Vein of Galen Aneurysmal Malformation in Monozygotic Twin

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Key words
- Embolization
- Gene analysis
- Identical twin
- Vein of Galen aneurysmal malformation
- Whole-exome sequencing

Abbreviations and Acronyms
ALK1: Activin receptor-like kinase 1
AV: Arteriovenous
BMPR2: Bone morphogenetic protein receptor type II
CNV: Copy number variation
ENG: Endoglin
KRIT1: KRIT1, ankyrin repeat containing
MR: Magnetic resonance
PDCD10: Programmed cell death 10
PTEN: Phosphatase and tensin homolog
RASA1: RAS p21 protein activator 1
SMAD4: Mothers against decapentaplegic homolog 4
TTTS: Twin-twin transfusion syndrome
VGAM: Vein of Galen aneurysmal malformation
WES: Whole-exome sequencing
XHMM: eXome-Hidden Markov Model

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BACKGROUND: **Vein of Galen aneurysmal malformation (VGAM) is a rare pediatric vascular malformation of the brain. Genetic backgrounds are not well elucidated. We report on a monozygotic twin with VGAM and his endovascular treatment, and the genetic analyses of the twins and their parents.**

CASE DESCRIPTION: **In a monochorionic, diamniotic pregnancy of a 28-year-old healthy woman, monozygotic twins were born by emergency caesarian section because of fetal distress of the smaller twin at 25 weeks' and 4 days' gestation. Although a postnatal cranial ultrasound failed to detect VGAM in the smaller twin, mild heart failure persisted. A brain magnetic resonance (MR) examination of this twin on day 82 revealed choroidal VGAM. The twin was treated successfully by two sessions of embolization at 6 and 8 months of age. An MR examination at 1 year showed minimal residual arteriovenous shunts. He developed normally similar to the normal co-twin, with a follow-up period of 1 year and 6 months. As for the affected twin, no germline mutation or copy number variations were identified in *ENG*, *ALK1*, *SMAD4*, *BMPR2*, *PTEN*, *RASA1*, *KRIT1*, *Marcavernin*, or *PDCD10* through whole-exome sequencing (WES).**

CONCLUSION: **We have reported a rare combination of a monozygotic twin and VGAM and the successful endovascular treatment. Phenotypic discordance in monozygotic twins established early in embryogenesis could be attributable to environmental or epigenetic factors.**

INTRODUCTION

Vein of Galen aneurysmal malformations (VGAMs) are rare pediatric vascular malformations of the brain. These malformations account for 1% of all intracranial vascular malformations and 30% of pediatric ones.[1] Embryologic events occurring between 6 and 11 weeks' gestation in the choroidal venous system of prosencephalon are presumed to result in this arteriovenous (AV) malformation.[2] Although genetic backgrounds are not well elucidated, the RASA1 (MIM #139150) mutation was reported to be associated with VGAM in 5 cases, and the Endoglin (*ENG*; MIM #187300) mutation was reported to be associated with VGAM 1 case.[3–5] Because monozygotic twins have essentially the same genomes, development of VGAM in only one twin could be attributable to environmental or epigenetic factors. We report on a patient with VGAM among monozygotic twins in monochorionic, diamniotic pregnancy. The patient underwent successful endovascular treatment. Detailed genetic analyses of the twins and parents were also discussed.

CASE PRESENTATION

The pregnancy of monochorionic, diamniotic twins was detected by ultrasound at the gestational period of 12 weeks and 5 days in a 28-year-old healthy woman who had no remarkable medical or family history. This was the first spontaneous pregnancy for the mother, and it was not induced by fertility drugs or treatment. Although both twins grew in the uterus without the complication of twin-twin transfusion syndrome (TTTS), fetal distress of a smaller twin (twin A) prompted an emergency caesarian section at 25 weeks' and 4 days' gestation. The birth weight of twin A was 774 g (−2.1 SD) with Apgar scores being 3 and 8 at 5 and 10 minutes, respectively. The larger twin (twin B) weighed 1200 g. No birthmarks or superficial anomalies were noticed in either twin at birth or thereafter. Although a postnatal cranial ultrasound failed to detect VGAM in twin A, mild cardiomegaly was depicted by a cardiothoracic ratio of 59% on plain X-ray film and reverse diastolic flow in the descending aorta showed by ultrasound persisted. Because a brain ultrasound detected a vascular anomaly on day 82, twin A underwent a brain magnetic resonance (MR) examination, which revealed choroidal VGAM (Figure 1). A brain MR examination of twin B on the same day was normal without any AV shunts. Heart failure in twin A was further managed with diuretics.

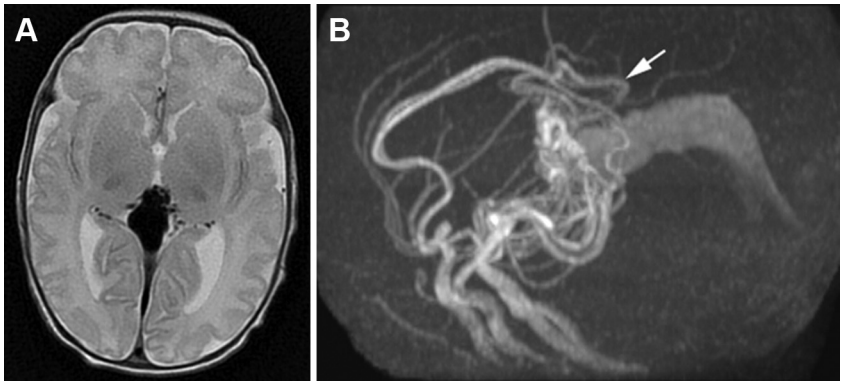

Figure 1. On day 82, T2-weighted image (**A**) of twin A shows a lesion in the Galenic cistern with flow void, indicative of the dilated great vein of Galen. (**B**) Magnetic resonance angiography (near lateral view) clearly demonstrates the angioarchitecture of the choroidal type of the vein of Galen aneurysmal malformation supplied by many choroidal arteries including the choroidal branch of the distal anterior cerebral artery (*arrow*).

Twin A was transferred to us on day 103 (estimated gestational age of 43 weeks and 2 days) to treat heart failure owing to VGAM. At admission, twin A weighed 2460 g. No apparent neurologic deficits were observed, but cranial bruits were audible anywhere around the head. We determined that an emergency embolization was not necessary; therefore, we planned to perform a scheduled embolization at 6 months. Medical management for heart failure was continued. This patient was discharged home on day 141 after birth, because his heart failure was well managed with medication and his weight had increased steadily. We performed the first transfemoral embolization at 6 months (body weight, 3.9 kg). Four feeding arteries (choroidal arteries) were occluded with 50%–75% glue injections (Figure 2). This embolization improved the patient's heart failure to such a degree that he no longer required diuretics. To occlude the remaining AV fistulas, the second intervention was performed at 8 months (body weight, 5.7 kg). Two additional feeders were occluded with 80% glue injections. Residual AV shunts were reduced markedly (Figure 3). An MR examination at 1 year showed minimal residual AV shunts, but was otherwise normal (Figure 4). Twin A remained neurologically normal and developed similarly to twin B at the last follow-up at 1 year and 6 months.

GENETIC ANALYSES

Methods

Affected twin A, unaffected twin B, and their parents were subjected to the whole-exome sequencing (WES) analysis. Experimental protocols were approved by the Committee for Ethical Issues at Yokohama City University School of Medicine. Written informed consent was obtained from the parents. WES was performed using genomic DNA obtained from saliva as described in the previous paper.[6] Copy number variation (CNV) analysis using WES data was performed by eXome-Hidden Markov Model (XHMM; https://atgu.mgh.harvard.edu/xhmm/tutorial.shtml) for whole exon-wide analysis,[7] and Nord's method for the analysis of target genes.[8]

Results

In WES, the read depth at a site means how thick the site is covered by each sequence read—in other words, how many times (x) a site is read in a WES. The thicker the depth is at a site, the more accurate the sequence at the site. The coverage of WES analysis means how much of the area of the targeted whole coding regions the WES covers. The more regions covered, the more comprehensive the analysis of the entire genome. We present WES mean depth and coverage to show the quality of the WES. WES covered more than 95.7%–97.2% of the total coding regions in RefSeq (NCBI Reference Sequence Database) by 10x read depth or more. The mean depth for the covered region was 83.6–89.4x. This means that the WES performance was good enough to proceed further to data analysis. As for twin A, no germline mutations or CNVs were identified in *ENG*, *ALK1* (activin receptor-like kinase 1), *SMAD4* (Mothers against decapentaplegic homolog 4), *BMPR2* (Bone morphogenetic protein receptor type II), *PTEN* (phosphatase and tensin homolog), *RASA1*, *KRIT1* (KRIT1, ankyrin repeat containing), *Marcavernin*, or *PDCD10* (programmed cell death 10) through WES. By comparing detected CNVs between twins A and B obtained by XHMM, we did not find any twin A–specific pathologic CNVs.

DISCUSSION

Twinning

Monozygotic twins are born at a rate of 3–4 in every 1000 births, which is fairly constant rate around the world. However, dizygotic twinning is more frequent than monozygotic twinning and varies by different geographical localities.[2,9] In fact in 1998, dizygotic twins were born at a rate of 4.6 per 1000 births in Japan, 10.5 per 1000 births in Germany, and 12.3 per 1000 births in The Netherlands.[2] Monozygotic twinning can cause a twofold to threefold increase in congenital anomalies in comparison to single births. Thus, approximately 10% of monozygotic twins are born with a congenital anomaly.[9] However, the mechanism of monozygotic twinning and its related anomalies are still elusive.

Embryology and Clinical Presentation of VGAM

VGAM is a rare brain AV malformation. The choroidal venous system is an important draining system of the prosencephalon in the early embryonal stage around 6–11 weeks gestation prior to the brain's venous system maturing. Failure of the choroidal venous system to develop normally can result in the persistence of AV shunts from choroidal vessels to the median prosencephalic vein of Markowski.[10] A dilated venous pouch is located in the velum interpositum and quadrigeminal cistern. When there are many arterial networks between the

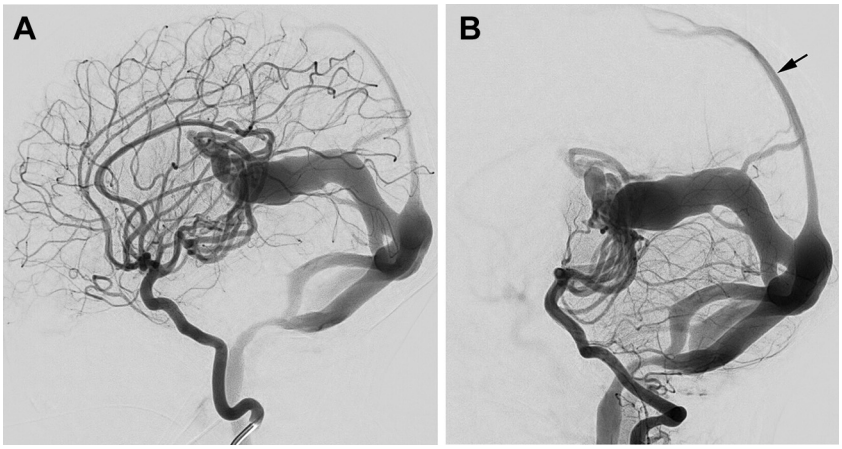

Figure 2. At 6 months, right internal carotid artery injection (**A**, lateral view) and left vertebral artery injection (**B**, lateral view) immediately before the first embolization shows vein of Galen aneurysmal malformation supplied by many choroidal arteries, and drained to the dilated straight sinus. (**B**) *Arrow* indicates the reflux of the arteriovenous shunts to the superior sagittal sinus.

feeding arteries and the dilated venous pouch, VGAM is called the *choroidal type*. When a few number of AV shunts are located on the wall of the dilated venous pouch, VGAM is called the *mural type*.

VGAM typically manifests with congestive heart failure in the neonatal period and the antenatal period. Many cases of VGAM manifesting in these periods are the choroidal type of VGAM. Infants with VGAM manifest hydrocephalus and macrocephaly, and older children exhibit developmental delays, seizure, and headache.[11,12] VGAMs appearing in infancy and childhood are mostly the mural type of VGAM.

VGAM in Twin and Familial VGAM

Steggerda et al.[13] reported on a monozygotic twin with VGAM in detail. A 32-year-old woman was pregnant with monochorionic, diamniotic twins, who developed TTTS. TTTS complicates approximately 10%–15% of monochorionic, diamniotic twin pregnancies, mostly in the second trimester, because of an unbalanced blood flow between the donor and recipient twins via placental vascular communication.[1] In this twin pair, umbilical cord coagulation and amniodrainage of the recipient twin (larger twin) were performed because of a cardiac abnormality of this twin at 18 weeks' gestation. The donor twin (smaller twin) was born weighing 800 g at 30 weeks' gestation by caesarean section because of fetal distress. He developed respiratory distress syndrome owing to VGAM, which was confirmed by MR imaging. Because of the small size of the infant, endovascular treatment was impossible, and he died of cardiorespiratory failure on day 49. An autopsy on the recipient twin showed a macerated fetus weighing of 93 g, having transposition of the great arteries and a large ventricular septal defect. Thus, these monozygotic twins with TTTS presented with VGAM and transposition of the great arteries, respectively. No genetic data was available in this twin pair.

Revencu et al.[14] reported on VGAM in monozygotic twins in associated with the *RASA1* mutation. Although a detailed description was not available, the co-twin did not present with AV shunts even with the same *RASA1* mutation.

Xu et al.[15] reported on a 44-year-old woman with asymptomatic VGAM who had no remarkable medical history except for a stillbirth pregnancy caused by VGAM. The authors did not describe the child with VGAM in detail (e.g., age of stillbirth, sex, presence of hydrops fetalis, diagnostic method of VGAM). This is the only case with family-associated VGAM in the literature. Jones et al.[16] reported a neonate with VGAM among triplets. This neonate had a birth weight of 1481 g and was treated with embolization in the chronic stage. No details, including sex, zygosity, genetic data, and clinical data of the remaining triplets, were reported.

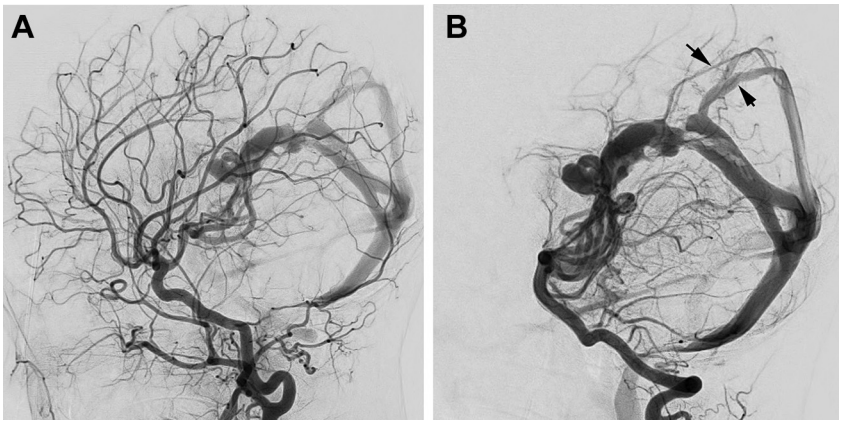

Figure 3. At 8 months, right common carotid artery injection (**A**, lateral view) and left vertebral artery injection (**B**, lateral view) just before the second embolization show markedly reduced arteriovenous shunts. *Arrow* indicates the duplicated falcine sinuses, which were not apparent previously.

Treatment of VGAM

Indications of treatment for VGAMs depend on clinical presentations and timing. Currently, transarterial embolization is the first-line treatment for VGAM.[3,12] Glue embolization is commonly preferred to coil embolization. For neonates, uncontrollable severe heart failure, even with aggressive medical treatment, prompts embolization. Hydrocephalus or macrocrania in infants is treated initially by embolization in lieu of a ventriculoperitoneal shunt operation because hydrovenous disorder is caused by brain AV shunts.[17] If the patient has marked

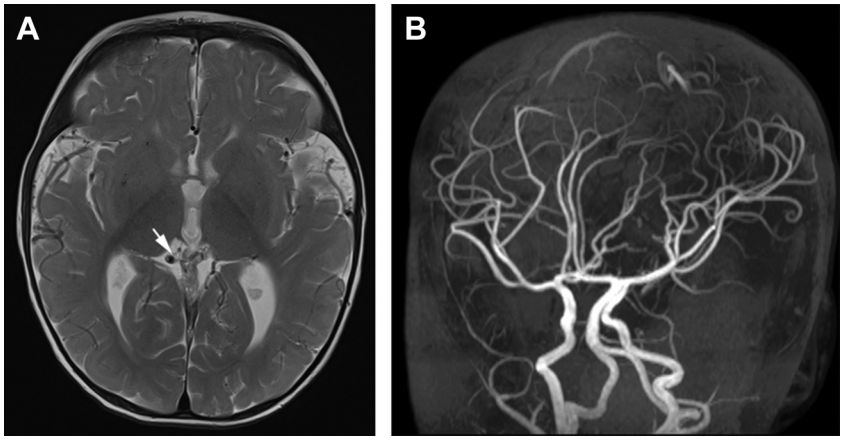

Figure 4. At 1 year, although the T2-weighted magnetic resonance (MR) imaging (**A**) shows possible small residual AV shunts (*arrow*), MR angiography (**B**) fails to show them.

brain damage, active treatment is usually withheld. Since treating low-birthweight neonates with brain AV shunts is challenging, a body weight greater than 2700 g is usually required for transfemoral embolization.[18] Although the twin patient presented here weighed approximately 2700 g on day 125, we postponed the first intervention until 6 months of age because his heart failure was well managed with medication.

Genetic Backgrounds of VGAM

Identical means completely the same, but genes and phenotypes in monozygotic twins are not completely identical. Genetically, they are nearly identical (>99%) but not completely so. Therefore, *monozygotic* is a more appropriate term than *identical*. An epigenetic difference between monozygotic twins includes CNV, which could result in discordant phenotypes[4]; however, this difference was not found in our twin patient. Environmental difference between a monozygotic twin pair can start soon after fertilization. A monochorionic placenta provides a different vascular environment; a small uterine cavity, designed for essentially one fetus, provides a different environment as well. VGAM in monozygotic twins under the circumstance of TTTS is reported only once in the literature,[13] and it is the result of a possible environmental factor in the vascular or hemodynamic influences in the early embryonal stage.

The causative genetic mutations and VGAM have been reported in 5 cases of the *RASA1*[14,19] mutation and 1 case of the *ENG* mutation.[5] *RASA1* encodes the protein p120RasGAP, which is an inhibitor of RAS p21 that controls cellular growth, proliferation, survival, and differentiation.[14] The *RASA1* mutation also causes Parkes-Weber syndrome (MIM #608355) and capillary malformation-arteriovenous malformation (MIM #608354). *ENG* codes for accessory protein receptors of the transforming growth factor-β receptor complex, and *ALK1* encodes for transmembrane kinase, which participates the transforming growth factor-β signaling. *ALK1* regulates endothelial proliferation and migration, and *ENG* promotes *ALK1* function in general.[20] The *ENG* mutation is causative of hereditary hemorrhagic telangiectasia type 1.[21] As for the pathogenesis of VGAM in our case, environmental or epigenetic effects on the smaller twin in the early embryonal stage when choroidal draining system matures to the adult form are a possibility. However, genetic factors, including *RASA1* and endoglin mutations, and CNVs were denied.

CONCLUSION

We report a rare combination of a monozygotic twin and VGAM without germline mutation or CNV. Phenotypical discordance in monozygotic twins could be attributable to environmental or epigenetic factors, or both.

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