Editorial commentary

INR INTERVENTIONAL NEURORADIOLOGY

The median vein of prosencephalon of Markowski: From morphology to genetics

Interventional Neuroradiology
1–5

DOI: 10.1177/1591019920935316
journals.sagepub.com/home/ine
SAGE

Masaki Komiyama

Vein of Galen aneurysmal malformation (VGAM) is one of the most challenging vascular malformations in pediatric population, especially in neonates. This vascular malformation has drawn a great attention of many physicians because of its characteristic morphology and clinical presentation. With the advent of modern diagnostic modalities and therapeutic methods, prognosis of VGAM has been drastically improved in the past three decades.[1] However, treatment of VGAM is still challenging, which is proved by the article of Drs. Georges Rodesch and Stanislas Smajda in Paris.[2] I would like to comment on VGAM related to their excellent article. Embryology of VGAM was first proposed by Raybaud et al.,[3,4] who disclosed that VGAM is a remnant of the embryonic median vein of prosencephalon (MVP, vena mediana prosencephali). This vein is named also median vein of Markowski by Hochstetter in 1938[5] and primitive internal cerebral vein (ICV) by Padget in 1957.[6] First, I should start with the work of Józef Antoni Markowski and his life.[7]

Professor Józef Markowski at the University of Lvov, Poland

Józef Markowski was born on October 29, 1874 in Lvov, Poland (Lviv, Ukraine now). He studied philosophy and medicine in the University of Lvov. When he was still a medical student, he started to work at the Descriptive and Topographical Anatomy at the University of Lvov, where Henryk Kadyi (1851–1912) was the first professor of the department. Kadyi was known that he reasoned the anatomic term of *arteria radicularis magna* for the artery of Adamkiewicz.[8] Markowski left Lvov in 1906 to study embryology and comparative anatomy in Austria and Italy. Markowski became the second and eventually the last professor of the department of Descriptive and Topographical Anatomy at the University of Lvov in 1913 and headed it until 1939. Markowski's initial work centered on the development of sternum and its classification, but his most important works were on the development of the meninges and cranial sinuses, which were published in 1911[9] and 1922.[10] Other than these, Markowski contributed to many fields including effects of nicotine on regions of the brain controlling breathing, and the research on lymphatics, and so forth. As easily imagined from his time and place, he experienced many adversities including two world wars during many years of his tenure of the position. Due to outbreak of the Second World War, the university was closed. He eventually became ill and left Lvov, and finally died on May 29, 1947.[7]

Embryology of the MVP

MVP in human is an embryonic vein that appears early at approximately 6th week of gestation and disappears at 11th week. This temporary vein, described by Jósef Markowski in detail,[9,10] collects venous blood from the primitive choroid plexuses through bilateral dorsal choroidal veins. The choroid plexuses play a major role in nurture of the early prosencephalon (telencephalon + diencephalon) together with *the meninx primitiva* after closure of the neural tube at around 26th day. Then, the nurturing role is rendered from the primitive choroid plexuses to the intrinsic vascularization of the neural tube. Anatomically, MVP is not located within the tela choroidea and runs within the *velum interpositum (cisterna fissurae transversae)* and *quadrigeminal cistern* to reach the dorsal dura as a bridging vein. Thus, the anterior extreme of MVP is located at the paraphysis near the interventricular foramen of Monro. It is postulated that MVP usually drains through the embryonic falcine sinus to the posterior superior sagittal sinus.[4] MVP regresses from rostral to caudal direction progressively, and only the caudal portion, distal to the points where ICVs connect to MVP, remains as the great vein of Galen. This process is called "cranial regression" of MVP. ICVs run in the tela choroidea

Osaka City General Hospital, Miyakojima, Osaka, Japan

Corresponding author:
Masaki Komiyama, Osaka City General Hospital, 2-13-22, Miyakojima-Hondori, Moyakojima, Miyakojima, Osaka 534-0021, Japan.
Email: komiyama@japan-mail.com

and receive blood flow from the choroid plexuses through the superior choroidal veins. In the meanwhile, development of the basal structure of the prosencephalon requires the increasing blood supply by perforating arteries together with development of the deep venous system. Deep venous blood is collected to ICVs, which further connect to the great vein of Galen.

Embryology of VGAM

VGAM might develop when still unknown triggers to induce arteriovenous (AV) shunts effect on the deep vascular structures. There are two groups of feeding arteries, i.e., the prosencephalic arteries of the tela choroidea and mesencephalic arteries of the quadrigeminal plate.[3,4] Modern embryological knowledge from a number of studies on the segmental rostrocaudal gene expression allocates the midbrain (mesencephalon) into the structure of forebrain, not into the hindbrain.[11] Consequently, it follows that the above-mentioned feeding arteries belong to the forebrain (prosencephalic) arteries. Thus, it is easy to understand that their draining vein at the early choroidal stage is the prosencephalic vein, i.e., MVP. Anatomically, AV shunts are located at MVP in the subarachnoid spaces, i.e., in the *velum interpositum* and *quadrigeminal cisterns*. In rare situation, AV shunts are located at superior choroidal vein first near the foramen of Monro, then drain to MVP. In most cases, however, AV shunts are located directly at MVP in Galenic and/or quadrigeminal cisterns. Thus, in rare situation, feeding arteries can converge to two points: superior choroidal vein at the foramen of Monro anteriorly and MVP in Galenic and quadrigeminal cisterns posteriorly (Figure 1). Similar case is presented in Figure 6 in Drs. Rodesch and Smajda's paper.[2] Recognition of the precise AV shunt point is important for proper therapeutic planning.

High-flow, high-volume AV shunts supplied mainly by choroidal arteries induce the dilatation (ectasia) of MVP although this dilatation is called

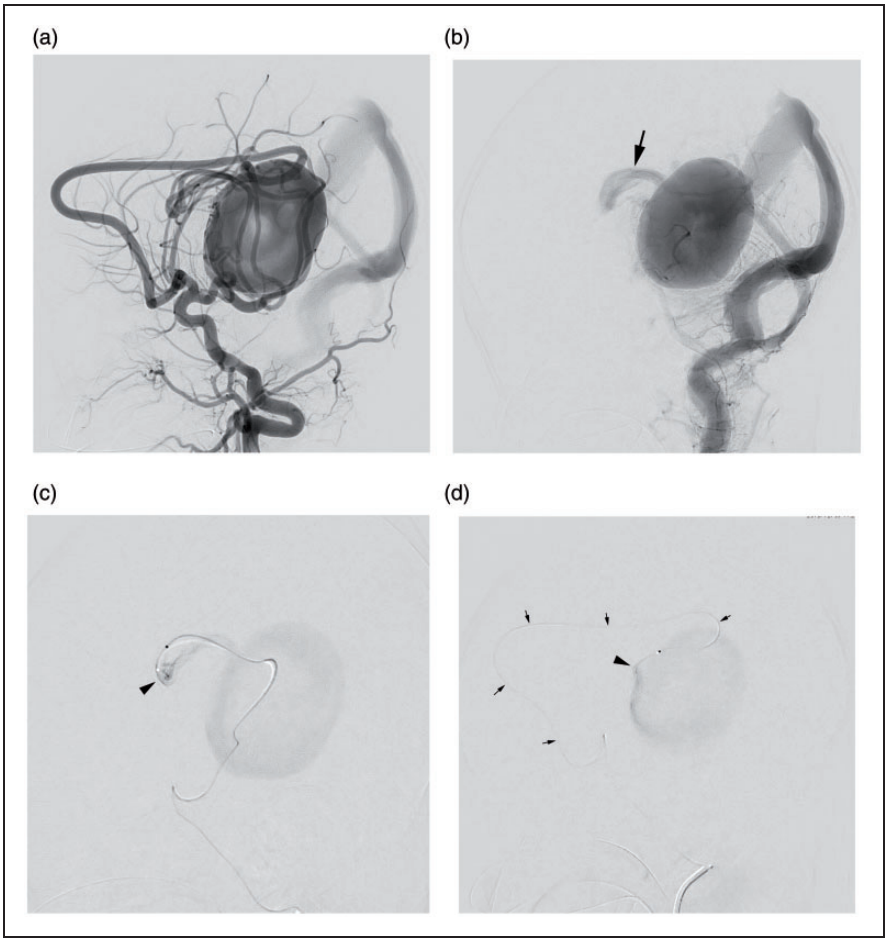

Figure 1. A 10-day-old boy with choroidal type of vein of Galen aneurysmal malformation. (a) Left common carotid artery injection (early arterial phase, lateral view). Aneurysmal dilatation is the remnant of the median vein of prosencephalon and is located within the subarachnoid space. (b) Left vertebral artery injection (late arterial phase, lateral view). Arrow indicates superior choroidal vein connecting to the remnant median vein of prosencephalon. (c) Selective injection from the microcatheter introduced in the right lateral posterior choroidal artery (lateral view). AV shunt point (arrowhead) is located at the junction from the feeder to superior choroidal vein at the foramen of Monro. (d) Selective injection from the microcatheter (arrows) introduced in the left anterior cerebral artery (lateral view). AV shunt point (arrowhead) is located at the anterior portion of the large varix.

aneurysmal malformation.[3,4] There are basically two types of angio-architecture for VGAM: choroidal and mural types. Choroidal type is more premature and clinically severe with many feeding arteries, some of which converge via the arterio-arterial maze, which then connects to the aneurysmal dilatation. Mural type is more mature and less severe clinically with one or two feeding arteries being directly connected to the wall of the aneurysmal dilatation. MVP does not regress as seen in the normal development, and it remains and drains the shunted blood to the posterior portion of the superior sagittal sinus through the falcine sinus. Straight sinus is often agenetic. Initially, it is believed that the persistent and large MVP is isolated from ICVs. However, it is proved that in many patients with VGAM, ICV is connected to the posterior portion of the dilated MVP at least on one side.[12] After treatment, these dormant connections become apparent due to disappearance of high-flow AV shunts. Embryologically, it cannot be said that VGAM is a developmental failure of Galenic venous system, but it is a developmental failure of "Markowski's venous system."

Phylogeny of the MVP

Dorsal sagittal, midline venous system is a prerequisite structure for vertebrates to collect all superficial venous drainages and conduit them to the extracranial venous system. Such dorsal venous structures have two different embryological anlages in vertebrates. Lower vertebrates have the single, large, straight cortical vein, which courses on midline in the subarachnoid space (Figure 2). Choroidal veins in amphibians and reptiles drain directly to this dorsal sagittal vein. In higher vertebrates, however, the dorsal midline venous collector is a venous sinus composed of the dura mater, i.e., superior (dorsal) sagittal sinus.[14] Higher vertebrates include birds and mammals. This structural difference is presumably caused by the expanding neopallium in birds and mammals while fishes, amphibians, and reptiles have the structures mainly composed of paleopallium and archipallium. These structural differences can be understood by the phylogenetic context, in which environmental changes from aquatic to terrestrial life of vertebrates have influenced to the leptomeningeal structures. Fishes have basically a single layer leptomeninx, and amphibians and reptiles have dual layers while birds and mammals (higher vertebrates) have triple layers, which allow to constitute the dural venous structure. In this sense, fishes, amphibians, and reptiles cannot have dural AV shunt, but can theoretically have a pial AV fistula at the dorsal sagittal vein, which is embryologically homologous to human VGAM.

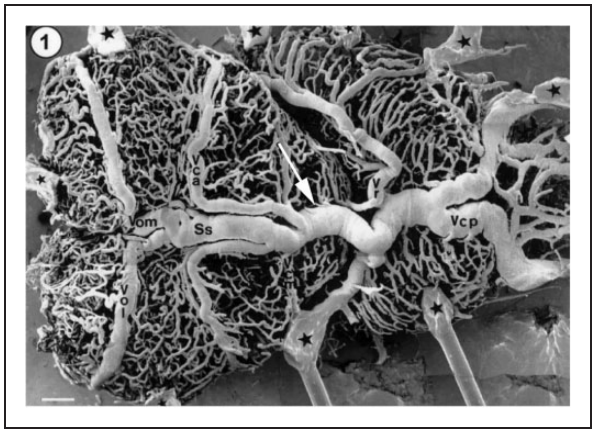

Figure 2. In hagfish (dorsal view of the venous drainage, vascular corrosion cast, left side is rostral), the dorsal sagittal vein (arrow) is homologous to the median vein of prosencephalon in human and courses within the subarachnoid space. All superficial veins drain to the dorsal sagittal vein. Quoted from Cecon's paper[13] with permission. Ss: sagittal sinus (vein), Vca: anterior cerebral vein, Vcp: posterior cerebral vein, Vol: lateral olfactory vein, and Vom: medial olfactory vein. Bar = 400 μm.

Genetics of VGAM (including correction of the reported data in literature)

In the past, there are several reports on the causative germline genes for VGAM. Most common mutation is RASA1 mutation and this syndrome is called as *c*apillary *m*alformation-*a*rterio*v*enous *m*alformation 1 (CM-AVM 1).[15] This syndrome is classically called CM-AVM, but to discriminate from the newly discovered syndrome caused by *EPHB4* gene mutation, number is added such as CM-AVM 1. Although clinical manifestations of *EPHB4* gene mutation mimic CM-AVM 1, marked difference is the presence of cutaneous telangiectasia, which is not common in CM-AVM 1. *EPHB4* mutation syndrome is called CM-AVM 2.[16]

The dorsal longitudinal vein in the zebra fish is phylogenetically homologue to MVP in mammals. Experiment to knock down *EPHB4* gene in the zebra fish resulted in formation of AV shunts at the dorsal longitudinal vein.[17] This suggests *EPHB4* gene is one of the causative genes of VGAM in human.

Only one VGAM patient with hereditary hemorrhagic telangiectasia 1 (HHT1, *endoglin* mutation) has been reported in the literature.[18] This newborn boy with severe heart failure, initially treated in another institution, was then followed by the present author for more than 10 years and now, he had started nosebleed, but had still not telangiectasia at the age of 12 years old. *Endoglin* mutation described in the paper[18] was *ENG*: p.Gln558fsX568 (c.1672-1684delGGGTC TCAAGACC), which was incorrect. It was confirmed as *ENG*: p.Gly558fs (c.1672-1684del13bp:ex12) by the present author's group (reported as family number 23 in Table 3a[19]). In the literature, there is another VGAM patient with HHT2 (*ACVRL1* mutation).[20] Unfortunately, from the case description including presented neuroradiological images, diagnosis of this

case is not VGAM. Thus, this case should not be included in the gene mutation list, which may cause VGAM. Duran et al.[21] recently reported the possible roles of mutations in chromatin modifier genes for the formation of VGAM.

In contrast to the germline mutation, recent researches on the pathogenesis of brain and spinal AVMs disclose that somatic mutation of *KRAS* and/or *BRAF* in the RAS-MAPK pathways causes brain and spinal AVMs with nidi,[22,23] but to my knowledge, there has been no report on *KRAS*/*BRAF* somatic mutations that caused VGAM.[24] Classic descriptions of the morphology of VGAM are important in diagnosis and therapeutic planning, but growing body of knowledge on genetics related to VGAM will shed light on understanding of the pathogenesis of this disease, and furthermore therapeutic implication in the near future.

Genetics cannot always solve the questions of pathogenesis of VGAM straightforwardly. As a matter of fact, among identical twins, one twin developed VGAM, and the other did not[25] despite the shared identical genes among them and the similar environmental circumstances in utero. Although many clinical aspects of VGAM are investigated so far, there still remain many questions to be answered. Ethical issues also exist in the treatment of neonatal VGAM patients who have already severe brain damages at the initial presentation. The cases presented by Drs. Georges Rodesch and Stanislas Smajda[2] contribute to understand state-of-the-art treatment in one of the most experienced institutes for pediatric vascular malformations in Europe and still challenging nature of this disease.

Acknowledgement

A part of this commentary was presented under the title of "Phylogenesis of the cerebral veins" in the second DEF seminar (Disease Education Forum) in Paris, 16–17 September 2019.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Masaki Komiyama https://orcid.org/0000-0003-0998-6315

References

1. Lasjaunias PL, Chng SM, Sachet M, et al. The management of vein of Galen aneurysmal malformations. *Neurosurgery* 2006; 59(Suppl 3): S184–S194; discussion S3–S13.
2. Rodesch G and Smajda S. Complications in pediatric interventional neuroradiology management. Reflections on a personal experience. *Interv Neuroradiol* (in press)
3. Raybaud CA and Strother CM. Persisting abnormal embryonic vessels in intracranial arteriovenous malformations. *Acta Radiol Suppl* 1986; 369: 136–138.
4. Raybaud CA, Strother CM and Hald JK. Aneurysms of the vein of Galen: embryonic considerations and anatomical features relating to the pathogenesis of the malformation. *Neuroradiology* 1989; 31: 109–128.
5. Hochstetter F. Übereine Varietät der Vena cerebralis basialis des Menschen nebst Bemerkungen über die Entwicklung bestimmter Hirnvenen. *Z Anat* 1938; 108: 311–336.
6. Padget D. The development of the cranial venous system in man form the view point of comparative anatomy. *Contr Embryol Carneg Inst* 1957; 611: 79–140.
7. Sokolowska-Pituch J, Walocha JA, Skrzat J, et al. In memory of professor Józef Markowski, an anatomist from Lvov. *Folia Morphol* 2007; 66: 360–364.
8. Kadyi H. *Über die Blutgefäße des menschlichen Rückenmarkers*. Lemberg: Gubrynowicz & Schmidt, 1889.
9. Markowski J. Über die Entwicklung der Sinus durae matris und der Hirnvenen bei menschlichen Embryonen15.5-49 mm. *Bulletin de l'Académie des Sciences de Cracovie Série B* 1911; 590–611.
10. Markowski J. Entwicklung der Sinus durae matris und der Hirnvenen des Menschen. *Bulletin international de l'Académie des Sciences et des Lettres. Classe des sciences mathematiques et naturelles. Serie B: sciences naturelles* 1921; (Numéro supplémentaire): 1–269.
11. Watson C, Bartholomaeus C and Puelles L. Time for radical changes in brain stem nomenclature – applying the lessons from developmental gene patterns. *Front Neuroanat* 2019; 13: 10.
12. Gailloud P, O'Riordan DP, Burger I, et al. Confirmation of communication between deep venous drainage and the vein of Galen after treatment of a vein of Galen aneurysmal malformation in an infant presenting with severe pulmonary hypertension. *AJNR Am J Neuroradiol* 2006; 27: 317–320.
13. Cecon S, Minnich B and Lametschwandtner A. Vascularization of the brains of the Atlantic and Pacific hagfishes, *Myxine glutinosa* and *Eptatretus stouti*: a scanning electron microscope study of vascular corrosion casts. *J Morphol* 2002; 253: 51–63.
14. Aurboonyawat T, Suthipongchai S, Pereira V, et al. Patterns of cranial venous system from the comparative anatomy in vertebrates. Part I, introduction and the dorsal venous system. *Interv Neuroradiol* 2007; 13: 335–344.
15. Revencu N, Boon LM, Mendola A, et al. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. *Hum Mutat* 2013; 34: 1632–1641.
16. Amyere M, Revencu N, Helaers R, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation* 2017; 136: 1037–1048.

17. Kawasaki J, Aegerter S, Fevurly RD, et al. RASA1 functions in EPHB4 signaling pathway to suppress endothelial mTORC1 activity. *J Clin Invest* 2014; 124: 2774–2784.
18. Tsutsumi Y, Kosaki R, Itoh Y, et al. Vein of Galen aneurysmal malformation associated with an endoglin gene mutation. *Pediatr* 2011; 128: e1307–e1310.
19. Komiyama M, Ishiguro T, Yamada O, et al. Hereditary hemorrhagic telangiectasia in Japanese patients. *J Hum Genet* 2014; 59: 37–41.
20. Chida A, Shintani M, Wakamatsu H, et al. ACVRL1 gene variant in a patient with vein of Galen aneurysmal malformation. *J Pediatr Genet* 2013; 2: 181–189.
21. Duran D, Zeng X, Jin SC, et al. Mutations in chromatin modifier and ephrin signaling genes in vein of Galen malformation. *Neuron* 2019; 101: 429–443.
22. Nikolaev SI, Vetiska S, Bonilla E, et al. Somatic activating KRAS mutations in arteriovenous malformations of the brain. *N Engl J Med* 2018; 378: 250–261.
23. Hong T, Yan Y, Li J, et al. High prevalence of KRAS/BRAF somatic mutations in brain and spinal cord arteriovenous malformations. *Brain* 2019; 142: 23–34.
24. Ota T and Komiyama M. Pathogenesis of non-hereditary brain arteriovenous malformation and therapeutic implications. *Interv Neuroradiol* 2020; 26: 244–253.
25. Komiyama M, Miyatake S, Terada A, et al. Vein of Galen aneurysmal malformation in monozygotic twin. *World Neurosurg* 2016; 91: 672.e11–672.e15.