

Restrictive cerebral cortical venopathy: A new clinicopathological entity

Zoya A Voronovich¹ , Kathy Wolfe², Kimberly Foster¹, Danielle Sorte^{1,3}
and Andrew P Carlson¹

Abstract

We present a case of a novel restrictive cerebral venopathy in a child, consisting of a bilateral network of small to medium cortical veins without evidence of arteriovenous shunting, absence of the deep venous system, venous ischemia, elevated intracranial pressure, and intracranial calcifications. The condition is unlike other diseases characterized by networks of small veins, including cerebral proliferative angiopathy, Sturge-Weber syndrome, or developmental venous anomaly. While this case may be the result of an anatomic variation leading to the congenital absence of or early occlusion of the deep venous system, the insidious nature over many years argues against this. The absence of large cortical veins suggests a congenital abnormality of the venous structure. The child's presentation with a seizure-like event followed by protracted hemiparesis is consistent with venous ischemia. We propose that this is likely to represent a new clinicopathological entity.

Keywords

9p21.1 deletion, cerebral proliferative angiopathy, cortical veins, deep venous system, developmental venous anomaly, intracranial calcifications, intracranial hypertension, *LINGO2*, stroke-like episode, venous ischemia, Sturge-Weber syndrome

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Introduction

Few pediatric diseases of the cerebral venous system have been identified. These conditions, such as developmental venous anomalies (DVAs) and venous malformations, are described as “rarely pathologic” and “as a rule, should not be treated.”¹ We present a previously unreported case of a congenital cerebral venopathy characterized by a network of small to medium veins, causing restricted venous drainage and ischemia. We argue that this abnormal venous anatomy ultimately leads to profound brain injury, as evidenced by intracranial calcifications (ICCs) and cerebral atrophy. Resulting intracranial hypertension was managed with a ventriculoperitoneal shunt.

Case report

History and presentation

A 16-year-old male with cerebral palsy, well-controlled focal epilepsy and cognitive impairment presented to our hospital after sustaining a seizure-like event, with subsequent persistent left-sided hemiplegia and obtundation of two days' duration. The child was obtunded on initial examination, and was withdrawing from central stimulus, with stronger movement of the right

extremities than the left. The child had a history of seizures, which were predominantly characterized as focal to bilateral tonic-clonic. He was previously treated with levetiracetam, but the treatment was discontinued after he was seizure free for several years. He was born at full term via cesarean section and required a two-month stay in the neonatal intensive care unit because of respiratory problems, without cardiopulmonary resuscitation. He required surgery for persistent ductus arteriosus, bilateral orchiopexy, and strabismus. He also had two instances of intussusception that did not require surgical intervention.

Imaging from 12 years ago demonstrated intraparenchymal calcifications and unspecified cerebral venous anomalies. Testing for TORCH infections was

¹Department of Neurosurgery, University of New Mexico Health Sciences Center, Albuquerque, USA

²Department of Neurology, University of New Mexico Health Sciences Center, Albuquerque, USA

³Department of Radiology, University of New Mexico Health Sciences Center, Albuquerque, USA

Corresponding author:

Andrew P Carlson, Department of Neurosurgery, University of New Mexico Health Sciences Center, MSC 10-5615, 2211 Lomas Blvd NE, Albuquerque, NM 87131, USA.

Email: AndrewCarlson@salud.unm.edu

reportedly negative. There was a question of the patient having an arteriovenous malformation, and he had at least one diagnostic cerebral catheter angiogram that identified venous anomalies, thought to represent changes related to deep venous occlusion.

Family history is significant for a brother with febrile seizures and hearing deficits. No other history of seizures, aneurysms, or connective tissue disease was reported.

Imaging and diagnostic findings

Head computed tomography (CT) demonstrated extensive bilateral intraparenchymal calcifications involving the cerebral, periventricular, and cerebellar regions, and associated with volume loss. The bilateral frontoparietal, parietal, and occipital calcifications appeared to be in a gyral distribution, although the frontal calcifications also had a white-matter component. The cerebellar calcifications were also bilateral and involved the dentate nuclei (see Figure 1). The calcifications appeared unchanged when compared to imaging from 13 years prior.

Magnetic resonance imaging (MRI) of the brain demonstrated extensive restricted diffusion of the right hemisphere subcortical white matter and extensive abnormal flow voids in the subarachnoid space (see Figure 2). T1 signal of the right hemisphere was isointense as compared to the left hemisphere, while T2 signal was slightly increased in the right hemisphere. The flow voids were similar in appearance to those demonstrated on MRI of the brain obtained 13 years prior. However, the findings of diffusion restriction were not seen on previous studies, and are consistent with the patient's new deficits. T2 optic nerve sheath diameters were 6.2 mm in the right eye and 7.3 mm in

the left eye, measuring above the 5.83 mm cutoff for elevated intracranial pressure (ICP).²

A digital subtraction angiogram (DSA) was performed to better characterize the vascular abnormalities. No abnormalities were seen in the arterial or capillary phases. However, the venous phase was profoundly abnormal bilaterally, characterized by an extensive network of small to medium veins that drained very slowly via extremely tortuous networks into the superior sagittal sinus. There was a paucity of large cortical veins. The transverse sinuses, the sigmoid sinuses, and the internal jugular veins were patent. There was no filling of the deep venous system or drainage into the vein of Galen and the straight sinus (see Figure 3). The absence of the deep venous system and the abundance of small cortical veins were noted on the child's DSAs from nine and 13 years prior to presentation, and appeared similar to the angiogram performed at presentation. No MR venogram was performed to our knowledge.

The angiographic findings raised the question of cerebral venous congestion leading to elevated ICP. Although an ophthalmologic examination did not demonstrate papilledema, a lumbar puncture performed under sedation demonstrated an opening pressure of 30 cm H₂O. A right parietal ventriculoperitoneal shunt was placed for management of intracranial hypertension.

The child's neurologic examination improved during the hospitalization, with increased wakefulness and improving left-sided strength. At two-month follow-up, the patient returned to his neurologic baseline. MRI obtained four months after presentation demonstrated resolution of diffusion restriction, decreased optic nerve sheath diameter bilaterally, and decreased ventricular size.

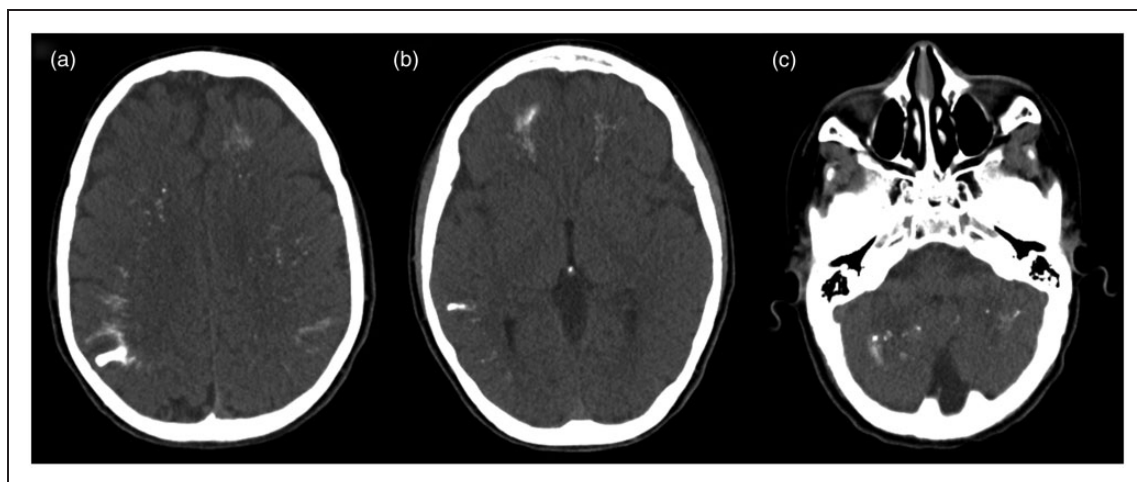


Figure 1. Head computed tomography (CT) without contrast demonstrated scattered extensive bilateral intraparenchymal calcifications with diffuse volume loss. (a) The frontoparietal, parietal, and occipital calcifications appeared to be in a gyral distribution. (b) The periventricular frontal calcifications appeared somewhat more pronounced when compared to the head CT from 12 years prior. (c) The bilateral cerebellar calcifications involve the dentate nuclei.

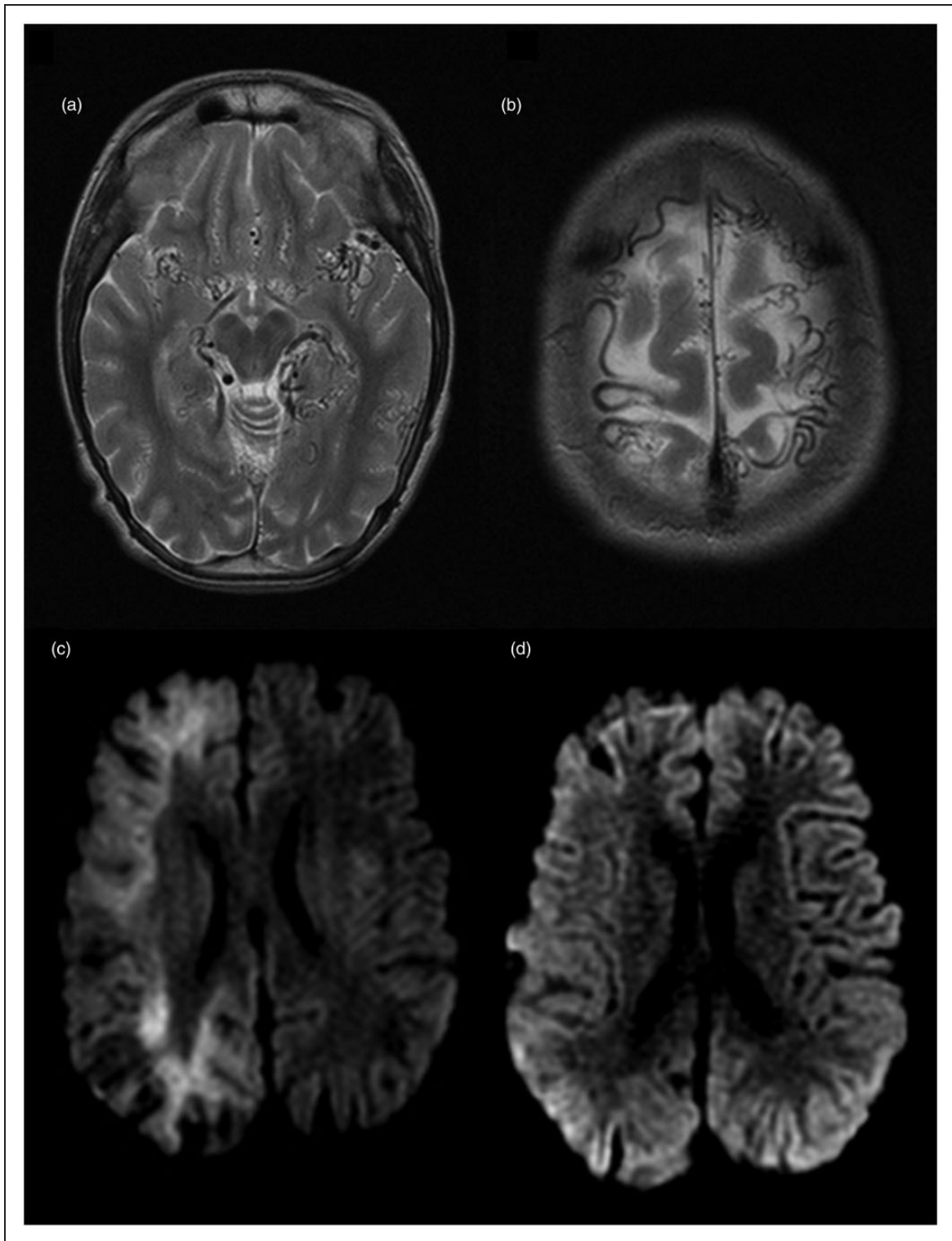


Figure 2. Magnetic resonance imaging (MRI) of the brain (1.5 Tesla) with and without contrast demonstrated extensive abnormal flow voids in the subarachnoid spaces, with predominance at the left Sylvian fissure and along the left anterior tentorium. The flow voids are diffuse as demonstrated by their presence (a) in the basal cisterns and (b) over the convexities. (c) The B1000 sequence demonstrated extensive diffusion restriction of the subcortical white matter throughout the majority of the right frontal, parietal, temporal, and occipital lobes, without corresponding T2 fluid-attenuated inversion recovery abnormality (not shown). (d) MRI brain B1000 sequence from nine years prior to presentation did not demonstrate the pattern of diffusion restriction observed in the MRI at presentation.

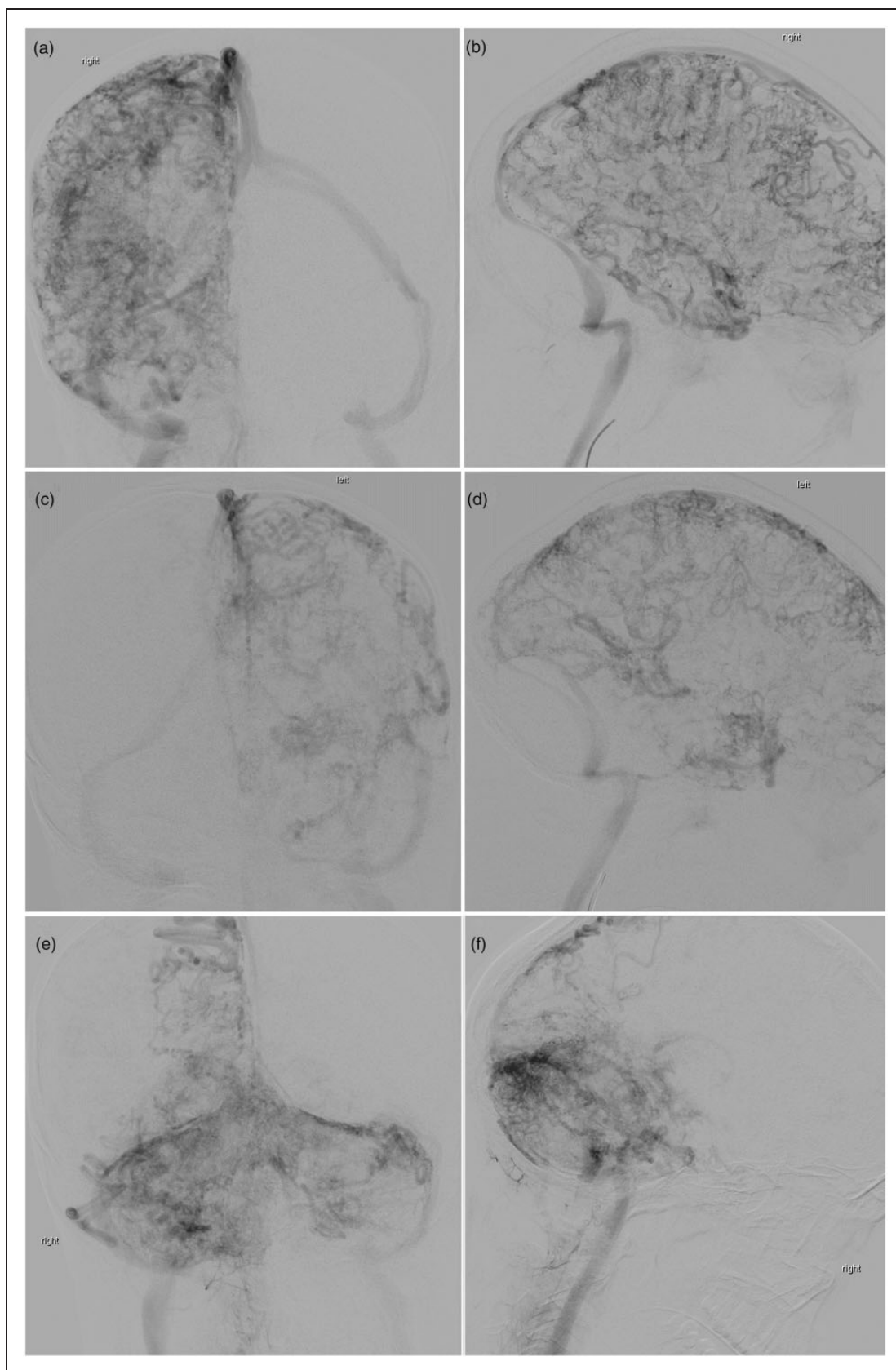


Figure 3. (a and b) The venous phase of the right internal carotid artery injection demonstrated an extensive network of very small veins, draining slowly into extremely tortuous medium-sized veins, and then into the superior sagittal sinus and the transverse sinuses. There was no filling of the deep venous system into the vein of Galen and the straight sinus. The torcula was high-riding. The sigmoid sinuses and the internal jugular veins were patent bilaterally. There was a delay in opacification due to the extremely delayed outflow from the cortical vessels. (b) and (c) The venous phase of the left internal carotid artery injection and of the right vertebral artery injection (d and e) demonstrated similar findings.

Genetic testing demonstrated 178 kb deletion of 9p21.1, including the *LINGO2* gene.

Discussion

We describe a case of a previously unreported restrictive cerebral venopathy in a 16-year-old male with seizure disorder and developmental delay, consisting of a diffuse network of small to medium cortical veins without evidence of arteriovenous shunting, and the absence of the deep venous system. These findings were associated with ICCs, elevated ICP, and a stroke-like episode. Our literature review did not yield any other cases of diffuse networks of small cortical veins without associated arteriovenous shunting.

Venous anatomy

The venous drainage pattern of the adult supratentorial structures is described as having a superficial system and a deep system. The superficial veins lie on the surface of the cerebral cortex, and drain the outer 1 to 2 cm of cortex and white matter via intracortical and subcortical veins in a centrifugal direction. The superficial medullary veins drain the deeper or gyral white matter. The pial veins collect blood from intracortical, subcortical, and superficial medullary veins, and coalesce into the larger cortical veins, which then continue toward their respective dural sinuses.³ The superficial veins ultimately drain to the superior sagittal sinus, the sphenoparietal sinus and the cavernous sinus, the inferior sagittal sinus and the vein of Galen, and the tributaries of the sinuses related to the tentorium cerebelli.⁴ The deep venous system drains centripetally from the more central white matter and paraventricular nuclei, such as the internal cerebral veins, the basal veins of Rosenthal, and their tributaries, including those draining the basal surface of the brain. The deep white matter first drains to the deep medullary veins, which converge into distinct zones as they transverse the white matter to connect with the subependymal veins. The superficial and the deep venous systems do interconnect: The anastomotic medullary veins connect the superficial and the deep medullary veins, and the transcerebral veins interconnect the pial veins and the subependymal veins.³ Compared to the usual configuration of the venous system, there is an absence of the basal veins of Rosenthal and the internal cerebral veins in this case. Additionally, the cortical veins of the superficial system do not appear to coalesce into larger cortical veins, and there is no clearly defined vein of Labbé, vein of Trolard, or superficial Sylvian (middle cerebral) vein. The extensive network of small veins may represent the dilation of the anastomotic medullary veins and the transcerebral veins to support the drainage of the deep white matter in the absence of prominent internal cerebral veins and basal veins of Rosenthal. However, most of these vessels seem to be in the subarachnoid space rather than the deep white matter.

It seems unlikely, therefore, that this is simply a reactive process to occlusion or to the absence of the deep venous system.

Cerebral venous development

Developmental events in the late embryologic and early fetal stages may be at the root of the observed abnormalities. Around week 6 of development, extrinsic diffusion can no longer sustain the neural tissue. The intrinsic vessels of the brain develop centripetally, originating from the initial surface capillary meshwork and extending to the metabolically active germinal zone, where they form arteriovenous loops. Thus, the true transcerebral veins are the first to develop. Raybaud⁵ infers that the subependymal veins are the next to develop, followed by the cortical-subcortical veins. He additionally notes that there is no literature describing how the vasculature of the subependymal collectors is formed from the vasculature of the germinal zone, nor how these collectors connect to the dorsal dural veins. Of note, the shift of dorsal venous drainage from a purely choroid one into the vein of Markowski to a common choroid and parenchymal drainage (including the tributaries of the subependymal veins) through the vein of Galen occurs around week 11. Given that the deep white matter and periventricular structures appear grossly normal in our patient, the intrinsic venous structures can be inferred to be sufficient for drainage. However, the absence of the vein of Galen and no notable presence of a persistent vein of Markowski (i.e. a vein of Galen malformation) are suggestive of a failure of the normal development of dorsal venous drainage at this stage.

Other entities with abnormal networks of small veins

The findings of our case are fundamentally different from those of other entities that involve abnormal networks of small veins, including cerebral proliferative angiopathy, DVAs, and Sturge-Weber syndrome (SWS). Cerebral proliferative angiopathy (CPA), as described by Lasjaunias et al., differs from our case in that CPA is characterized by “the small caliber of a multitude of feeding arteries and draining veins,”⁶ while our case involves abnormalities of the venous phase only and does not have arteriovenous shunting. More recent reports have also identified arteriovenous fistula, flow-related aneurysm,⁷ and intracranial hemorrhage^{7,8} in CPA, neither of which were observed in our patient. Leptomeningeal angiomatosis of SWS may have a similar radiographic appearance to our case.⁹ Our patient also shares some clinical features with SWS, including ICCs likely associated with venous congestion,¹⁰ a stroke-like episode,¹¹ and the dilation of small veins.¹² Poor drainage of the deep venous system has also been identified in SWS,¹³ but dilation of the deep venous system is more frequently cited.¹⁴

Ultimately, our patient does not have leptomeningeal angiomatosis, and does not carry the somatic mutation in the *GNAQ* gene, located on 9q21.2, that appears to be the major genetic factor in SWS.¹⁵ Interestingly, Lasjaunias et al. presented the findings of transcortical bilateral collateral circulation involving striate veins bilaterally and the transcallosal vein on the right side in a 19-month-old-boy presenting with a seizure, persistent hemiparesis, but without port-wine stain. Although this case demonstrated an extensive bilateral network of small veins, a few large cortical veins were also visualized, and the deep venous system was not only present but appeared to provide a significant route of cerebral drainage. Cortical vein occlusion without venous sinus impairment was suggested as the underlying mechanism. The case was thought to be consistent with the spectrum of cerebrofacial venous metamerism syndrome (CVMS), a term that appears to have fallen out of favor relative to SWS type III that accounts for 10% of the cases without cutaneous findings.¹⁰ DVAs are characterized by a network of enlarged subependymal or subpial venous channels of the caput medusa formation, extending toward one or more enlarged transependymal veins acting as collectors. The absence or disruption of either the deep or the superficial venous drainage system has been suggested as the cause of the compensatory development of the transparenchymal medullary venous drainage pathway of the DVA.¹⁶ The absence of the deep venous system, and the enlarged venous structures on the cortical surface are seen in our patient. However, the angiogram did not demonstrate the coalesced transparenchymal collectors characteristic of DVAs, and our patient's angiographic findings are diffuse and involve both hemispheres.

Intracranial hypertension

We propose that our patient's abnormal cortical venous architecture cannot support a normal rate of venous outflow, thus leading to an imbalance relative to the arterial inflow, and resulting in increased ICP, as described by Wilson.¹⁷ Interestingly, the appearance of the small tortuous veins and slow venous drainage we observed was quite similar to the severe pseudopheibitic pattern first noted in dural arteriovenous fistulas in association with venous congestion and intracranial hypertension.¹⁸ Bilateral optic nerve sheath dilation further supported the concern for intracranial hypertension, which was confirmed with a lumbar puncture. Lack of papilledema on the ophthalmologic examination can be seen in the setting of acute rise of ICP,¹⁹ and does not negate concerns for intracranial hypertension in our patient. Cerebrospinal fluid diversion was pursued to prevent the sequelae of long-term elevated ICP, and to lower ICP in hopes of decreasing the size of the venous infarct, as suggested by recent animal studies.²⁰ Furthermore, there is a lack of techniques to address small-vein congestion directly, and the child's

venous sinuses were widely patent, with no evidence of stenosis to consider stenting or open techniques, such as sino-jugular bypass.²¹ Although his clinical condition began to improve even prior to shunting, the resolution of ischemia without progression to infarct may have been helped by the decrease in ICP, as evident by the reduction in the optic nerve sheath diameters on follow-up MRI.

Venous ischemia and the stroke-like episode

The MRI findings of diffusion restriction, without associated fluid-attenuated inversion recovery change, are suggestive of cytotoxic edema as would be seen in early stages of ischemia.²² Our patient's recovery of function, the resolution of diffusion restriction, and the lack of encephalomalacia on follow-up are consistent with a venous etiology of ischemia. The ischemic penumbra and the number of cells that are only functionally impaired are thought to be larger in venous stroke as compared to arterial stroke, which explains the relatively indolent course and good clinical recovery that can be seen in venous stroke.²³ The event may have been triggered by the seizures sustained by the patient, as these would lead to hyperperfusion in the ictal-onset zone,²⁴ and thus exacerbate the venous congestion. The absence of recent seizures as a trigger may explain why the patient has not had a prior episode of hemiparesis. On the other hand, another physiologic event, such as dehydration and/or fever related to the patient's recent illness, may have led to worsened venous congestion and/or tolerance thereof, resulting both in venous ischemia and seizures. Of note, similar episodes of protracted—but ultimately recovered—hemiparesis are also reported in SWS as “stroke-like episodes,” and were similarly attributed to venous congestion and ischemia.^{25,26} Interestingly, findings of venous wall thickening and “sluggish flow” have also been correlated to the brain lesions related to the stroke-like episodes of the very different disorder of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.²⁷

Calcifications

Intracranial calcifications (ICCs) observed in our patient may be the result of cell damage from prior insults, or from deposition of calcium in the vessels. ICCs found in patients younger than 20 years old and located outside the choroid plexus and the pineal gland are pathologic. Although specific associations, such as those seen in Aicardi-Goutières syndrome and in post-infectious etiologies, are recognized,²⁸ ICCs are usually an “epiphenomenon of low diagnostic specificity.”²⁹ Vascular pathology is typically thought to result in dystrophic ICCs, where damaged cell membranes allow excess calcium influx.^{30,31} However, histologic analysis of ICCs in SWS revealed them to be of the vascular type secondary to “calcium incrustation” of the

vessels,³⁰ rather than due to the traditionally proposed cell damage due to “chronic hypoxic state caused by inadequate venous drainage and venous hypertension”³² that we also would have expected to see in our patient. There were no notable changes in our patient’s ICCs over the years preceding his presentation, or on the follow-up MRI SWI sequence, within the limitations of the shunt valve artifact. The lack of recent changes is unsurprising given the reversal of the ischemia as described above. Similar to observations made in SWS, our patient’s ICCs may contribute to his epilepsy and cognitive delay.³³

Conclusion

We present a case of a novel cerebral venopathy in a child, characterized by a diffuse network of small cortical veins without evidence of arteriovenous shunting, absence of the deep venous system, ICCs, elevated ICP, and a stroke-like episode. The condition is unlike other diseases characterized by networks of small veins, including CPA, SWS, or DVA. Our case is most similar to a case of CVMS briefly described by Lasjaunias et al., yet is still more extreme because of the absence of large cortical veins. The development of subependymal veins and their connection to the vein of Galen may be the key to understanding this malformation, but these are unfortunately poorly understood. The case is ultimately illustrative of acute and chronic consequences of venous congestion, such as ischemia and calcifications. We look forward to learning of similar cases in hopes of gaining a better understanding of this condition.

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ORCID iD

Zoya A Voronovich  <http://orcid.org/0000-0001-5322-5316>

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