



Vasospasm Following Hemispherectomy: A Case Report of a Novel Complication

Amr Morsi¹, Andres Maldonado⁴, Dennis La³, Ahsan N.V. Moosa², Elia Pestana-Knight², William Bingaman¹

Key words

- COL4A1 gene mutation
- Diffuse cerebral ischemia
- Hemispherectomy
- Vasospasm

Abbreviations and Acronyms

ACMG: American College of Medical Genetics

EEG: Electroencephalogram

ICU: Intensive care unit

From the Departments of ¹Neurosurgery and ²Neurology and ³Genomic Medicine Institute, Cleveland Clinic Foundation, Cleveland, Ohio; and ⁴Department of Neurosurgery, University of Illinois College of Medicine Peoria, Peoria, Illinois, USA

To whom correspondence should be addressed:

Amr Morsi M.D.

[E-mail: morsia@ccf.org]

Citation: *World Neurosurg.* (2020) 137:357-361.

<https://doi.org/10.1016/j.wneu.2020.02.020>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2020 Elsevier Inc. All rights reserved.

INTRODUCTION

Anatomic hemispherectomy was first introduced independently by Dandy and L'Hermite for the treatment of malignant glioma of the cerebral hemisphere in 1928.¹ The use of this radical procedure in epilepsy was first employed by the Canadian neurosurgeon McKenzie² in 1938 with the purpose of treating intractable seizures associated with infantile-type hemiplegia. In 1950, the first pediatric hemispherectomy series consisting of 12 patients with infantile-type hemiplegia and seizures was published by Krynauw.³ Since then, the procedure has undergone various technical modifications to improve seizure-free outcomes and minimize complication rates. However, anatomic hemispherectomy soon became associated with a delayed complication known as superficial cerebral hemosiderosis.⁴ This led the procedure to be largely abandoned until 1983, when Rasmussen⁵ presented functional hemispherectomy, a more limited resection with preservation

■ **BACKGROUND:** Hemispherectomy has been shown to be successful in treating medically intractable epilepsy, with favorable seizure-free outcomes. However, the procedure is technically challenging with high rates of in-hospital complications. We present a unique case of functional hemispherectomy complicated by diffuse cerebral vasospasm and subsequent death in a patient with COL4A1 gene mutation.

■ **CASE DESCRIPTION:** A 17-year-old boy presented with right hemispheric epilepsy and a previously diagnosed autosomal dominant heterozygous COL4A1 gene mutation (c.4380T>G;p.Cys1460Trp). Functional hemispherectomy was performed without complications. On postoperative day 8, he developed an acute decline in neurologic status requiring urgent intubation for airway protection. Magnetic resonance imaging revealed areas of restricted diffusion throughout bilateral hemispheres that was explained by severe vasospasm and minimal cerebral blood flow seen on cerebral angiography. Intra-arterial calcium channel blocker infusion and balloon angioplasty were attempted without improvement in perfusion. With a worsening clinical picture, he was transitioned to comfort care and died.

■ **CONCLUSIONS:** This is the first report in the literature describing global vasospasm and delayed cerebral ischemia following hemispherectomy in a patient carrying COL4A1 gene mutation. We postulate that his COL4A1 gene mutation might have resulted in this exaggerated vasospasm despite minimal residual postoperative subarachnoid hemorrhage burden. This hypothesis needs to be studied in animal models of this genetic disorder.

of frontal and occipital lobes along with complete hemispheric disconnection that retained the therapeutic effectiveness of anatomic hemispherectomy while reducing complication rates. Rasmussen's functional hemispherectomy approach gained popularity in the ensuing years and has been further modified to allow for even less tissue resection with more refined, less invasive disconnection techniques.

Anatomic and functional hemispherectomy procedures have been shown to be successful in treating medically intractable epilepsy in patients with diffuse unilateral hemispheric disease, with seizure-free outcomes ranging from 52% to 79%.⁶ Despite high success rates and favorable seizure-free outcomes, hemispherectomy is technically challenging with high rates of in-hospital complications. A more recent article used the Nationwide

Inpatient Sample database to report on in-hospital complication rates documented in a large population of patients undergoing hemispherectomy over a 23-year period.⁷ This series found that among 1611 hospitalizations for hemispherectomy procedures, the most common in-hospital complication was the need for a blood transfusion (30%), followed by meningitis (10%), hydrocephalus (8%), postoperative hematoma/stroke (8%), adverse pulmonary events (8%), and mortality (2%). Cerebral vasospasm and resulting delayed cerebral ischemia have been reported in the literature as rare complications of transphenoidal and transcranial surgeries for the treatment of craniopharyngioma and pituitary tumors.^{8,9} To our knowledge, diffuse cerebral vasospasm as a complication of hemispherectomy has not been previously reported in the

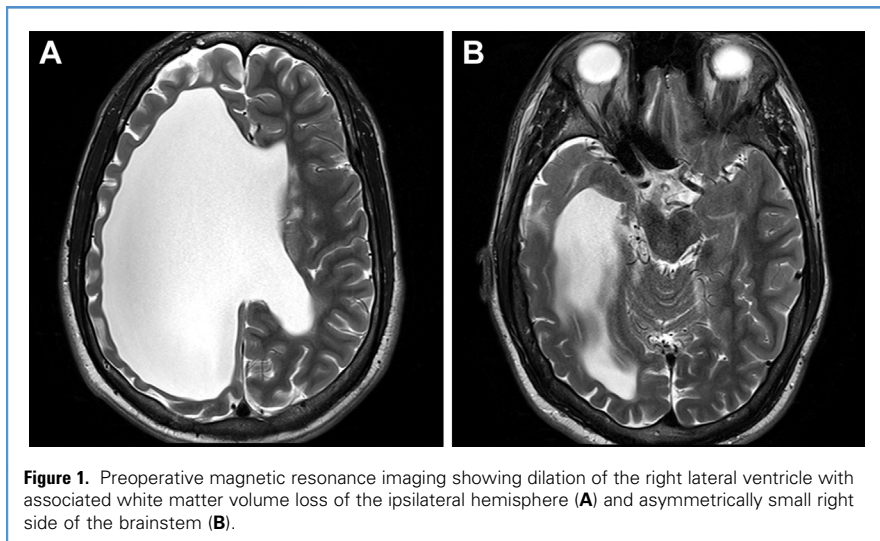


Figure 1. Preoperative magnetic resonance imaging showing dilation of the right lateral ventricle with associated white matter volume loss of the ipsilateral hemisphere (A) and asymmetrically small right side of the brainstem (B).

literature. We present here a unique case of functional hemispherectomy complicated by diffuse cerebral vasospasm, delayed cerebral ischemia, and subsequent death in a patient with a missense variant in the *COL4A1* gene.

CASE DESCRIPTION

Presentation

A 17-year-old boy presented with medically refractory right hemispheric focal epilepsy, left hemiplegia, left hemianopia, and developmental delay secondary to a vascular brain injury in the perinatal period. The patient was born at term gestation to a 26-year-old primigravida mother by induced vaginal delivery using forceps. Apgar scores were 1, 3, and 5 at 1, 5, and 10 minutes. He was found to be hypoxic with a collapsed lung requiring several days of assisted mechanical ventilation. Initial seizures started in the neonatal period and were treated with phenobarbital during infancy. This was later switched to oxcarbazepine when seizures recurred at 2 years of age, triggered by a fever. He was reported to be seizure-free until the age of 15 when seizures recurred and became refractory to medical treatment despite multiple antiepileptic drug trials. The seizures started with an abdominal aura, followed by repetitive swallowing movements, and then shaking of the lower extremities. The seizures lasted 2–4 minutes and occurred once a week. An

autosomal dominant heterozygous *COL4A1* gene mutation (c.4380T>G; p.Cys1460Trp) was diagnosed. The variant was not observed in >140,000 people from the general population.¹⁰ The substitution from cysteine to a tryptophan at residue 1460 affects the formation of a disulfide bond that could lead to decreased stability of the *COL4A1* encoded protein.¹¹ The variant was classified according to American College of Medical Genetics (ACMG) guidelines as likely pathogenic.¹²

Preoperative Evaluation

Magnetic resonance imaging showed marked dilation of the right lateral ventricle associated with white matter volume loss of the ipsilateral hemisphere and asymmetrically small right side of the brainstem. Mild dilation of the left lateral ventricle in the peritrigonal region was also noted. Major intracranial arterial structures and dural venous sinuses showed typical flow void, suggesting patency by spin echo criteria (Figure 1A and B). Video electroencephalogram (EEG) monitoring revealed pervasive interictal epileptiform abnormalities, sleep activated right hemispheric runs of epileptiform discharges in the right central chain, and recorded epigastric auras and autonomic seizures with right hemispheric ictal EEG patterns. The case was presented at our institutional epilepsy management meeting and approved for right functional hemispherectomy.

Surgical Approach

After general endotracheal anesthesia was obtained, the patient was placed with the right side up. The head was prepared and draped. A straight incision was marked over the right hemisphere and subsequently infiltrated with local anesthesia. Skin incision was made with a No. 10 scalpel, the temporalis muscle was undermined, and a central right craniotomy flap was performed. The dura mater was tacked up and opened sharply. The underlying brain was abnormal in appearance owing to the patient's remote right hemispheric insult. The dilated ventricle was entered, and disconnection of the corpus callosum and frontal, temporal, parietal, and occipital lobes was successfully achieved. Dissection and subsequent resection of the mesial temporal structures, excluding the rudimentary later temporal lobe, were conducted in a subpial fashion without violating the pia mater. Once the disconnection was completed, an intraventricular drain was placed. The dura was closed, the bone flap was secured, and the wound was approximated in a standard fashion. Estimated blood loss was 100 mL, and total procedure time was 2 hours and 20 minutes.

Postoperative Course

There were no intraoperative complications, and the patient emerged from anesthesia with a neurologic examination the same as his baseline. He was extubated and subsequently transferred to the pediatric intensive care unit (ICU) for closer monitoring, per standard of care. The immediate postoperative course was uncomplicated. A computed tomography scan of the head on day 1 following surgery showed expected postoperative changes (Figure 2A and B), and the external ventricular drain was opened to drain cerebrospinal fluid. The external ventricular drain was set to 10 mm Hg with a recorded output of 32 mL of serosanguineous fluid, which eventually cleared before removal of the drain on postoperative day 3.

The patient was eventually transferred out of the ICU to a regular nursing floor and was recovering well with plans for home discharge with outpatient physical therapy. However, on postoperative day 8, the day of his discharge, he had a sudden change in his neurologic examination

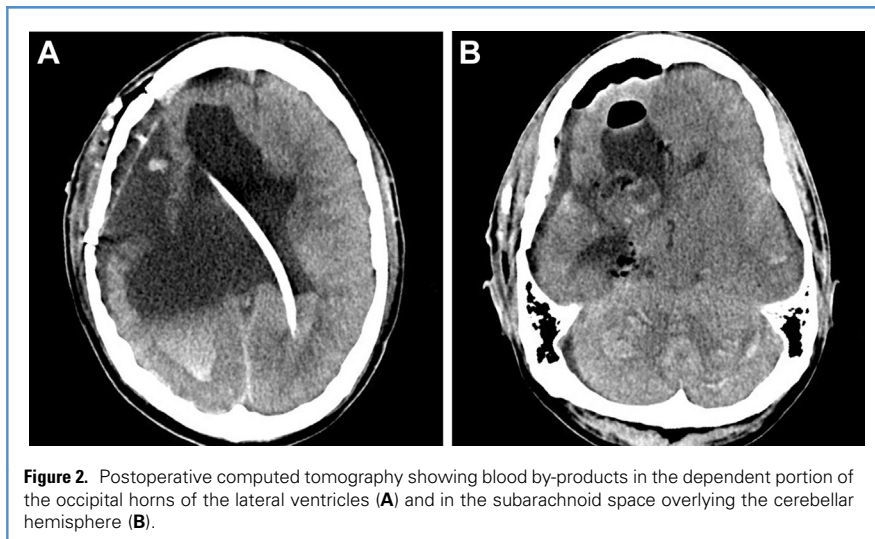


Figure 2. Postoperative computed tomography showing blood by-products in the dependent portion of the occipital horns of the lateral ventricles (A) and in the subarachnoid space overlying the cerebellar hemisphere (B).

where he became less responsive and exhibited mild nuchal rigidity, increased tonic of extremities, and hemodynamic changes in the form of tachycardia and hypertension. He was afebrile but had a leukocytosis of 21,600/ μ L that was thought to be reactive. Computed tomography scan of the head was stable, and EEG showed evidence of severe diffuse encephalopathy with no epileptiform discharges or EEG seizures. The patient's clinical condition continued to deteriorate requiring readmission to the ICU and intubation for airway security. A right-sided external ventricular drain was placed to rule out elevated intracranial pressure and to obtain cerebrospinal fluid samples for a workup for infection, after

which antibiotics were initiated for empirical treatment of meningitis. Intracranial pressure was within normal limits, and cerebrospinal fluid cultures yielded no organisms.

The patient's condition failed to improve, and magnetic resonance imaging obtained on postoperative day 9 revealed extensive areas of restricted diffusion suggesting acute infarction throughout most of the bilateral cerebral hemispheres (Figure 3A and B). This prompted emergent diagnostic cerebral angiography, which revealed severe vasospasm with minimal cerebral blood flow within intracranial vessels including the basilar artery, M1 segment of the middle cerebral artery and A1 segment of

the anterior cerebral artery bilaterally. Intra-arterial calcium channel blocker infusion (verapamil and nicardipine) along with balloon angioplasty were attempted without significant improvement in cerebral perfusion (Figure 4A–D). Following the procedure, the patient was aggressively treated for vasospasm in the neurologic ICU for 3 days. With a progressively worsening clinical picture, family members decided to transition to comfort care, and the patient died shortly afterwards. No postmortem examination was performed per the family's wishes.

DISCUSSION

This case describes a pediatric patient with medically refractory right hemispheric epilepsy in the setting of porencephaly and COL4A1 gene mutation. The patient underwent an uncomplicated disconnective hemispherectomy and later developed diffuse cerebral vasospasm, refractory to treatment, resulting in his demise. Dominant acting mutations in the COL4A1 gene, encoding the type IV collagen alpha 1 chain, are documented to be associated with porencephaly and infantile hemiparesis and have been recognized as a further monogenic cause of cerebral microangiopathy that can manifest with strokes in adulthood.^{13,14} Several COL4A1 pathogenic genomic variants have been reported, most of which are missense changes leading to a substitution of a glycine in the Gly-Xaa-Yaa triple helical domain and are assumed to have a dominant-negative effect. No clear genotype-phenotype correlation is present.¹⁵ The mutation carries a broad phenotypic spectrum including cerebrovascular disease and involvement of various systems, including ocular, renal, muscular, and cardiac features.¹⁵

Successful epilepsy surgery has been reported in 3 children with COL4A1 gene mutations.¹⁶ One patient with a COL4A1 gene mutation reportedly underwent a complete corpus callosotomy,¹⁷ while another patient underwent a functional hemispherectomy procedure after a failed corpus callosotomy.¹⁸ The third patient underwent resection of a concomitant left temporo-occipital dysplasia.¹⁶ No intracranial hemorrhage or other perioperative complications were reported

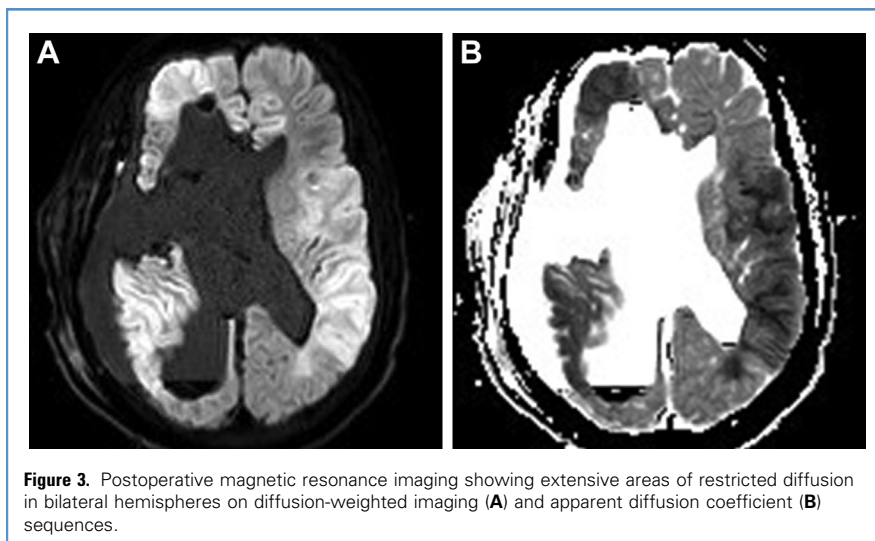


Figure 3. Postoperative magnetic resonance imaging showing extensive areas of restricted diffusion in bilateral hemispheres on diffusion-weighted imaging (A) and apparent diffusion coefficient (B) sequences.

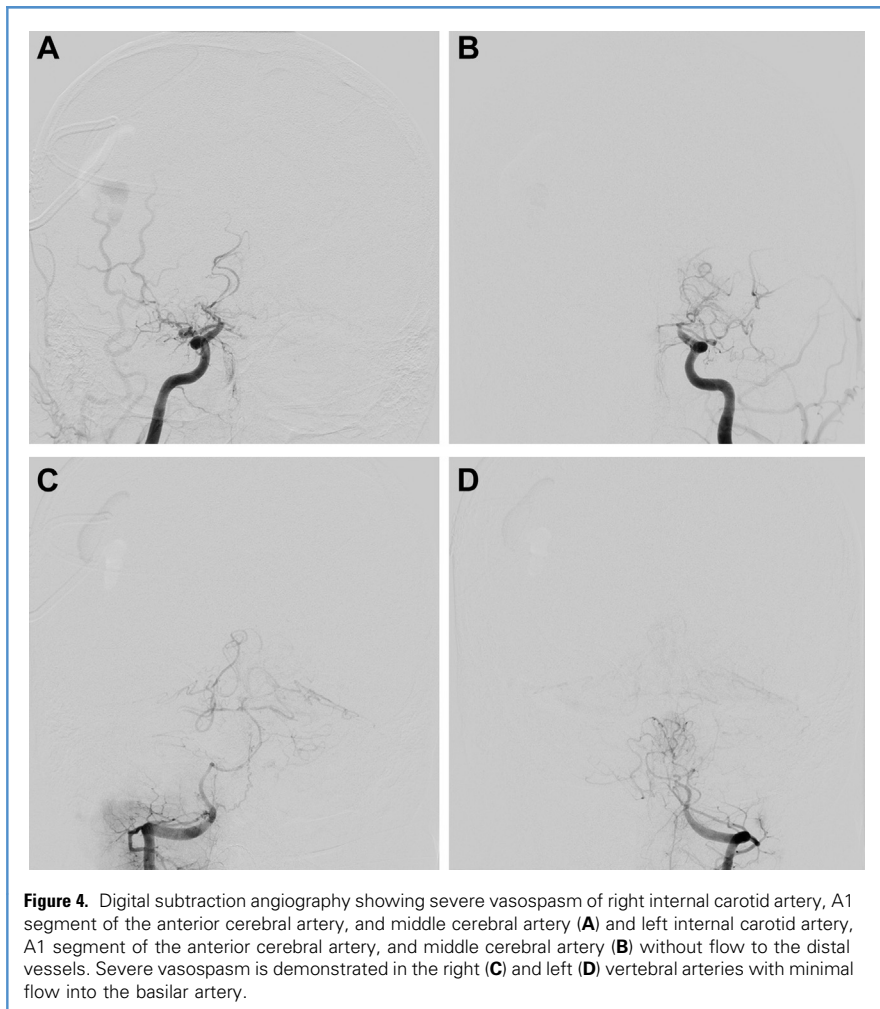


Figure 4. Digital subtraction angiography showing severe vasospasm of right internal carotid artery, A1 segment of the anterior cerebral artery, and middle cerebral artery (A) and left internal carotid artery, A1 segment of the anterior cerebral artery, and middle cerebral artery (B) without flow to the distal vessels. Severe vasospasm is demonstrated in the right (C) and left (D) vertebral arteries with minimal flow into the basilar artery.

in these cases even after reoperations. In the current case, the patient underwent functional hemispherectomy with an uncomplicated intraoperative and immediate postoperative course. It was not until the day of discharge, 8 days following his surgery, that he had a sudden and drastic change in his neurologic status. The inciting event for his worsening neurologic status was not clearly identified. There was no recorded hypoxia or significant hypotension immediately before his clinical deterioration. The angiographic evidence of severe diffuse cerebral vasospasm is likely due to the presence of blood by-products in the subarachnoid space.

CONCLUSIONS

To our knowledge, this is the first report in the literature describing vasospasm and

subsequent ischemic stroke following a hemispherectomy procedure in a patient carrying *COL4A1* mutation. We postulate that his *COL4A1* gene mutation might have resulted in this exaggerated vasospasm despite not being a significant subarachnoid hemorrhage burden resulting in extensive cerebral injury. Whether hemispherectomy, which involves less tissue destruction, less blood vessel manipulation, and fewer residual blood by-products, reduces the risk of such a complication compared with hemispherectomy remains unclear and understudied. This might be due to the rarity of the condition or underreporting of vasospasm as a potential complication. This hypothesis needs to be further studied in animal models of this genetic disorder. In addition, epilepsy surgery outcomes in patients with *COL4A1* gene mutation need to be better understood. Genetic testing for

COL4A1 gene mutation should be recommended for children with early-onset refractory epilepsy in the setting of porencephaly and schizencephaly, as these are the more common abnormalities reported in patients with *COL4A1* gene mutation.

REFERENCES

- Dandy WE. Removal of right cerebral hemisphere for certain tumors with hemiplegia: preliminary report. *JAMA*. 1928;90:823-825.
- McKenzie K. The present status of a patient who had the right cerebral hemisphere removed. *JAMA*. 1938;111:168-183.
- Krynauw R. Infantile hemiplegia treated by removal of one cerebral hemisphere. *S Afr Med J*. 1950;24:539-546.
- Oppenheimer D, Griffith H. Persistent intracranial bleeding as a complication of hemispherectomy. *J Neurol Neurosurg Psychiatry*. 1966;29:229-240.
- Rasmussen T. Hemispherectomy for seizures revisited. *Can J Neurol Sci*. 1983;10:71-78.
- Moosa AN, Gupta A, Jehi L, et al. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. *Neurology*. 2013;80:253-260.
- Vadera S, Griffith SD, Rosenbaum BP, et al. National trends and in-hospital complication rates in more than 1600 hemispherectomies from 1988 to 2010: a Nationwide Inpatient Sample study. *Neurosurgery*. 2015;77:185-191 [discussion: 191].
- Ricarte I, Funchal B, Miranda Alves M, et al. Symptomatic cerebral vasospasm and delayed cerebral ischemia following transsphenoidal resection of a craniopharyngioma. *J Stroke Cerebrovasc Dis*. 2015;24:e271-e273.
- Chong MY, Quak SM, Chong CT. Cerebral ischaemia in pituitary disorders—more common than previously thought: two case reports and literature review. *Pituitary*. 2014;17:171-179.
- Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536:285-291.
- Bateman A. UniProt: A worldwide hub of protein knowledge. *Nucleic Acids Res*. 2019;47:D506-D515.
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-424.
- Vahedi K, Alamowitch S. Clinical spectrum of type IV collagen (*COL4A1*) mutations: a novel genetic multisystem disease. *Curr Opin Neurol*. 2011;24:63-68.
- Lanfranconi S, Markus HS. *COL4A1* mutations as a monogenic cause of cerebral small vessel

- disease: a systematic review. *Stroke*. 2010;41:e513-e518.
15. Meuwissen MEC, Halley DJJ, Smit LS, et al. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. *Genet Med*. 2015;17:843-853.
16. Zagaglia S, Selch C, Nisevic JR, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. *Neurology*. 2018;91:e2078-e2088.
17. Papandreou A, Tisdall MM, Chong WK, Cross JH, Harkness WF, Varadkar SM. COL4A1 mutations should not be a contraindication for epilepsy surgery. *Childs Nerv Syst*. 2014;30:1467-1469.
18. Hino-Fukuyo N, Kikuchi A, Iwasaki M, et al. Dramatic response after functional hemispherectomy in a patient with epileptic encephalopathy carrying a de novo COL4A1 mutation. *Brain Dev*. 2017;39:337-340.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any

commercial or financial relationships that could be construed as a potential conflict of interest.

Received 25 December 2019; accepted 3 February 2020

Citation: World Neurosurg. (2020) 137:357-361.

<https://doi.org/10.1016/j.wneu.2020.02.020>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2020 Elsevier Inc. All rights reserved.