients with adequate studies exhibited abnormalities of dural venous drainage, consisting of a falcine sinus, a falcine venous loop or either focal or diffuse lack of opacification of normal dural sinuses"

P. Lasjaunias[1,2]
K. Ter Brugge[2]
L. Lopez Ibor[1]
M. Chiu[2]
O. Flodmark[3]
S. Chuang[4]
J. Goasguen[5]

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

- *"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

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ORIGINAL RESEARCH
INTERVENTIONAL

Occlusion of Posterior Fossa Dural Sinuses in Vein of Galen Malformation

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

AJNR Am J Neuroradiol 37:1092–98 Jun 2016

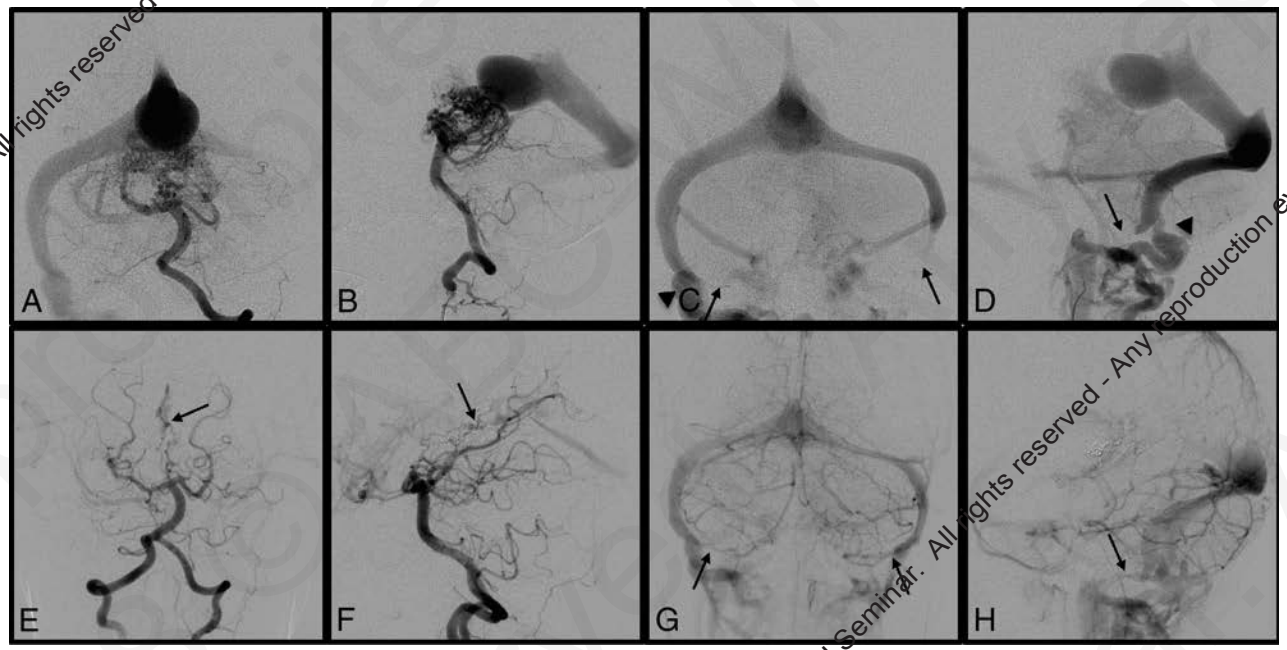

FIG 1. Case 8. A 13-month-old boy was diagnosed with VGM due to macrocrania and prominent scalp and facial veins. Left vertebral artery angiograms before the first embolization demonstrated a VGM in the arterial phase (*A* and *B*) and complete occlusion of the left sigmoid sinus and near-occlusion of the right sigmoid sinus in the venous phase (*C* and *D*, *arrows*). 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.

P. Lasjaunias[1,2]
K. Ter Brugge[2]
L. Lopez Ibor[1]
M. Chiu[2]
O. Flodmark[3]
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Hemangiomas and Vascular Malformations in Infants and Children: A Classification Based on Endothelial Characteristics

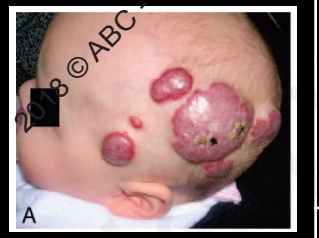
John B. Mulliken, M.D., and Julie Glowacki, Ph.D.
Boston, Mass.

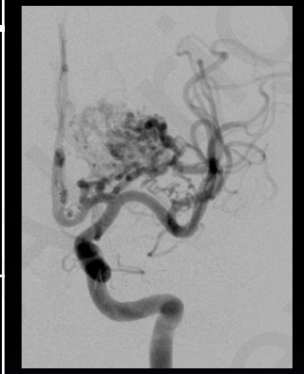
PLASTIC AND RECONSTRUCTIVE SURGERY, *March 1982*

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

-Confucius

Hemangiomas	*Malformations*
Proliferating phase Involuting phase	Capillary Venous Arteriovenous Lymphatic
Endothelial cell proliferation	Normal endothelial cell cycle
Rapid postnatal growth and slow involution	Grow commensurately with the child
Female:male, 5:1	Female:male, 1:1





PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

TABLE 2 2014 ISSVA Classification of Vascular Anomalies

Vascular Anomalies				
Vascular Tumors	Vascular Malformations			
	Simple	Combined	Of Major Named Vessels	Associated With Other Anomalies
Benign	CM	See Table 5	See text	See Table 6
Locally aggressive or borderline	LM			
	VM			
Malignant	AVM			
	Arteriovenous fistula			

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?

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The Management of Vein of Galen Aneurysmal Malformations

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Ricardo Garcia-Monaco, M.D.
Department of Diagnostic and Interventional Neuroradiology, Hopital de Bicêtre, Le Kremlin Bicêtre, France, and Department of Radiology,

OBJECTIVE: The vein of Galen aneurysmal malformation (VGAM) is a arteriovenous malformation involving the vein of Galen forerunner. This arteriovenous malformation with venous drainage into a dilated, but al of Galen. Reports of endovascular treatment of VGAM in the literat disease from a purely technical viewpoint and often fail to provide sa results. To focus the therapeutic challenge to a strictly morphological fundamental aspects of neonatal and infant anatomy and fluid physiolog 20 years, our approach to VGAM has remained the same. Our experie patients with VGAM who were studied in Hospital Bicêtre between October 2002, allows us to describe the angioarchitecture, natural his ment of VGAM in neonates, infants, and children.

METHODS: Of our cohort of 317 patients, 233 patients were treated 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

Neurosurgery 59:S3-184-S3-194, 2006 DOI: 10.1227/01.NEU.0000237445.39514.16 www.neurosurgery-online.com

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

	Embolization	Abstention	Lost to follow-up	Total
Neonates	88 (5)	45	7	140
Infants	103 (8)	16	6	125
Children	42 (4)	6	4	52
Total	233 (17) 73.5%	67 (21.1%)	17 (5.4%)	317

TABLE 4. Bicêtre neonatal evaluation score[a]

Points	Cardiac function	Cerebral function	Respiratory function	Hepatic function	Renal function
5	Normal	Normal	Normal	—	—
4	Overload, no medical treatment	Subclinical, isolated EEG abnormalities	Tachypnea, finishes bottle	—	—
3	Failure; stable with medical treatment	Nonconvulsive intermittent neurologic signs	Tachypnea, does not finish bottle	No hepatomegaly, normal hepatic function	Normal
2	Failure; not stable with medical treatment	Isolated convulsion	Assisted ventilation, normal saturation $FIO_2 < 25\%$	Hepatomegaly, normal hepatic function	Transient oliguria
1	Ventilation necessary	Seizures	Assisted ventilation, normal saturation $FIO_2 > 25\%$	Moderate or transient hepatic insufficiency	Unstable diuresis with treatment
0	Resistant to medical therapy	Permanent neurological signs	Assisted ventilation, desaturation	Abnormal coagulation, elevated enzymes	Anuria

[a] EEG, electroencephalogram; FIO_2, fractional inspired oxygen. Maximal score = 5 (cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) + 3 (renal) = 21.

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

Vein of Galen Malformations in Neonates: New Management Paradigms for Improving Outcomes

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Johanna T. Fifi, MD*
Yasunari Niimi, MD*
Salvatore Presti, MD‡
Rafael Ortiz, MD*
Saadi Ghatan, MD§
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BACKGROUND: Untreated patients with symptomatic neonatal presentation of vein of Galen aneurismal 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 aneurismal malformation

Neurosurgery 70:1207–1214, 2012 DOI: 10.1227/NEU.0b013e3182417be3 www.neurosurgery-online.com

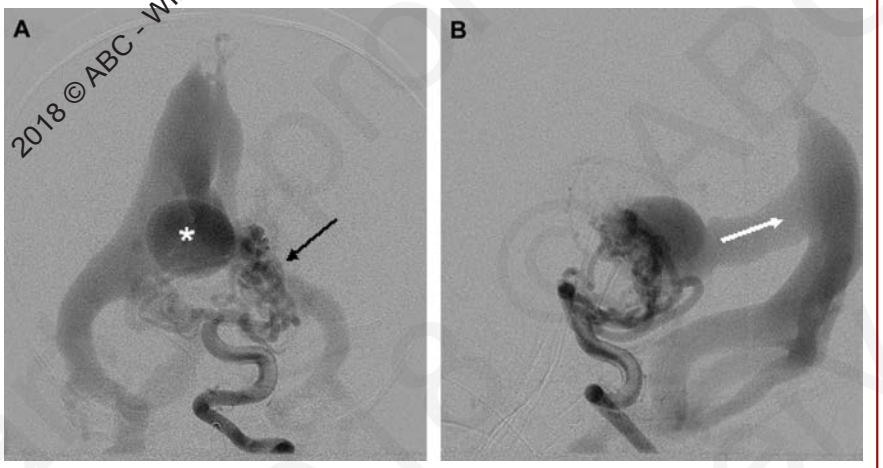

FIGURE 3. *Frontal (**A**) and lateral (**B**) digital subtraction angiogram (DSA) of the left vertebral artery shows multiple tortuous fistulas (black arrow) into the dilated aneurismal vein (white asterisk). The embryonic falcine sinus (white arrow) is visualized. There is no restriction in the venous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

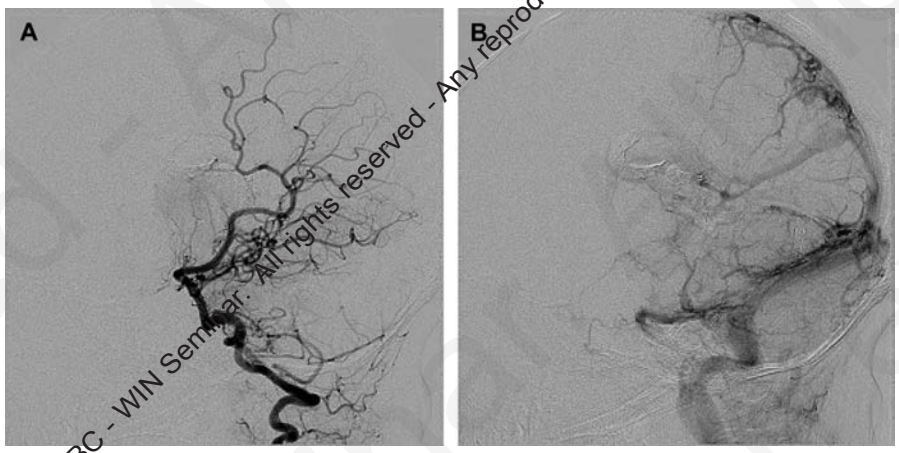

FIGURE 4. *A, lateral view of the left vertebral artery DSA in the arterial phase after 4 endovascular embolizations demonstrates complete angiographic obliteration of the VGAM with preservation of all normal arteries. B, the venous phase shows remodeling of the normal appearing venous system, in a baby with normal development.*

Vein of Galen Malformations in Neonates: New Management Paradigms for Improving Outcomes

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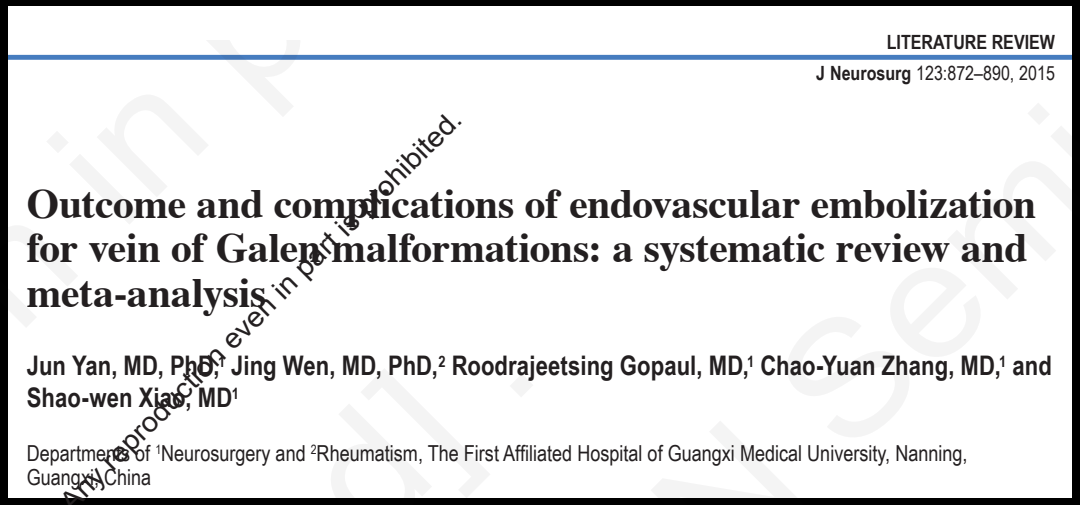
KEY WORDS: Congenital malformation, Congestive heart failure, Intracranial arteriovenous malformation, Neonate, Therapeutic embolization, Vein of Galen aneurismal malformation

Neurosurgery 70:1207–1214, 2012 DOI: 10.1227/NEU.0b013e31824417be3 www.neurosurgery-online.com

TABLE. Clinical Details of Patients Undergoing Neonatal Embolization for VGAM

Sex	Cesarean Delivery	Diagnosed	Weeks Term	Birth Weight, g	MRI Pretreatment	Procedural Complications	Postprocedure Hemorrhage	Angiographic Closure	Total Sessions	Developmental Milestones
M	Yes	Birth	36	2897	No stroke	None	No	Yes	6	Achieving milestones
F	Yes	Day 9	34	1810	No stroke	None	Yes	Died	1	Expired
M	Yes	In utero	38	4165	No stroke	None	No	Yes	2	Achieving milestones
M	Yes	In utero	36	3409	No stroke	None	Yes	Yes	4	Achieving milestones
F	Yes	Birth	39	3400	No stroke	None	No	Yes	6	Achieving milestones
M	No	Day 2	38	2930	No stroke	Stroke (microcatheter rupture)	No	95%	6	Mild left-sided weakness
F	Yes	In utero	37	2386	No stroke	None	No	95%	2	Achieving milestones
F	Yes	In utero	38	4204	Occipital infarcts	None	Yes - into stroke	Yes	6	Mild motor and language delay
M	Yes	In utero	36	2825	Parietal necrosis	None	Yes - into stroke	Yes	3	Seizures and delay



LITERATURE REVIEW

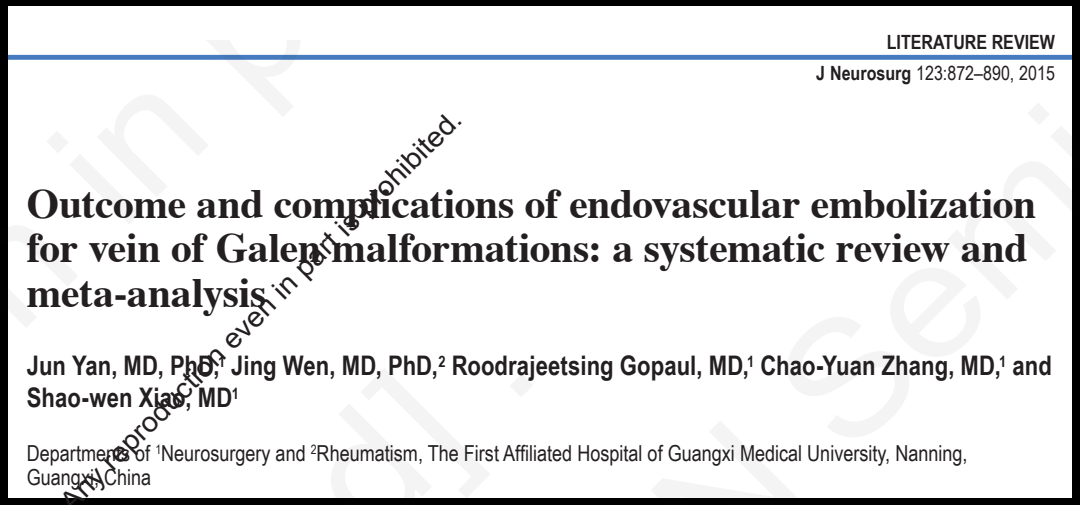
J Neurosurg 123:872–890, 2015

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, MD[1]

Departments of [1]Neurosurgery and [2]Rheumatism, 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%



LITERATURE REVIEW

J Neurosurg 123:872–890, 2015

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, MD[1]

Departments of [1]Neurosurgery and [2]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%

vancement in endovascular techniques. During time interval 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 outcome of patients with VGAMs. With the development of science and technology,

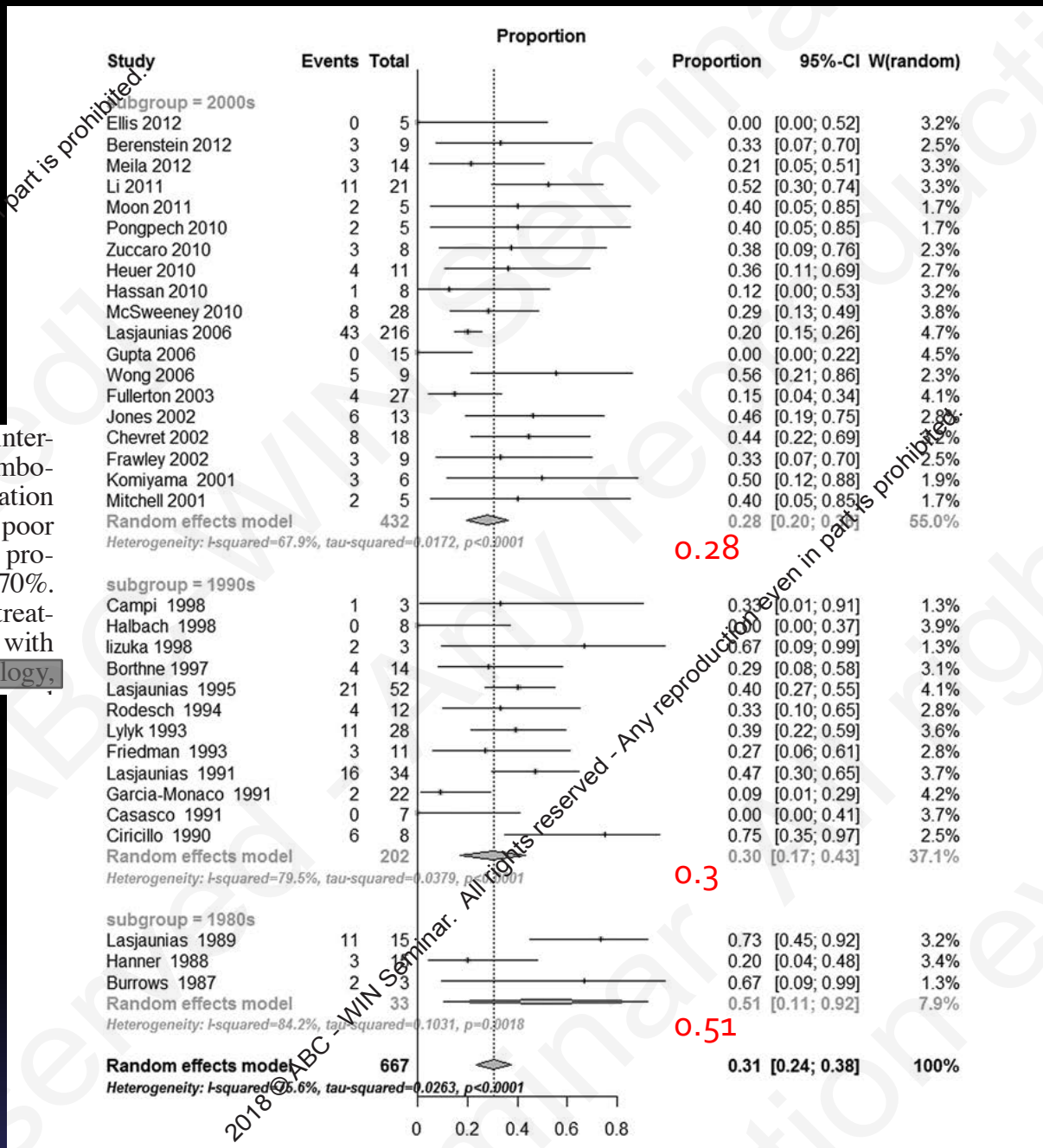


FIG. 3. Estimates of the proportion of the poor outcome, including the 95% CI from the random-effects model and the number of patients for each study.

LITERATURE REVIEW
J Neurosurg 123:872–890, 2015

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Methodological Quality

- 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

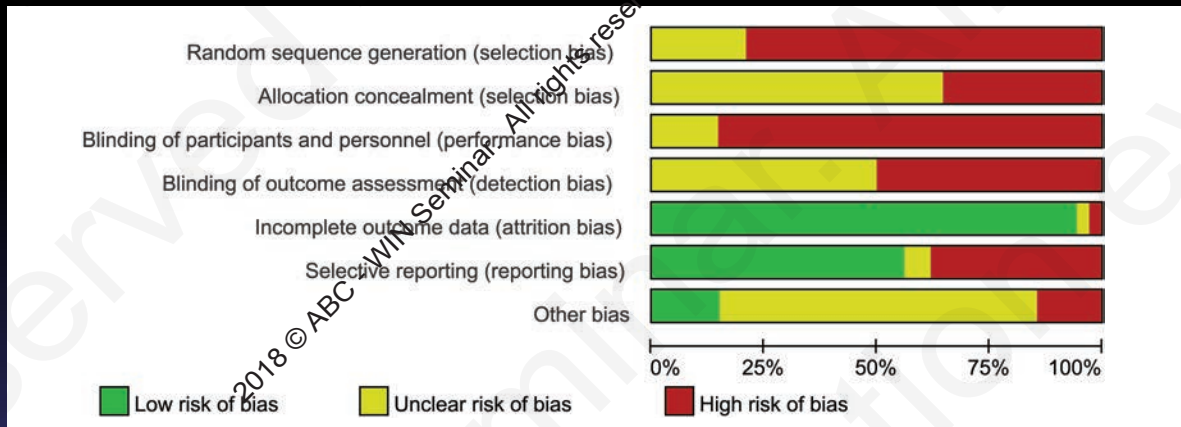
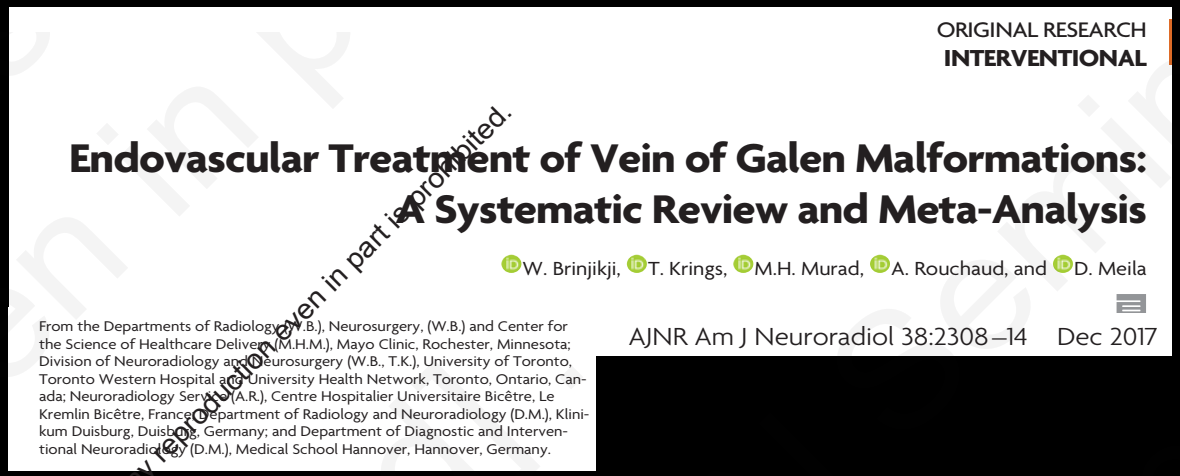


FIG. 6. Risk of bias graph. Review of our judgment about each risk of bias item presented as percentages across all included studies. Figure is available in color online only.



ORIGINAL RESEARCH
INTERVENTIONAL

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 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.

AJNR Am J Neuroradiol 38:2308–14 Dec 2017

- 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

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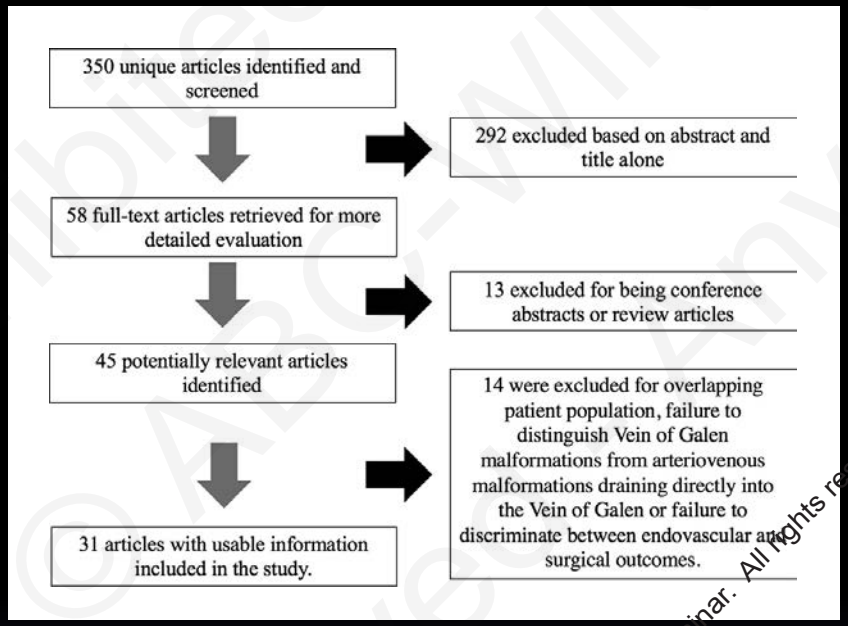

- 31 articles remained, describing 578 patients
- Yan et al. 2015: 34 studies (out of 421 screened) describing 667 patients

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

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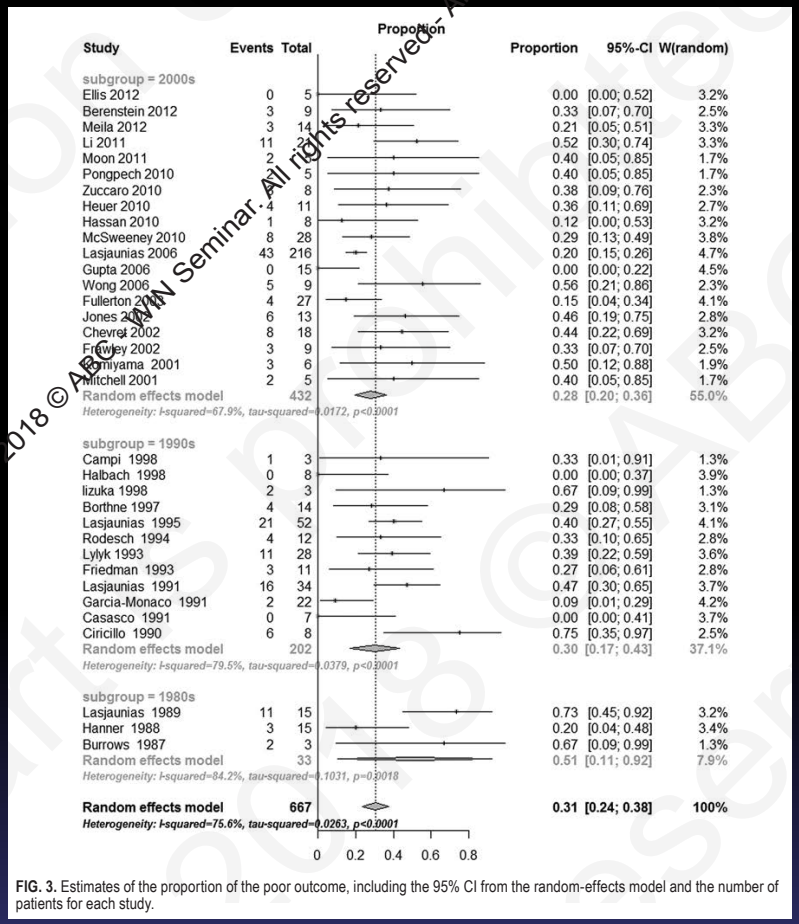


FIG. 3. Estimates of the proportion of the poor outcome, including the 95% CI from the random-effects model and the number of patients for each study.

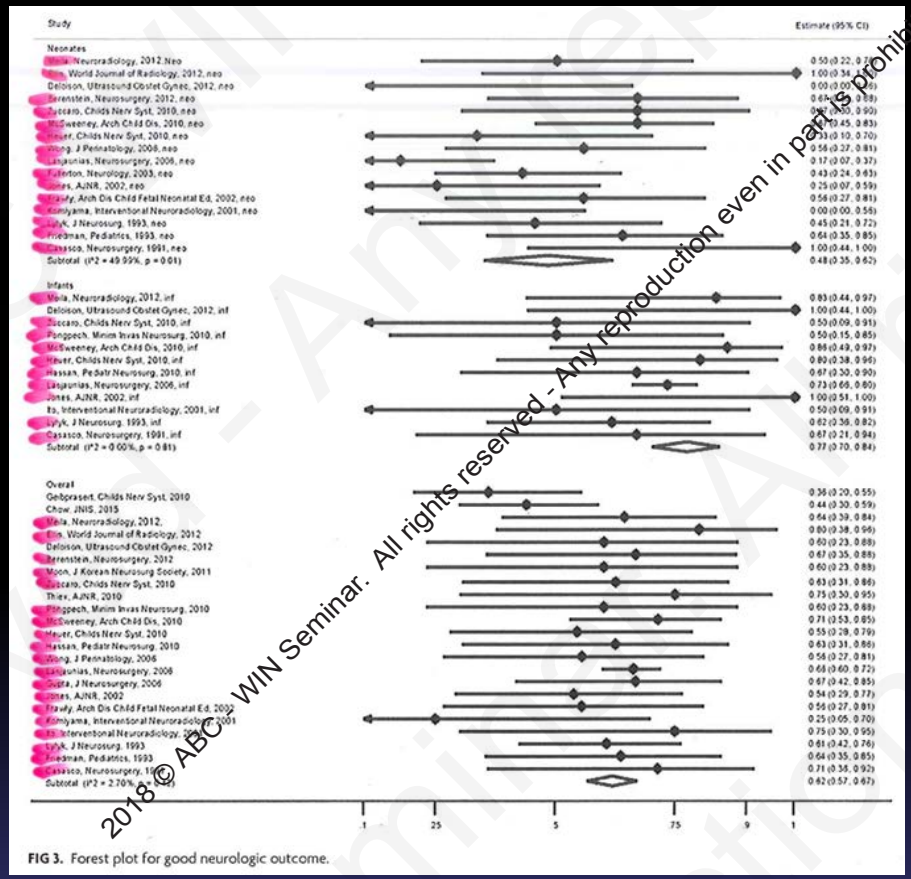
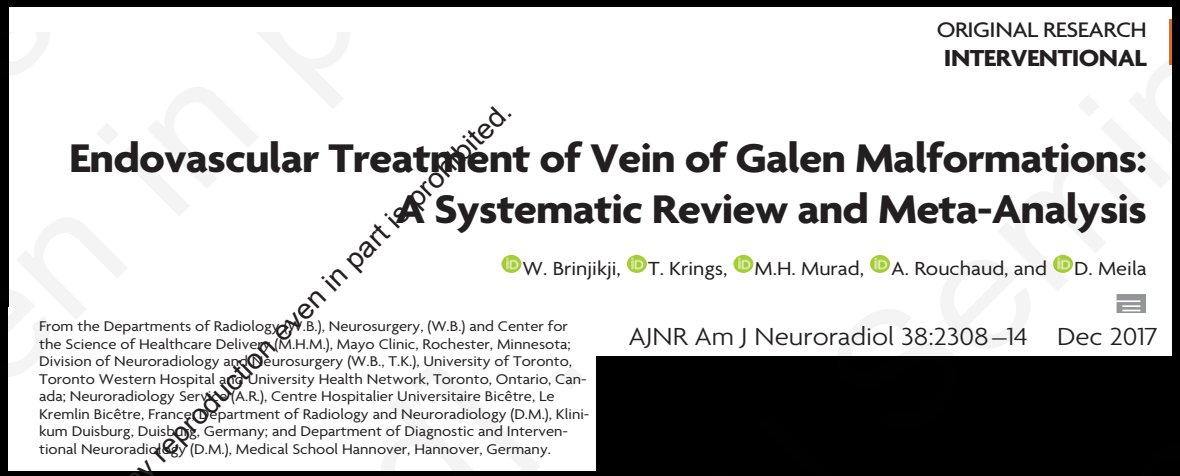


FIG 3. Forest plot for good neurologic outcome.



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AJNR Am J Neuroradiol 38:2308–14 Dec 2017

- ***Analysis of outcomes for children older than 2 years of age could not be performed due to lack of sufficient studies***
- Mean f/u ranged from 0.5 to 6.8 years (median 2 years)
- 42% neonates, 45% infants, 13% children (Yan et al., neonates: 44%, infants 41%, children and adults 12%)
- 68.7% were male (sex data available for 252/578 patients)
- Presentation (available for 318/578 patients): CHF (63%), hydrocephalus (27%), seizure (11.6%). ICH was present in 8.2%

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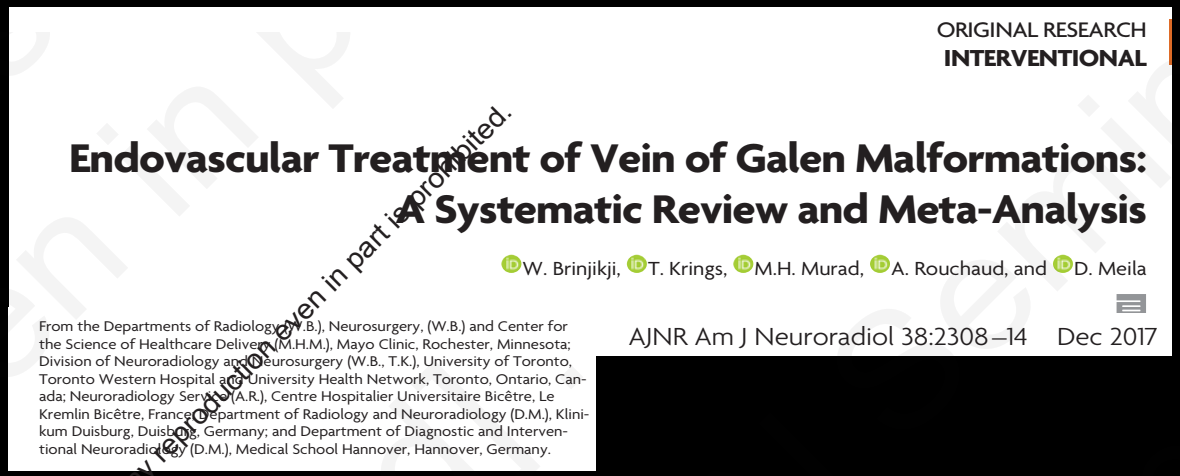
Systematic review outcomes

	Overall Rate (95% CI)	I^2 (%)	Neonate Rate (95% CI)	I^2 (%)	Infant Rate (95% CI)	I^2 (%)	*P* Value, Neonate vs Infant
Technical complications	19.0 (12.0–27.0)	48.9	29.0 (17.0–41.0)	7	10.0 (0.0–27.0)	45	.07
Perioperative hemorrhage	9.0 (4.0–15.0)	52	12.0 (3.0–23.0)	21	4.0 (0.0–16.0)	21	.25
Perioperative ischemia	1.0 (0.0–2.0)	0	3.0 (0.0–10.0)	0	0.0 (0.0–2.0)	0	.03
Non-neurologic complications	2.0 (0.0–4.0)	0	1.0 (0.0–7.0)	0	1.0 (0.0–8.0)	0	1
Technical mortality	1.0 (0.0–5.0)	37	2.0 (0.0–8.0)	0	0.0 (0.0–2.0)	0	.03
Complete occlusion	56.0 (46.0–66.0)	49	59.0 (45.0–73.0)	0	56.0 (17.0–91.0)	74	1
All-cause mortality	14.0 (8.0–20.0)	47	27.0 (15.0–41.0)	57	1.0 (0.0–4.0)	0	<.0001
Poor neurologic outcome	21.0 (17.0–26.0)	0	22.0 (15.0–31.0)	0	16.0 (10.0–23.0)	0	.01
Good neurologic outcome	62.0 (57.0–67.0)	3	48.0 (35.0–62.0)	50	77.0 (70.0–84.0)	0	<.0001

Yan et al.

- Pooled outcome: 68% good (3-4), 31% poor (0-2)
- Overall mortality: 16%



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AJNR Am J Neuroradiol 38:2308–14 Dec 2017

- 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%)

Ultrasound Obstet Gynecol 2012; **40**: 652–658
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.11188

Hidden mortality of prenatally diagnosed vein of Galen aneurysmal malformation: retrospective study and review of the literature

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

**Department of Obstetrics and Fetal Medicine and SFAPE (Société Française d'Amélioration des Pratiques Echographique), 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*

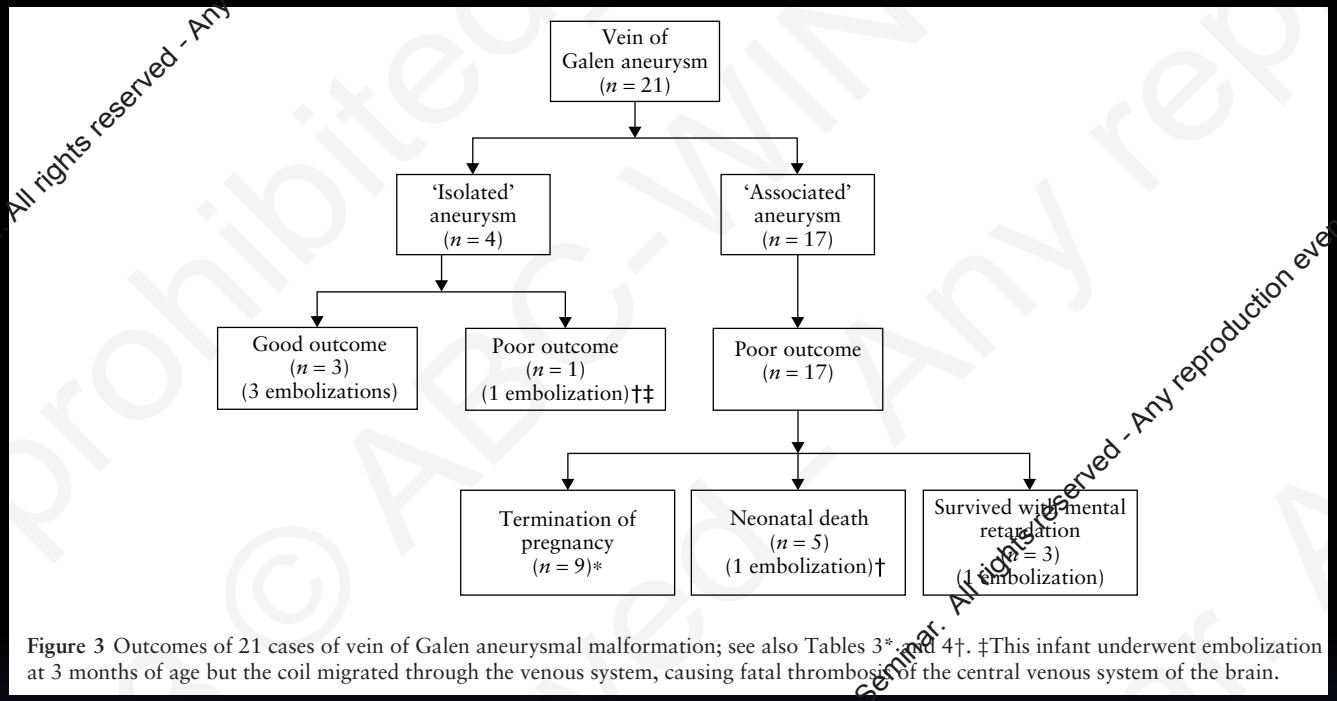

Figure 3 Outcomes of 21 cases of vein of Galen aneurysmal malformation; see also Tables 3* and 4†. ‡This infant underwent embolization at 3 months of age but the coil migrated through the venous system, causing fatal thrombosis of the central venous system of the brain.

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%)

Ultrasound Obstet Gynecol 2017; **50**: 192–199
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17224

Vein of Galen aneurysmal malformation (VGAM) in the fetus: retrospective analysis of perinatal prognostic indicators in a two-center series of 49 cases

D. PALADINI[1], B. DELOISON[2], A. ROSSI[3], G. E. CHALOUHI[2], C. GANDOLFO[3], P. SONIGO[4], S. BURATTI[5], A. E. MILLISCHER[4], G. TUO[6], Y. VILLE[2], A. PISTORIO[7], A. CAMA[8] and L. J. SALOMON[2]

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

Table 4 Fetoneonatal outcome in 49 cases of vein of Galen aneurysmal malformation

Outcome		*%*	*% of ongoing pregnancies*
Late TOP	15	30.6	—
Intrauterine fetal death	1	2.0	2.9
Neonatal death	11	22.4	32.3
Infant death	1	2.0	2.9
Alive and well*	18	36.7	52.9
Alive with sequelae*†	3	6.1	8.8

*Mean follow-up, 20 (range, 0–72) months. †One case each of: seizures in a case of hydrocephalus treated with ventriculo-peritoneal shunt; periventricular leukomalacia; spastic tetraparesis, which is currently being investigated for genetic mutations due to recurrence of cerebral arteriovenous malformation in second pregnancy (not included in present report) 5 years after index case. TOP, termination of pregnancy.

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)

	Brain damage (n/*N* (%))		
	Yes	*No*	P
Straight sinus dilatation			0.0099†
Yes ($n = 21$)	10/21 (47.6)	11/21 (52.4)	
No ($n = 17$)	1/17 (5.9)	16/17 (94.1)	
VGAM vol ≥ 20 000 mm^3*			0.036†
Yes ($n = 29$)	12/29 (41.4)	17/29 (58.6)	
No ($n = 13$)	1/13 (7.7)	9/29 (31.0)	
Tricuspid regurgitation			0.0012‡
Yes ($n = 16$)	11/16 (68.8)	5/16 (31.3)	
No ($n = 33$)	7/33 (21.2)	26/33 (78.8)	
Aortic isthmus reversed flow			0.035†
Yes ($n = 14$)	6/14 (42.9)	8/14 (57.1)	
No ($n = 15$)	1/15 (6.7)	14/15 (93.3)	

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 mm^3. †Fisher's exact test. ‡Chi-square test. vol, volume.

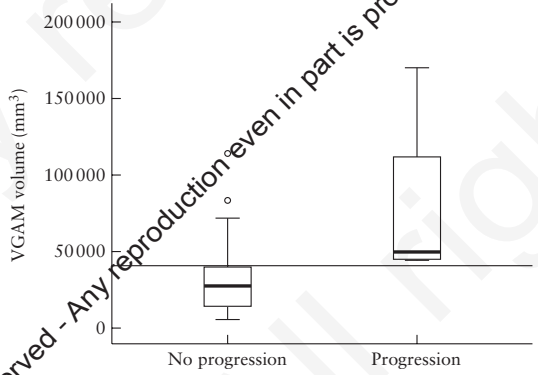

Figure 3 Box-and-whiskers plot showing relationship between vein of Galen aneurysmal malformation (VGAM) volume measured on magnetic resonance imaging and prenatal progression of lesion. Boxes and internal lines represent median and range, whiskers represent interquartile range and circles represent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

Published Neonatal Outcomes

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J Neurosurg 123:872–890, 2015

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Authors & Year	Country	Total	Neonate (<1 mo)
Ellis et al., 2012	US	5	2
Berenstein et al., 2012	US	9	9
Meila et al., 2012	Germany	14	8
Li et al., 2011	Canada	21	7
Moon et al., 2011	Korea	5	3
Pongpech et al., 2010	Thailand	5	0
Zuccaro et al., 2010	Argentina	8	4
Heuer et al., 2010	US	11	7
Hassan et al., 2010	Egypt	8	0
McSweeney et al., 2010	England	28	21
Lasjaunias et al., 2006	France	216	23
Gupta et al., 2006	India	15	0
Wong et al., 2006	Australia	9	9
Fullerton et al., 2003	US	27	21
Jones et al., 2002	US	13	8
Chevret et al., 2002	France	18	18
Frawley et al., 2002	Australia	9	9
Komiyama et al., 2001	Japan	6	3
Mitchell et al., 2001	Australia	11	4
Campi et al., 1998	France	3	2
Halbach et al., 1998	US	8	2
Iizuka et al., 1998	Japan	3	2
Borthne et al., 1997	Norway	14	5
Lasjaunias et al., 1997	France	52	31
Rodesch et al., 1994	France	12	0
Lylyk et al., 1993	US	28	11
Friedman et al., 1993	US	11	11
Lasjaunias et al., 1991	Canada	34	13
García-Monaco et al., 1991	France	22	19
Casasco et al., 1991	Argentina	7	1
Ciricillo et al., 1990	US	8	8
Lasjaunias et al., 1989	France	15	NA
Hanner et al., 1988	US	15	NA
Burrows et al., 1987	Canada	3	1

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

1/3rd don't survive
1/3rd good neurocognitive outcome
1/3rd poor neurocognitive outcome

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

UK VGAM cohort study

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**

Vijeya Ganesan, Fergus Robertson, Adam Rennie
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

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RASA1

Am. J. Hum. Genet. 73:1240–1249, 2003

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

Iiro Eerola,[1] Laurence M. Boon,[1,2] John B. Mulliken,[3,4] Patricia E. Burrows,[3,5] Anne Dompmartin,[6] Shoji Watanabe,[7] Romain Vanwijck,[2] and Miikka Vikkula[1]

[1]Laboratory of Human Molecular Genetics, Christian de Duve Institute of Cellular Pathology, and [2]Centre for Vascular Anomalies, Division of Plastic Surgery, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels; [3]Vascular Anomalies Center, [4]Division of Plastic Surgery, and [5]Division of Interventional Radiology, Children's Hospital, Harvard Medical School, Boston; [6]Division of Dermatology, CHU Caen, France; and [7]Department of Plastic and Reconstructive Surgery, Showa University School of Medicine, Tokyo

HUMAN MUTATION 29(7), 959–965, 2008

RESEARCH 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. Boon,[1,3] John B. Mulliken,[4] Odile Enjolras,[5] Maria Rosa Cordisco,[6] Patricia E. Burrows,[4] Philippe Clapuyt,[7] Frank Hammer,[7] Josée Dubois,[8] Eulalia Baselga,[9] Francesco Brancati,[10] Robin Carder,[11] José Miguel Ceballos Quintal,[12] Bruno Dallapiccola,[10] Gayle Fischer,[13] Ilona J. Frieden,[14] Maria Garzon,[15] John Harper,[16] Jennifer Johnson-Patel,[17] Christine Labrèze,[18] Loreto Martorell,[19] Harriet J. Paltiel,[4] Annette Pohl,[20] Julie Prendiville,[21] Isabelle Quere,[22] Dawn H. Siegel,[14] Enza Maria Valente,[10] Annet Van Hagen,[23] Liselot Van Hest,[23] Keith K. Vaux,[24] Asuncion Vicente,[25] Lisa Weibel,[16] David Chitayat,[26] and Miikka Vikkula[1]*

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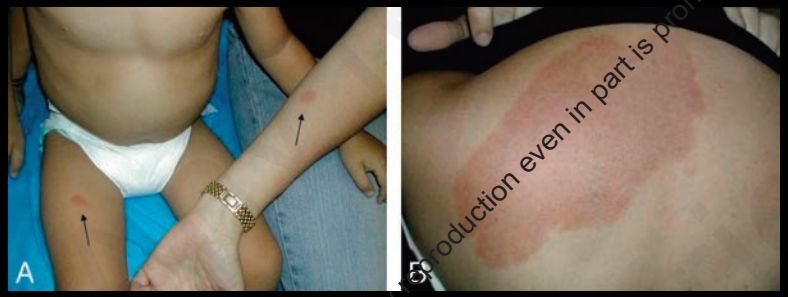

Two conceptual problems here:

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

HHT

Journal of Pediatric Genetics 2 (2013) 181–185
DOI 10.3233/PGE-13067
IOS Press

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

Ayako Chida[a,b], Masaki Shintani[b], Hajime Wakamatsu[a], Yoshiyuki Tsutsumi[c], Yuo Iizuka[d], Nanako Kawaguchi[b], Yoshiyuki Furutani[b], Kei Inai[b], Shigeaki Nonoyama[a] and Toshio Nakanishi[b,*]
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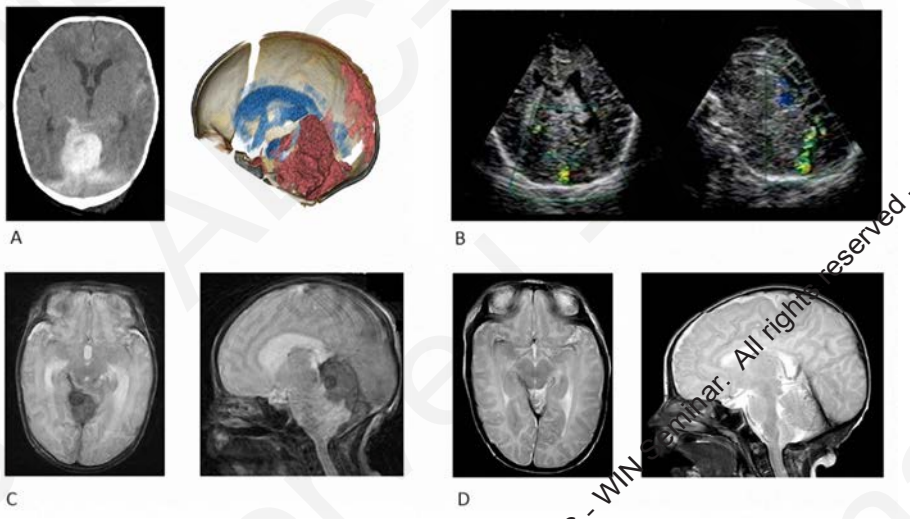


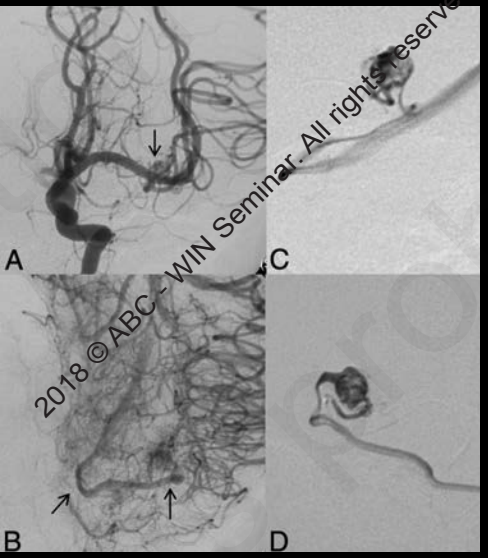
Fig. 2. Analysis of images from proband. (A) Axial (left) non-enhanced reconstruction computed tomography on the day of birth demonstrating subarachnoid hemorrhage with a hematoma around galenic cistern. Three-dimensional computed tomography (right) demonstrating bleeding in the parietal superior sagittal sinus, confluence, right transverse sinus, and right sigmoid sinus. (B) Axial (left) and sagittal (right) color Doppler imaging at 1-day-old demonstrating a large hematoma around the median vein 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.

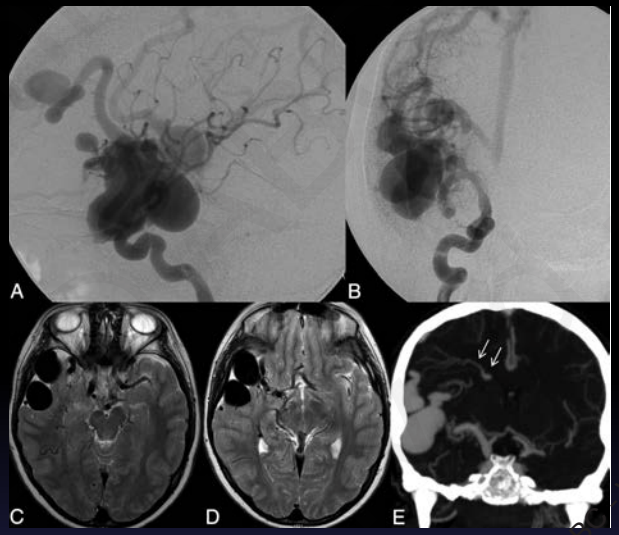
HHT

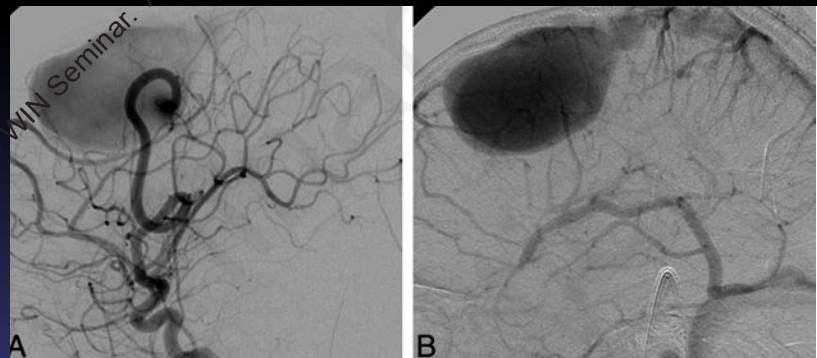
Neurovascular Manifestations in Hereditary Hemorrhagic Telangiectasia: Imaging Features and Genotype-Phenotype Correlations

T. Krings, H. Kim, S. Power, J. Nelson, M.E. Faughnan, W.L. Young, K.G. terBrugge, and the Brain Vascular Malformation Consortium HHT Investigator Group

AJNR Am J Neuroradiol 36:863–70 May 2015







Molecular genetics of Vein of Galen malformations

Daniel Duran[1], Philipp Karschnia[1], Jonathan Gaillard[1], Jason K. Karimy[1], Mark W. Youngblood[1], Michael L. DiLuna[1], Charles C. Matouk[1], Beverly Aagaard-Kienitz[2], Edward R. Smith[3], Darren B. Orbach[4], Georges Rodesch[5], Alejandro Berenstein[6], Murat Gunel[1,7,8], and Kristopher T. Kahle[1,8,9]

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J Neurosurgery Pediatrics, *in press*

Table 1. VOGM-associated genetic variants

#	Gene	Coding variant	Exon	Type of mutation	Protein variant	Year	Source
1	***RASA1***	c.2977del	24	frameshift deletion	p.Arg993Valfs	2013	Revencu et al
2	***RASA1***	c.2125C>T†	16	stop gain	p.Arg709*	2013	Revencu et al, Heuchan et al
3	***RASA1***	c.3024del	24	frameshift deletion	p.Glu1008Aspfs	2013	Revencu et al
4	***RASA1***	c.2288A>T	17	missense	p.Glu763Val	2008	Revencu et al
5	***RASA1***	c.2532_2536del	19	frameshift deletion	p.Leu845Thrfs	2008	Revencu et al
6	***RASA1***	c.2119C>T	16	missense	p.Arg707Cys	2013	Heuchan et al
7	***RASA1***	c.2912T>C	23	missense	p.Leu971Ser	2013	Heuchan et al
8	***RASA1***	c.1678G>T	12	stop gain	p.Glu560*	2013	Chida et al
9	***ACVRL1***	c.652C>T	6	missense	p.Arg218Trp	2013	Chida et al
10	***ENG***	c.1672_1684del	12	frameshift deletion	p.Gln558fs	2011	Tsutsumi et al

† Reported separately by two publications

Molecular genetics of Vein of Galen malformations

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J Neurosurgery Pediatrics, *in press*

- Familial VGAM – index case in Xu et al. with an infant who died of VGAM
- 2 families have been reported with multiple VGAM in the same generation: successive pregnancies in Kwong et al. (identical RASA1 mutation in both siblings and the asymptomatic mother) and no identifiable mutation in the twins in Chida et al.

Adult Presentation of a Familial-Associated Vein of Galen Aneurysmal Malformation: Case Report

David S. Xu, BS
Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

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Michael E. Hurley, MD
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Christopher S. Eddleman, MD, PhD
Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

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Departments of Neurological Surgery and Radiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Neurosurgery 67:E1845–E1851, 2010 DOI: 10.1227/NEU.0b013e3181fa00d8

Childs Nerv Syst (2015) 31:1033–1035
DOI 10.1007/s00381-015-2750-2

BRIEF COMMUNICATION

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

Yune Kwong[1] · Maria Cartmill[2] · Tim Jaspan[3] · Mohnish Suri[4]

Journal of Pediatric Genetics 2 (2013) 181–189
DOI 10.3233/PGE-13067
IOS Press

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

Ayako Chida[a], Masaki Shintani[b], Hajime Wakamatsu[a], Yoshiyuki Tsutsumi[c], Yuo Iizuka[d], Nanako Kawaguchi[b], Yoshiyuki Furutani[b], Kei Inai[b], Shigeaki Nonoyama[a] and Toshio Nakanishi[b,*]

Table 1
Summary of VGAM patients

Patient number	Serial number	Gene mutation or variant	Sex	Age at diagnosis	History and presentation	Complication and family history	Unique imaging findings	Treatment	Outcome	Reference
1	P3389	-	M	Fetal age of 34 wk	Bradycardia, hypoxia	-	-	Catheter embolization	İntact	-
2	P3431	RASA1 (c.1678 G>T E560X)	M	Fetal age of 35 wk	Retractive breathing, groaning, cardiomegaly	-	-	Catheter embolization	Mental and motor retardation, epilepsy	-
3	P3858	-	F	2 d of age	Hypoglycemia, cardiomegaly	Patient's twin sibling : VGAM suspected	-	Catheter embolization	Severe mental and motor retardation, epilepsy	-
4	P3865	ACVRL1 (c.652 C>T R218W)	F	1 d of age	Pale skin, bradycardia, anemia, hypothemia	-	SAH, hematoma around VGAM	Craniotomy for removal hematoma	İntact	This study

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.

Molecular genetics of Vein of Galen malformations

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J Neurosurgery Pediatrics, *in press*

- 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

Pediatric and Developmental Pathology 9, 52–55, 2006
DOI: 10.2350/06-05-0060.1

CASE REPORTS

Twin-to-Twin Transfusion Syndrome, Vein of Galen Malformation, and Transposition of the Great Arteries in a Pair of Monochorionic Twins: Coincidence or Related Association?

Sylke Steggerda,[1*] Enrico Lopriore,[1] Marieke Sueters,[2] Margot Bartelings,[3] Frank Vandenbussche,[2] and Frans Walther[1]

[1]Division of Neonatology, Department of Pediatrics, J6-S, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, The Netherlands
[2]Division of Fetal Medicine, Department of Obstetrics, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, The Netherlands
[3]Department of Anatomy and Embryology, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, The Netherlands

WORLD NEUROSURGERY, HTTP://DX.DOI.ORG/10.1016/J.WNEU.2016.07.031

Vein of Galen Aneurysmal Malformation in Monozygotic Twin

Masaki Komiyama[1], Satoko Miyatake[2], Aiko Terada[1], Tomoya Ishiguro[1], Hiroyuki Ichiba[3], Naomichi Matsumoto[2]

From the Departments of [1]Neurointervention and [2]Neonatology, Osaka City General Hospital, Osaka; and [3]Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Molecular genetics of Vein of Galen malformations

Daniel Duran[1], Philipp Karschnia[1], Jonathan Gaillard[1], Jason K. Karimy[1], Mark W. Youngblood[1], Michael L. DiLuna[1], Charles C. Matouk[1], Beverly Aagaard-Kienitz[2], Edward R. Smith[3], Darren B. Orbach[4], Georges Rodesch[5], Alejandro Berenstein[6], Murat Gunel[1,7,8], and Kristopher T. Kahle[1,8,9]

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

HUMAN MUTATION 29(7), 959–965, 2008

RESEARCH 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. Boon,[1,3] John B. Mulliken,[4] Odile Enjolras,[5] Maria Rosa Cordisco,[6] Patricia E. Burrows,[4] Philippe Clapuyt,[7] Frank Hammer,[7] Josée Dubois,[8] Eulalia Baselga,[9] Francesco Brancati,[10] Robin Carder,[11] José Miguel Ceballos Quintal,[12] Bruno Dallapiccola,[10] Gayle Fischer,[13] Ilona J. Frieden,[14] Maria Garzon,[15] John Harper,[16] Jennifer Johnson-Patel,[17] Christine Labrèze,[18] Loreto Martorell,[19] Harriet J. Paltiel,[4] Annette Pohl,[20] Julie Prendiville,[21] Isabelle Quere,[22] Dawn H. Siegel,[14] Enza Maria Valente,[10] Annet Van Hagen,[23] Liselot Van Hest,[23] Keith K. Vaux,[24] Asuncion Vicente,[25] Lisa Weibel,[16] David Chitayat,[26] and Miikka Vikkula[1]*

TABLE 2. **Phenotype of Individuals With CM-AVM with (I) or Without (II) RASA1 Mutation***

RASA1 mutation				Phenotype of individuals with CM-AVM with (I) or without (II) RASA1 mutation			
Family	Nucleotide change	Putative effect at amino acid level	Mutation carriers[a]	CM[a]	AVM/AVF[a]	PKWS[a]	Symptoms and associated features[b]
37	c.2532_2536delTTTAA	p.Leu845ThrfsX38	2(dn)	4	1	0	De novo mutation in monozygotic twins; VGAM and CF in one

Molecular genetics of Vein of Galen malformations

Daniel Duran[1], Philipp Karschnia[1], Jonathan Gaillard[1], Jason K. Karimy[1], Mark W. Youngblood[1], Michael L. DiLuna[1], Charles C. Matouk[1], Beverly Aagaard-Kienitz[2], Edward R. Smith[3], Darren B. Orbach[4], Georges Rodesch[5], Alejandro Berenstein[6], Murat Gunel[1,7,8], and Kristopher T. Kahle[1,8,9]

J Neurosurgery Pediatrics, *in press*

RASA1 Somatic Mutation and Variable Expressivity in Capillary Malformation/Arteriovenous Malformation (CM/AVM) Syndrome

Colleen F. Macmurdo,[1] Whitney Wooderchak-Donahue,[2,3] Pinar Bayrak-Toydemir,[2,3] Jenny Le,[2] Matthew B. Wallenstein,[1] Carlos Milla,[1] Joyce M. C. Teng,[4] Jonathan A. Bernstein,[1] and David A. Stevenson[1]*

Am J Med Genet Part A 170A:1450–1454.

- 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

ANNALS *of* SURGERY

VOL. LXII DECEMBER, 1915 No. 6

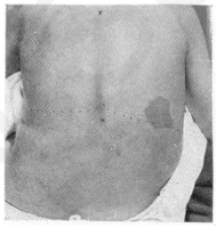
HÆMANGIOMA OF THE SPINAL CORD

ASSOCIATED WITH SKIN NÆVI OF THE SAME METAMERE*

BY STANLEY COBB, M.D.

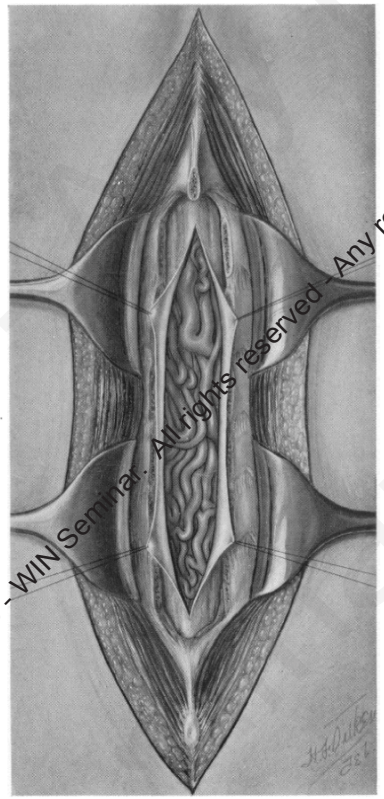
OF BOSTON, MASS.

HÆMANGIOMATA 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 [15] of 400 cases and Flateau's [14] of 213). A thorough review of the literature, however, brings to light seven cases beside the one here reported.



Capillary malformation of the skin

FIG. 1.—Photograph six weeks after operation, showing upper level of anæsthesia (dotted line) crossing lower portion of nævus, and operative incision (between crosses).



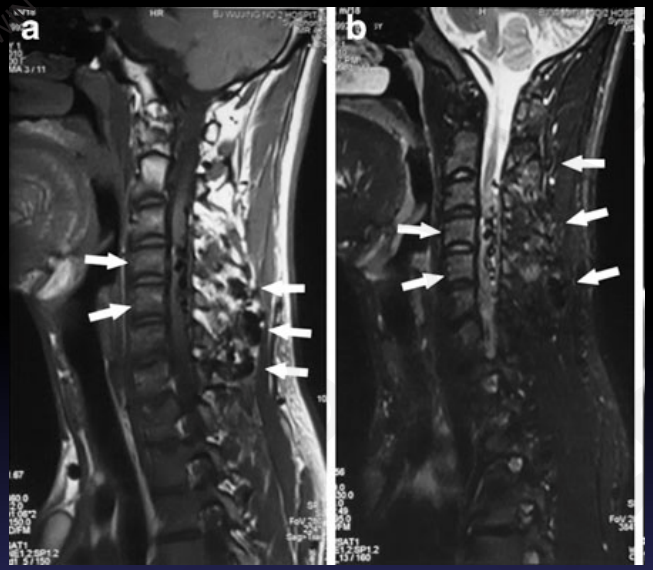
Metameres - Cobb Syndrome

Acta Neurochir (2011) 153:1657–1661
DOI 10.1007/s00701-011-1025-2

CASE REPORT

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

Peng Gao · Hongqi Zhang · Feng Ling



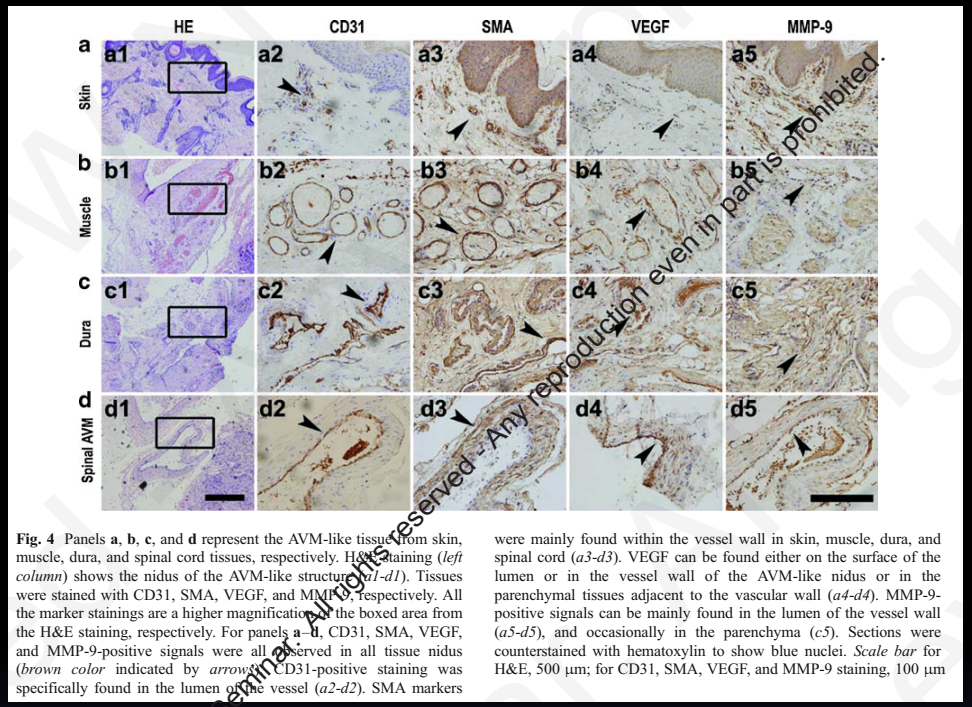


Fig. 4 Panels **a**, **b**, **c**, and **d** represent the AVM-like tissues from skin, muscle, dura, and spinal cord tissues, respectively. H&E staining (*left column*) shows the nidus of the AVM-like structures (*a1-d1*). Tissues were stained with CD31, SMA, VEGF, and MMP-9, respectively. All the marker stainings are a higher magnification of 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 (*a5-d5*), and occasionally in the parenchyma (*c5*). 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

ORIGINAL ARTICLE

Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in *GNAQ*

Matthew J. Shirley, Ph.D., Hao Tang, Ph.D., Carol J. Gallione, B.A., Joseph D. Baugher, Ph.D., Laurence P. Frelin, M.S., Bernard Cohen, M.D., Paula E. North, M.D., Ph.D., Douglas A. Marchuk, Ph.D., Anne M. Comi, M.D., and Jonathan Pevsner, Ph.D.

N ENGL J MED 368;21 NEJM.ORG MAY 23, 2013

Mutant GNAQ

Wild-type GNAQ

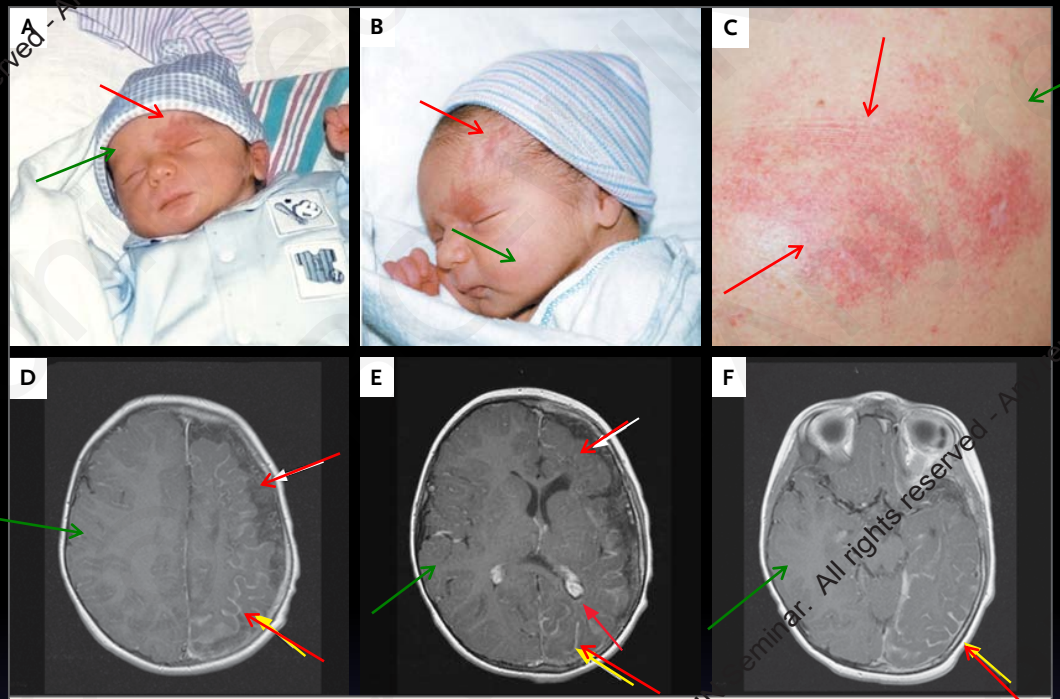


Figure 1. Representative Photographs and Magnetic Resonance Imaging (MRI) Scans from Study Participants with the Sturge–Weber Syndrome or Isolated Port-Wine Stains.

Somatic Activating Mutations in *GNAQ* and *GNA11* Are Associated with Congenital Hemangioma

Ugur M. Ayturk,[1,2,9] Javier A. Couto,[3,9] Steven Hann,[1] John B. Mulliken,[3,4] Kaitlin L. Williams,[1] August Yue Huang,[1,2] Steven J. Fishman,[4,5] Theonia K. Boyd,[6] Harry P.W. Kozakewich,[4,6] Joyce Bischoff,[5,7] Arin K. Greene,[3,4] and Matthew L. Warman[1,2,4,8,*]

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

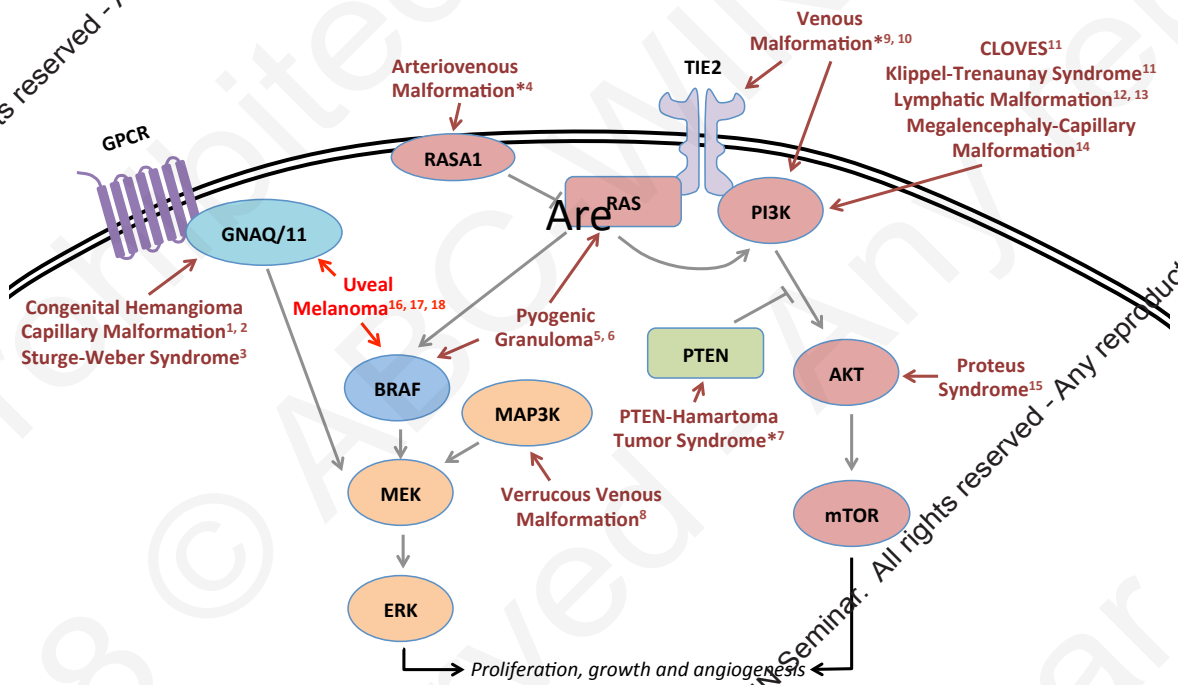


Figure S2: Somatic mutations in genes that are associated with congenital vascular tumors and malformations in humans. Mutations in genes encoding several different protein components of MAP kinase and mTOR signaling pathways have been identified in affected tissue from individuals with a vascular tumor 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 [1-18]. 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,[2,6] Dennis J. Konczyk,[1] Jeremy A. Goss,[1] Steven J. Fishman,[3] John B. Mulliken,[1] Matthew L. Warman,[2,4,5] and Arin K. Greene[1,*]

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

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

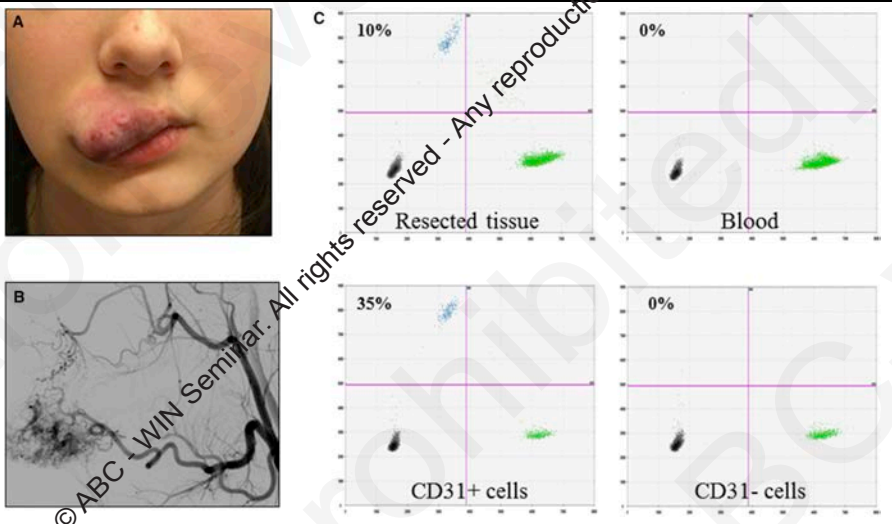
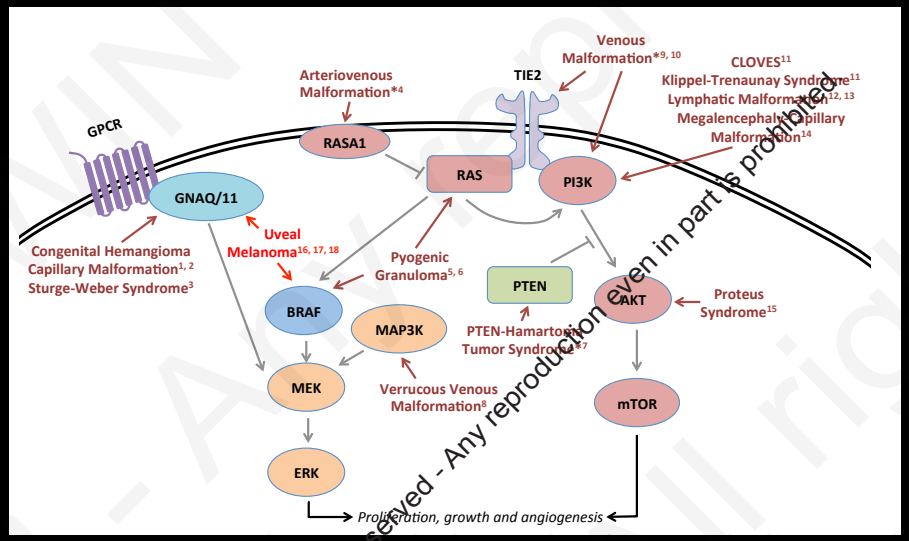


Figure 3. AVM Endothelial Cells Enriched for the *MAP2K1* Mutation
(A) Photograph of an upper labial AVM (participant 13) from which CD31$^+$ and CD31$^-$ cells were separated.
(B) Angiogram prior to resection shows arteriovenous shunting.
(C) ddPCR assay results performed on DNA extracted from the AVM (resected tissue), endothelial (CD31$^+$), and non-endothelial (CD31$^-$) cells, and peripheral blood. Droplets containing mutant only, mutant and wild-type, or wild-type only alleles appear in left upper, right upper, and right lower quadrants, respectively (empty droplets are in the left lower quadrant). Percentages of mutant alleles in each sample are indicated (droplet counts are provided in Table 2).



- 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 (?)

CLOVES

REPORT

Somatic Mosaic Activating Mutations in *PIK3CA* Cause CLOVES Syndrome

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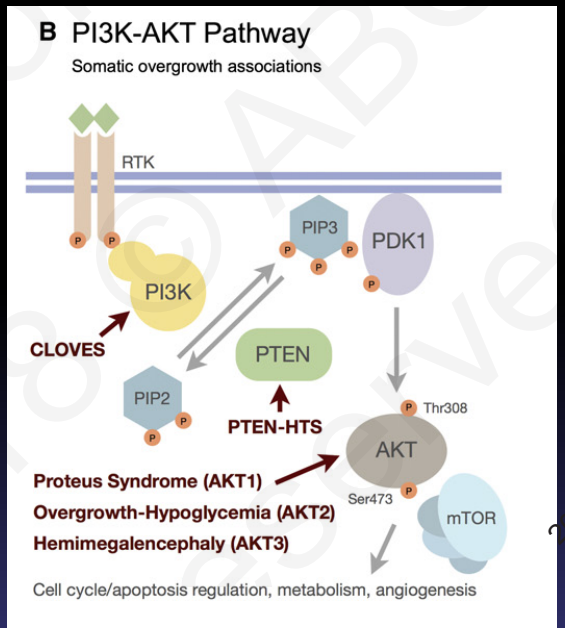
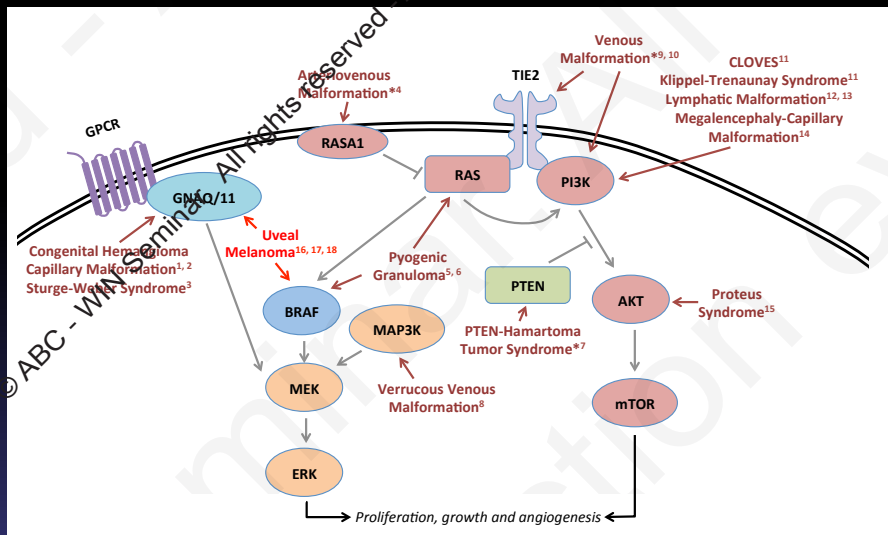
Congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies (CLOVES) is a sporadically occurring, nonhereditary disorder characterized by asymmetric somatic hypertrophy and anomalies in multiple organs. We hypothesized that CLOVES syndrome would be caused by a somatic mutation arising 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 *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 *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





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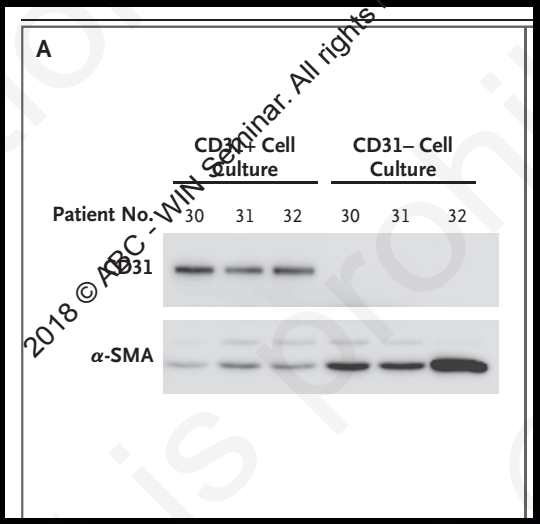
ORIGINAL ARTICLE

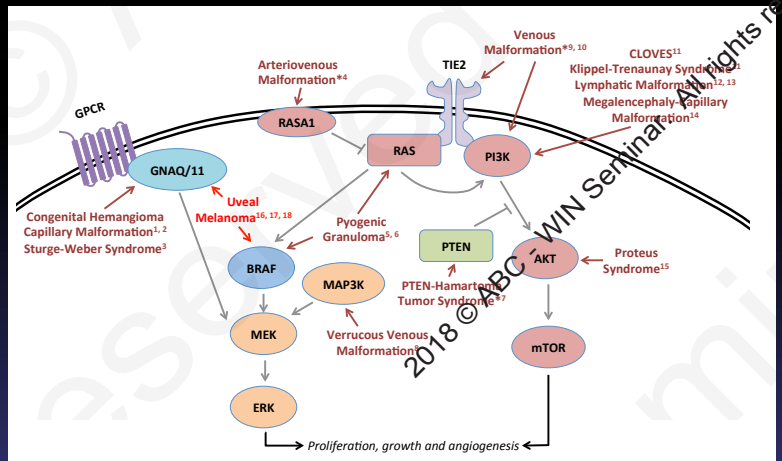
Somatic Activating *KRAS* Mutations in Arteriovenous Malformations of the Brain

S.I. Nikolaev, S. Vetiska, X. Bonilla, E. Boudreau, S. Jauhiainen, B. Rezai Jahromi, N. Khyzha, P.V. DiStefano, S. Suutarinen, T.-R. Kiehl, V. Mendes Pereira, A.W. Herman, T. Krings, H. Andrade-Barazarte, T. Tung, T. Valiante, G. Zadeh, M. Tymianski, T. Rauramaa, S. Ylä-Herttuala, J.D. Wythe, S.E. Antonarakis, J. Frösen, J.E. Fish, and I. Radovanovic



RESULTS

We detected somatic activating *KRAS* mutations in tissue samples from 5 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 ($KRAS^{G12V}$) 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.



ORIGINAL RESEARCH ARTICLE

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

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Sources of Funding, see page 1045

Key Words: arteriovenous fistula ■ arteriovenous malformation ■ capillary ■ genetics ■ linkage ■ vascular disease ■ vascular endothelial function ■ venous

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

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Circulation. 2017;136:1037–1048. DOI: 10.1161/CIRCULATIONAHA.116.026886 September 19, 2017 1037

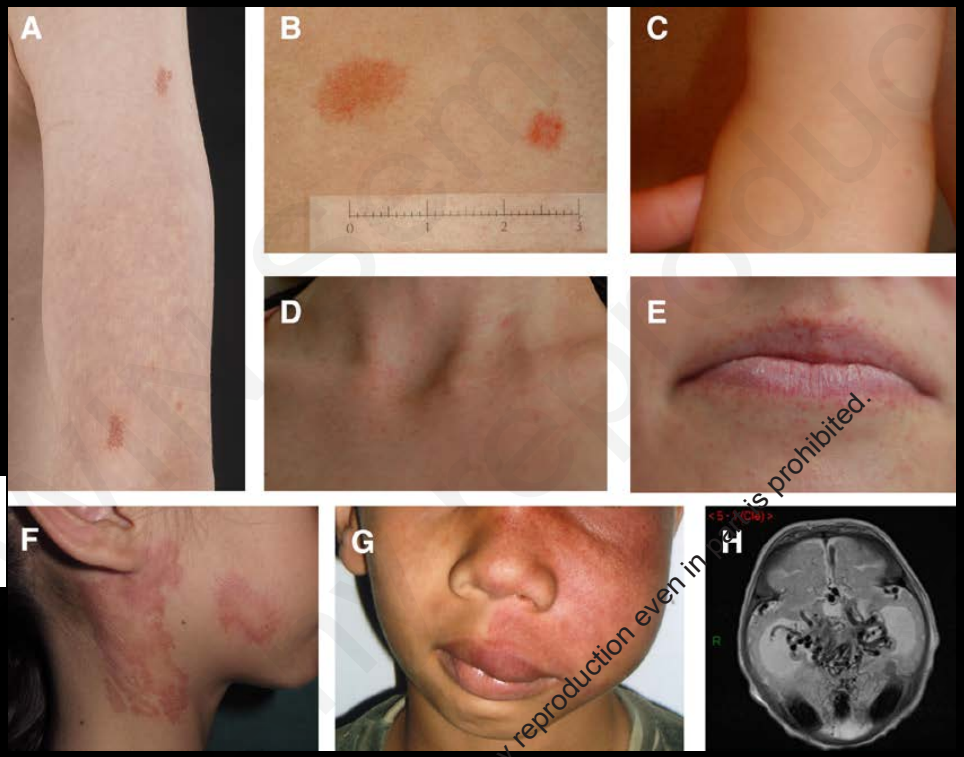

Figure 3. Phenotypic spectrum associated with EPHB4 mutations.
A, Multifocal capillary malformations (CMs) and Mongolian spots. **B,** Multifocal CMs. C, Multifocal CMs with white surrounding halo. **D,** Multiple telangiectasias on upper thorax. **E,** Multiple labial and peribuccal telangiectasias. **F,** Multifocal CMs with geographic borders and pale central zone. **G,** Arteriovenous malformations on the face. **H,** Vein of Galen aneurysmal malformation. **I,** Parkes Weber syndrome in right leg.

- Penetrance 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)

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- 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

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- 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

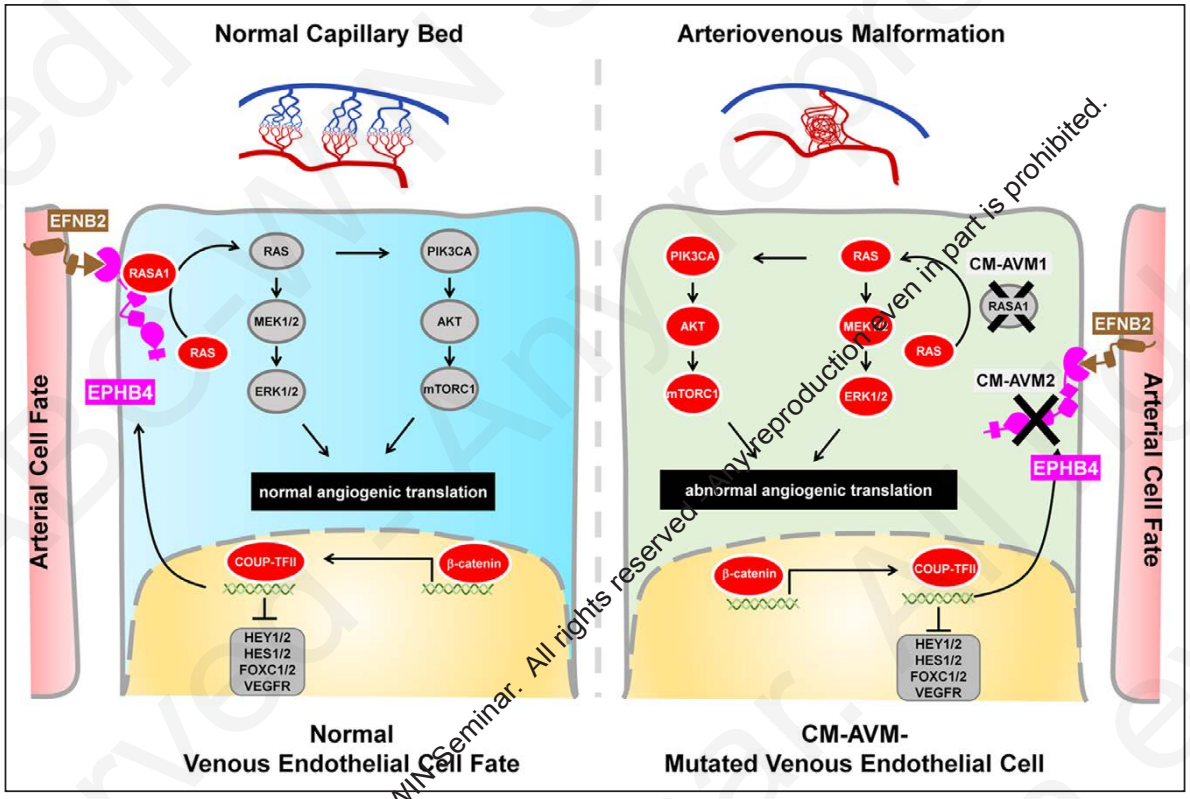


Figure 4. Role of EPHB4 in AVM formation.
Artery-fated angioblasts (red) express EphrinB2 and inhibit expression of venous markers (EPHB4 and Chicken ovalbumin upstream promoter transcription factor II, COUP-TFII). Venous-fated endothelial cells (blue) express COUP-TFII, and thereby the EphrinB2 receptor EPHB4, and suppress 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

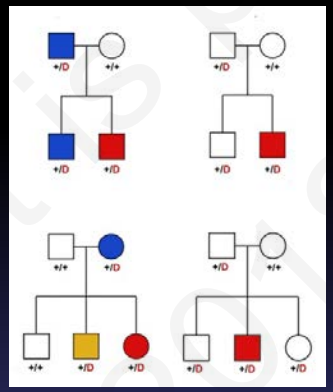
- International **collaborative** effort
  - Initiated in 2016
- NIH-financed - Centers for Mendelian Genomics
- Current participants:
  - Kristopher T. Kahle (**Principal Investigator**), Richard P. Lifton, Murat Gunel, Daniel Duran – **Lead genomics team** (Yale)
  - Darren B. Orbach, Edward R. Smith (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

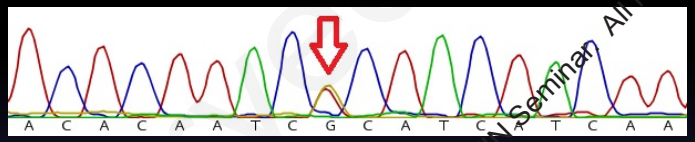
- Patient recruitment – REQUIRES MULTICENTER, COLLABORATIVE EFFORT → **Over 50 radiographically-confirmed VGAM patients** and their parents have been exome sequenced to date.
- Hassle-free DNA collection through buccal swabs → Pipeline allows for international shipments through certified mail.
- Large-scale,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

Workflow

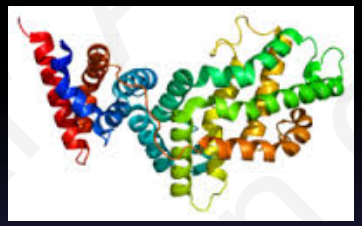
Patient and family recruitment



Sequencing / bioinformatic analysis
mutation discovery

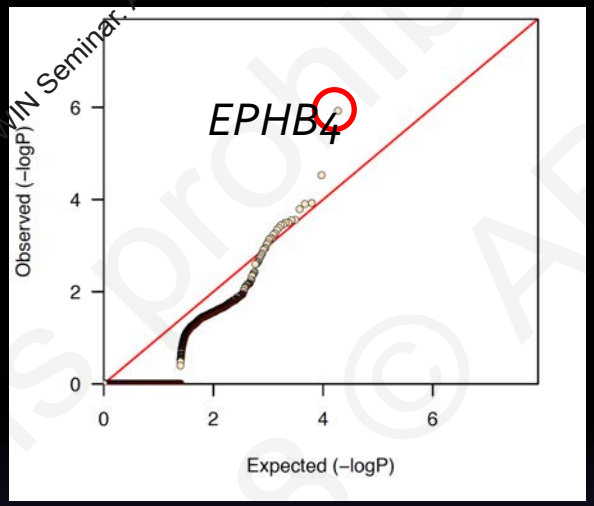


Functional validation



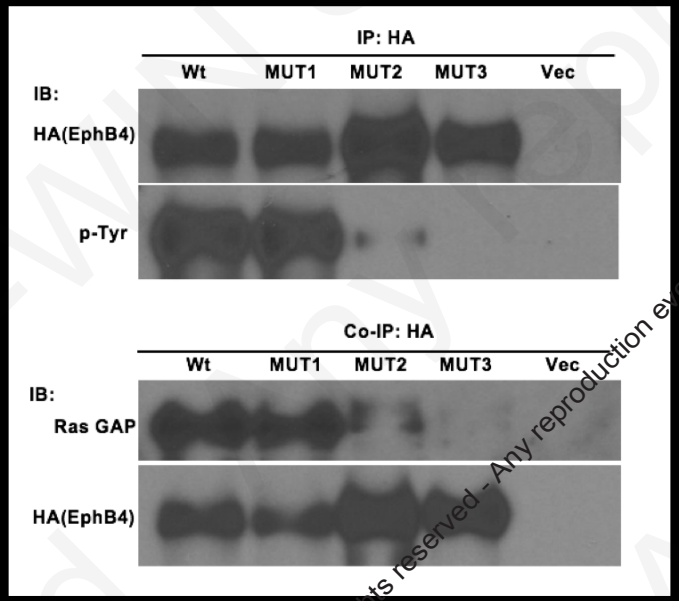
Salient findings

- 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*.



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

AND

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.?

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Developmental Cell
Article

Developmental Cell *42*, 1–17, September 11, 2017

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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. Gilette,[1] Shek Man Chim,[8] Folasade A. Sofela,[1,4] Michelle M. DeLisle,[1,4] Alon Celber,[1] Brenda J. Barry,[1,4,9] Sarah MacKinnon,[3] Linda R. Dagi,[3,7] Jeremy Nathans,[9,10,11,12] and Elizabeth C. Engle[1,4,5,7,9,13,*]

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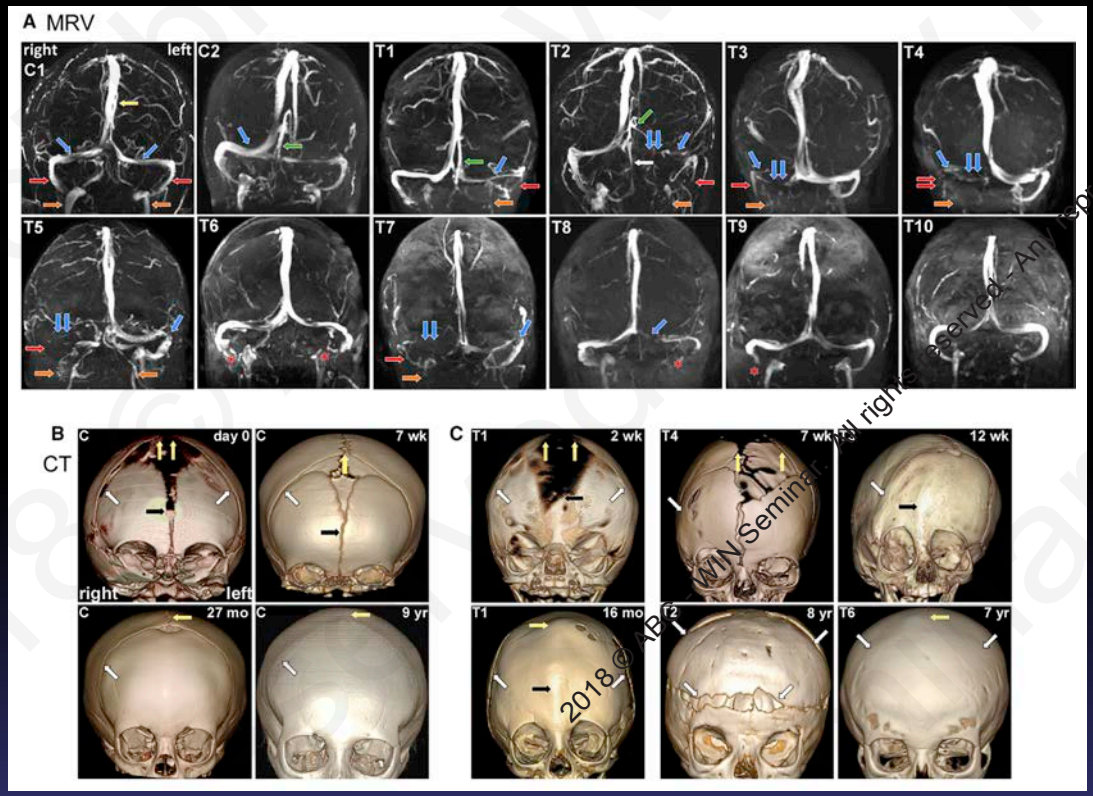

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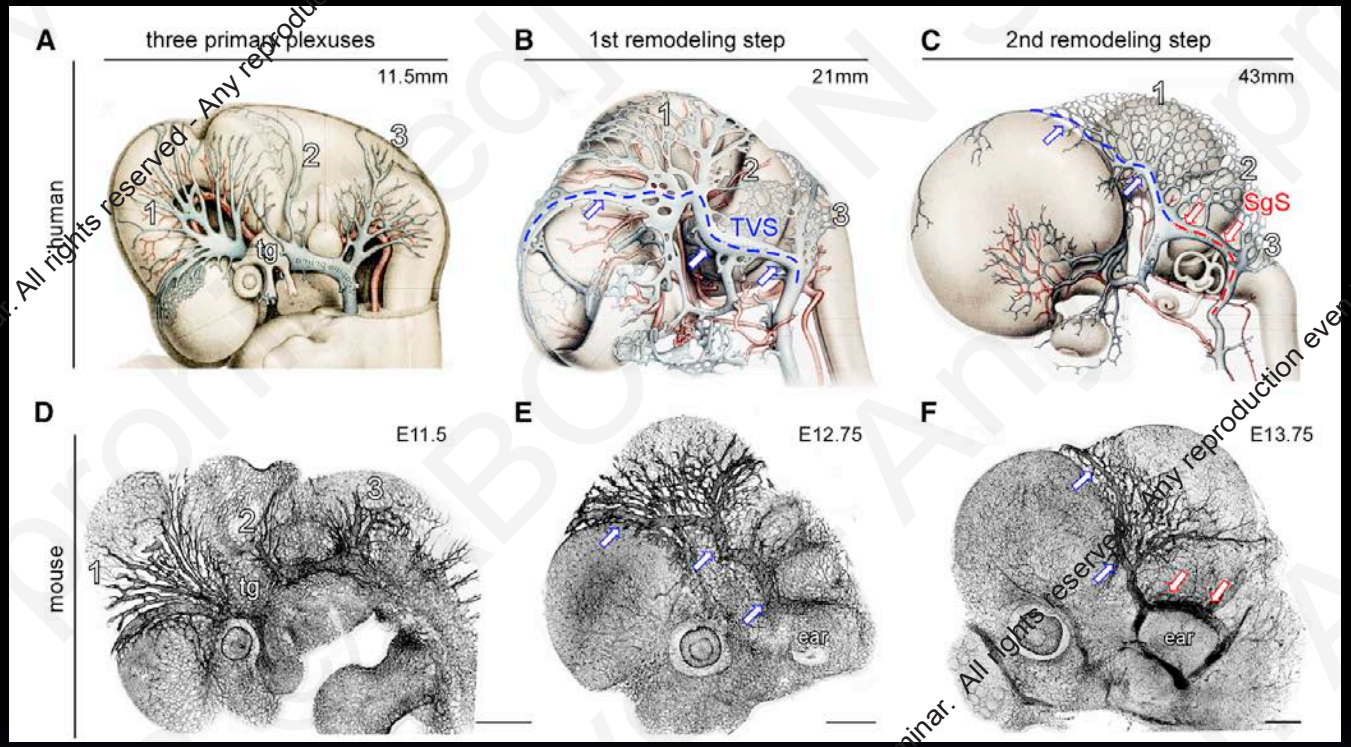

Figure 2. CV Growth and Remodeling Is Temporally and Spatially Coupled with Skull Development

(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 (temBone, 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.

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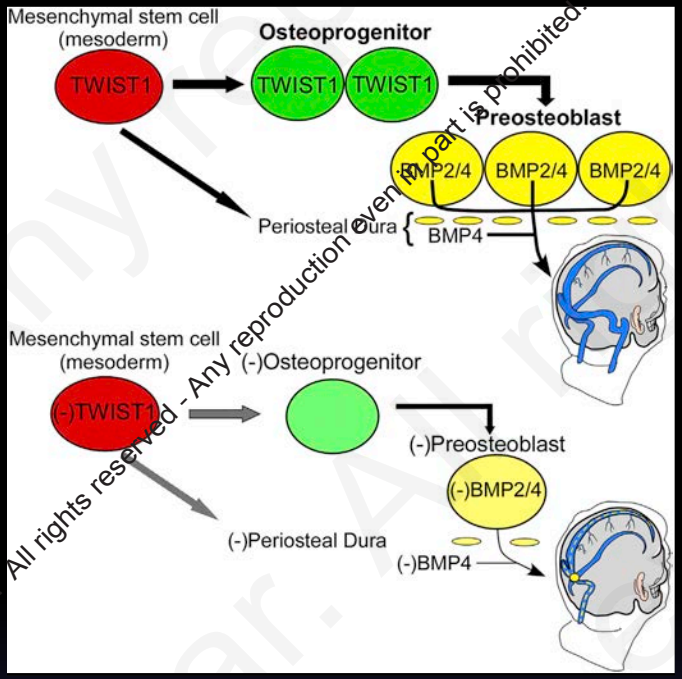
- Humans with Twist1 mutations and craniosynostosis have dural venous sinus abnormalities
- The investigators developed tools that allowed specific spatial manipulation of the Twist1 pathway within specific cell types (skull, dura, pia/arachnoid, endothelial cells)
- Surprisingly, Twist1 is dispensable 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!



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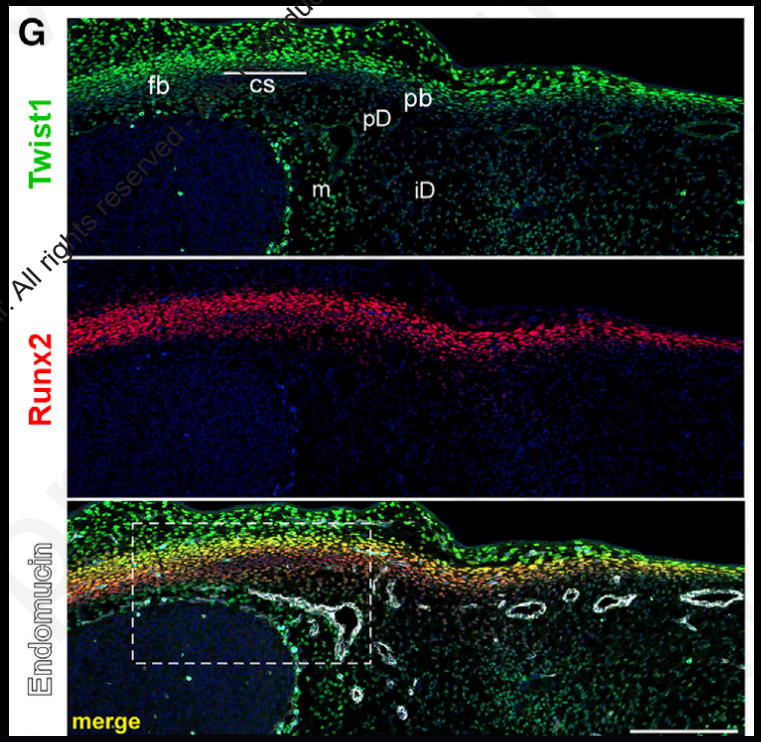

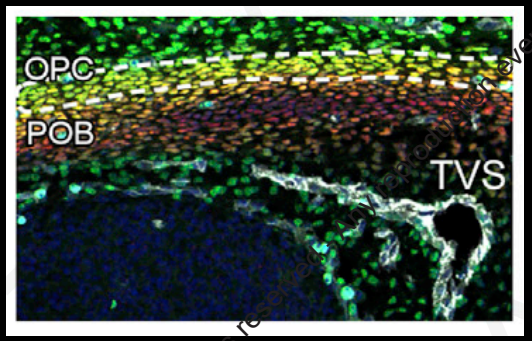

(G) E12.5 transverse section through the head at the level indicated in the top panel of (H). High levels of Twist1 expression co-localize with Runx2 in the frontal and parietal bone periosteum (frBone [fb] and parBone [pb]) and in the coronal suture (corSuture [cs]). Weaker expression is seen in periosteal 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.

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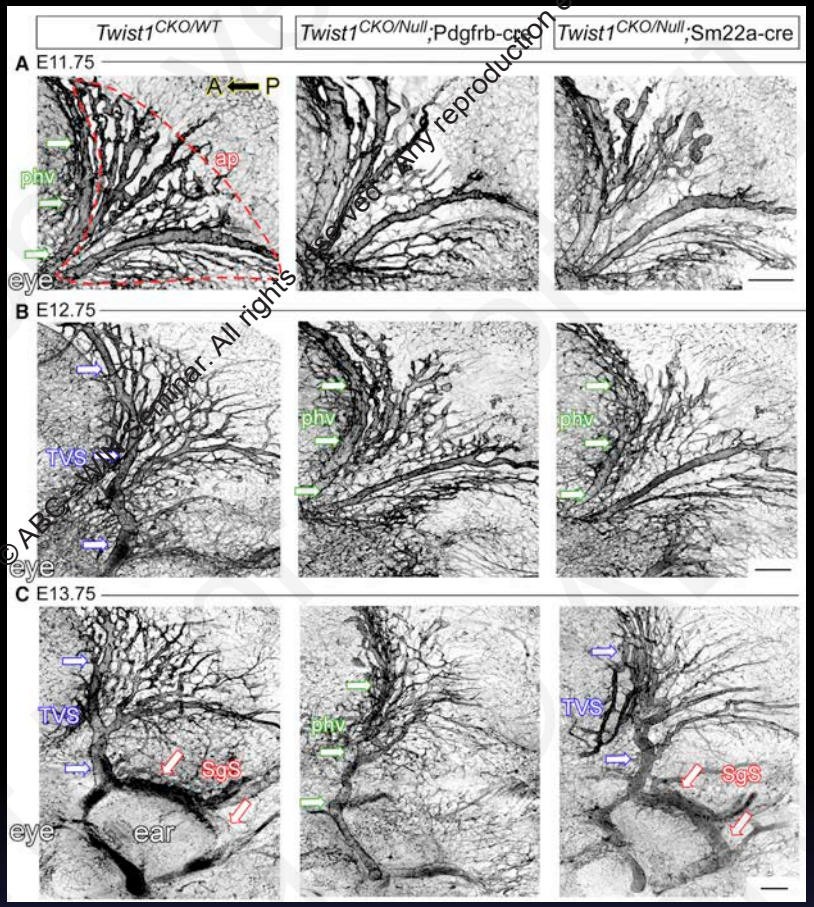

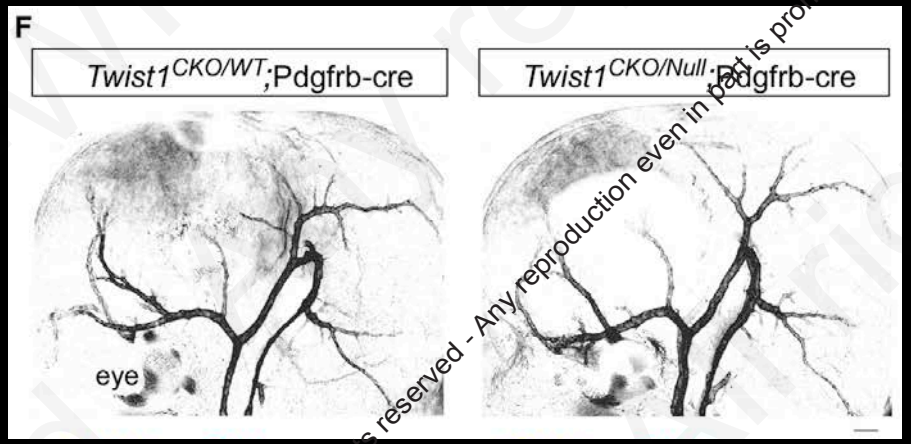

Figure 3. *Twist1* Mutants Have Perturbed CV Development Despite Normal Arterial Growth and Remodeling

(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 *Twist1*$^{CKO/-}$;Pd-Cre (n = 4) and *Twist1*$^{CKO/-}$;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 *Twist1*$^{CKO/-}$;Pd-Cre (n = 5) and *Twist1*$^{CKO/-}$;Sm-Cre (n = 6) embryos. antPlexus branching remains reduced. (C) By E13.75, the SgS remodels 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 *Twist1*$^{CKO/-}$;Pd-Cre embryos (n = 5).

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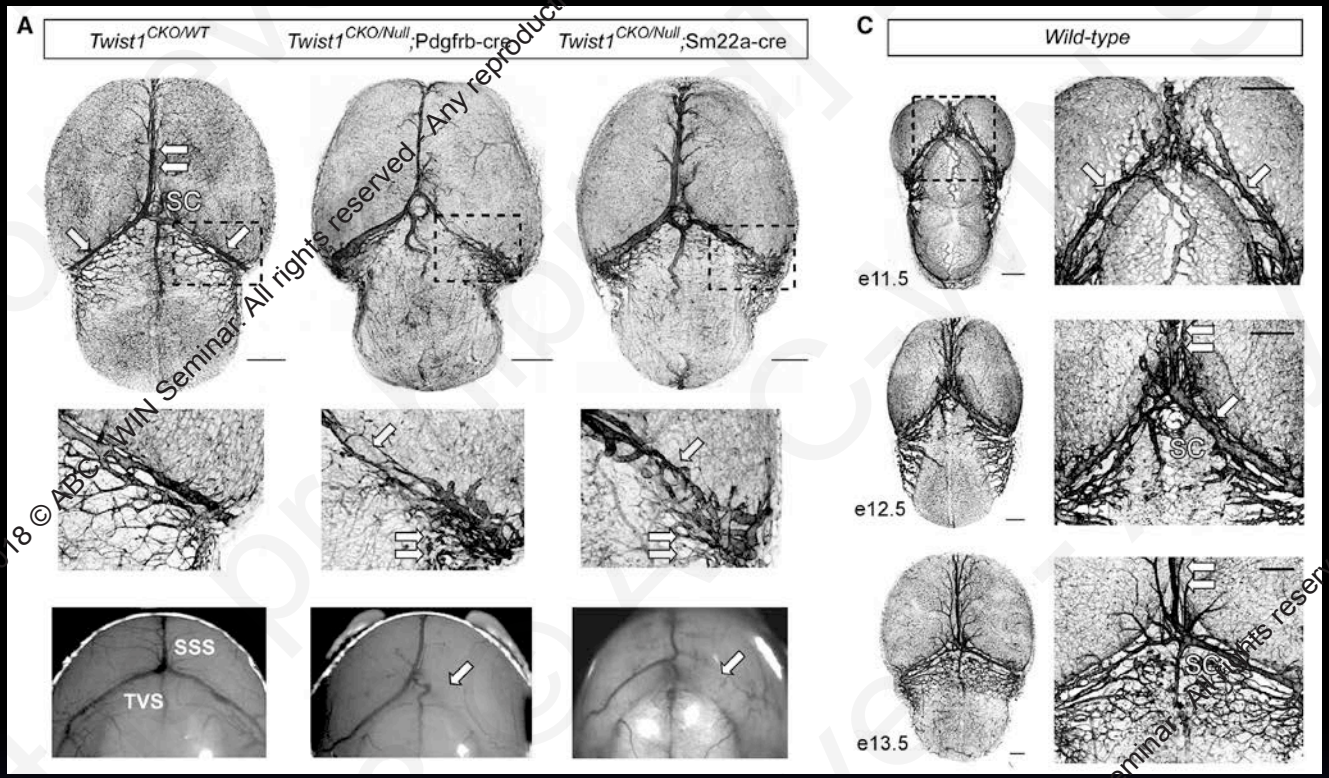

Figure 4. Wild-Type Mice Have TVS Morphogenetic Variation that Is Skewed toward Unilateral Regression in *Twist1* Mutant Mice

(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 *Twist1*$^{CKO/-}$;Pd-Cre and Sm-Cre mutants. Bottom: unilateral regression of the TVS (arrow) is fully penetrant and complete by E15.5 in *Twist1*$^{CKO/-}$;Pd-Cre and Sm-Cre mutants.

(E) Top: E18.5 *Twist1*$^{CKO/-}$;Sm-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 *Twist1*$^{CKO/-}$;Sm-Cre embryos and the right side is

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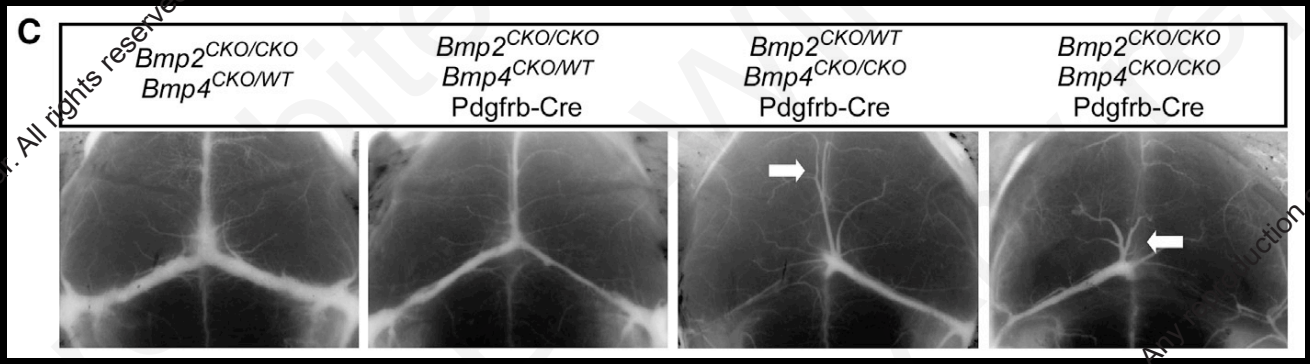

Figure 6. BMP2 and BMP4 Are Required for CV Growth and Remodeling

(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 minor vessel is hypoplastic or absent. The SSS is often hypoplastic, truncated, and/or split (arrows).

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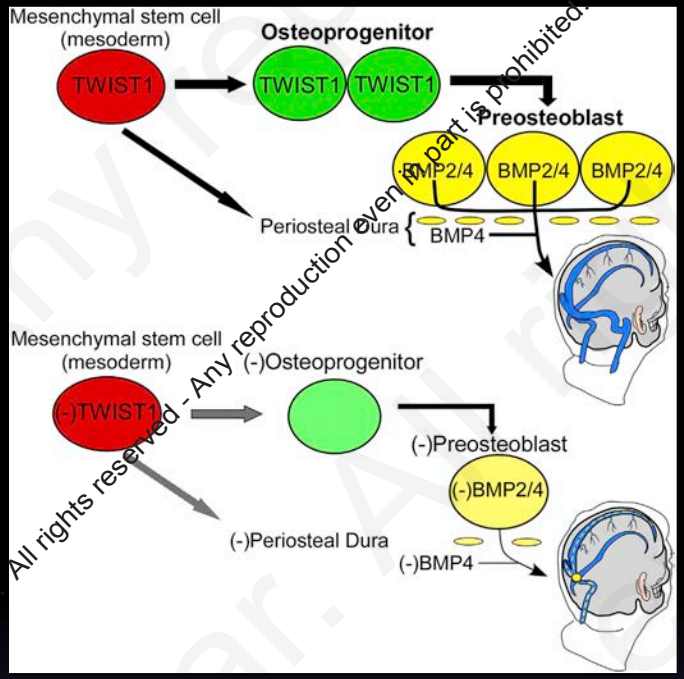
- Venous sinus malformations result from primary or secondary loss of paracrine BMP signaling from preosteoblasts and dura
- Dural venous sinus angiogenesis is strongly dependent on the development of neighboring tissue, and likely upon the growth environment of each fetus
- Arterial development is unaffected. 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 (eg 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

Snow in the Sahara Desert near the town of Ain Sefra, Algeria

Thank You